1.0 Title Page

Clinical Investigational Plan (CIP) Information	
Title:	Multicenter, prospective, randomized study comparing the diagnostic yield of colon capsule endoscopy versus computed tomographic colonography in a screening population (the TOPAZ study)
CIP Number:	MA-213 / COVGIC20543
Version Date:	October 08, 2017
Revision:	4.0
Sponsor:	Given Imaging LTD Medtronic 2 Hacarmel St. New Industrial POB 258, 20692 Yoqneam, Israel

This investigational plan contains confidential information for use by Investigators participating in the Medtronic clinical evaluation of the PillCam® COLON 2 Capsule endoscopy system. It should be maintained in a secure location. It should not be copied or made available for review by any unauthorized person or firm.

Summary of Changes to CIP			
Revision	**Section**	**Description of Change**	**Reason for Change**
1	N/A	N/A	N/A
2.0	4.0, 8.0, 8.7.1, 8.10.1, 8.10.2, 8.11.3	Added "tested for renal function using a blood test (eGFR)" and "Subjects with GFR < 45 will be discontinued from the study."	Since there are concerns around the CTC bowel prep, radiologists advised that renal screening should be performed at the baseline visit.
2.0	4.0	Added planned study duration.	To comply with our internal CIP checklist.
2.0	4.0	Removed "randomization will be stratified by study site."	Randomization will be performed 1:1 and not by study site.
2.0	7.0	Added "PillCam® COLON 2 capsule is ingested by the patient after bowel preparation, with a sip of water. The device does not incorporate any medicinal product, human blood derivative or tissues of animal origin."	To comply with our internal CIP checklist.
2.0	16.1	Added "In addition, it is intended for detection of colon polyps in patients with evidence of gastrointestinal bleeding of lower GI origin. This applies only to patients with major risks for colonoscopy or moderate sedation, but who could tolerate colonoscopy and moderate sedation in the event a clinically significant colon abnormality was identified on capsule endoscopy."	In accordance with the PillCam® COLON expanded indication.
2.0	N/A	Minor updates and minor clarifications were made throughout the protocol. These	Minor updates and clarifications were needed in the protocol to

		minor changes did not affect the purpose or requirements of the study.	meet global regulatory requirements or to make minor corrections.
3.0	4.0, 8.0	Removed "Europe" from study site.	Due to complexity of the study, only US sites will be included.
3.0	4.0, 8.7.1	Added "for African Americans only, subject is between 45-75 years of age" in inclusion criteria.	Average risk for CRC in African American population is between ages 45-75.
3.0	4.0, 8.7.1,	Added individuals without 'family history of either CRC or adenomas in a first degree relative before age 60 years. Subjects with 2 second degree relative affected with with CRC are also considered average risk."	Specified "average risk" per American Gastroenterological Association Guidelines on Colorectal Cancer Screening.
3.0	4.0, 8.7.2	Deleted "or at any time in the past if not tested within the last 6 months, defined as creatinine, blood urea nitrogen (BUN) outside of normal reference range" from exclusion criteria no. 9 (definition of renal disease).	Sufficient to report "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."
3.0	8.10.2	Added "waist circumference and cigarette smoking history" to baseline assessment.	These assessments are included in the clinical report form (CRF) for screening.
3.0	8.6.1, 8.6.3, 15.0	Removed "sub-investigator" designation for radiologist.	It is not deemed necessary to assign radiologists as sub-investigators. To ensure clinical compliance across sites, there will be only one Site Principal Investigator (gastroenterologist) and no 'Sub-Investigators.'
3.0	8.6.1	Added "either performing the capsule or colonoscopy procedure" for gastroenterologist designated as Site Principal Investigator.	To clarify that the title of "Site Principal Investigator" is not limited only to the gastroenterologist performing capsule endoscopy; the Site Principal Investigator can be the

			gastroenterologist performing either capsule endoscopy or colonoscopy.
3.0	8.11.2, 9.2, Appendix D	Removed sections on matching procedure and analysis.	Details on polyp matching algorithms are not yet finalized.
3.0	9.4. 11.0, 11.8	Removed requirement of collecting bowel preparation AEs.	Payers are not concerned about AEs related to the bowel prep as much as they are about AEs related to the procedures and the device.
3.0	11.4, 11.6, 11.10. 11.11	Added "Serious Adverse Device Effect," "Customer Complaint," "Adverse Event Recording," and "Adverse Event Reporting" sections.	To comply with our internal CIP checklist.
3.0	11.9	Added "death" to Adverse Event Outcome Classification section.	Per ICH-GCP guidelines.
3.0	13.1	Added code of federal regulations (CFRs) applicable to the study in "Statement of Compliance" section.	To comply with our internal CIP checklist.
3.0	13.6	Modified "Insurance" section.	To comply with our internal CIP checklist.
3.0	17.2	Changed number of years from "5 years" to "2 years" for retention of subject files and other source data after the completion or termination of the study.	To comply with Medtronic's retention of record policy and local regulations.
3.0	Appendices A1 and A3	For the sentence, "Subjects will be allowed to leave the unit 10 hours after capsule ingestion if the capsule is not yet excreted," deleted "10 hours after capsule ingestion" and replaced it with "only after the second boost was administered."	If subject cannot be monitored for the entire procedure duration in the clinic, the subject may leave the clinic after administering the second boost while still connected to the system.

3.0	Appendix A4	Added "Local reader results will be read within 2 weeks and kept at the subject binder until confirmatory OC."	To provide additional procedural details for local reader results.
3.0	Appendix C1	Removed Senna dosage requirement (12 mg)	Sites requested to allow both 12 and 15 mg Senna tablets, so we removed the 12 mg specification in the protocol.
3.0	Appendix D	Added patient procedure preference sample questionnaires.	To provide examples of patient preference questionnaire that may be used in the study.
3.0	Appendix E	Added matching algorithm section	To provide details on polyp-matching algorithm.
3.0	N/A	Minor updates and minor clarifications were made throughout the protocol. These minor changes did not affect the purpose or requirements of the study.	Minor updates and clarifications were needed in the protocol to meet global regulatory requirements or to make minor corrections.
4.0	4.0	Added Clinical events committee (CEC) statement to protocol.	CEC consensus panel was added to adjudicate any discrepancies regarding OC polyp size measurements. Accuracy based on pathology classification was added as additional analysis

2.0 Principal Investigator Signature Page

Principal Investigator Signature Page

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Version	4.0

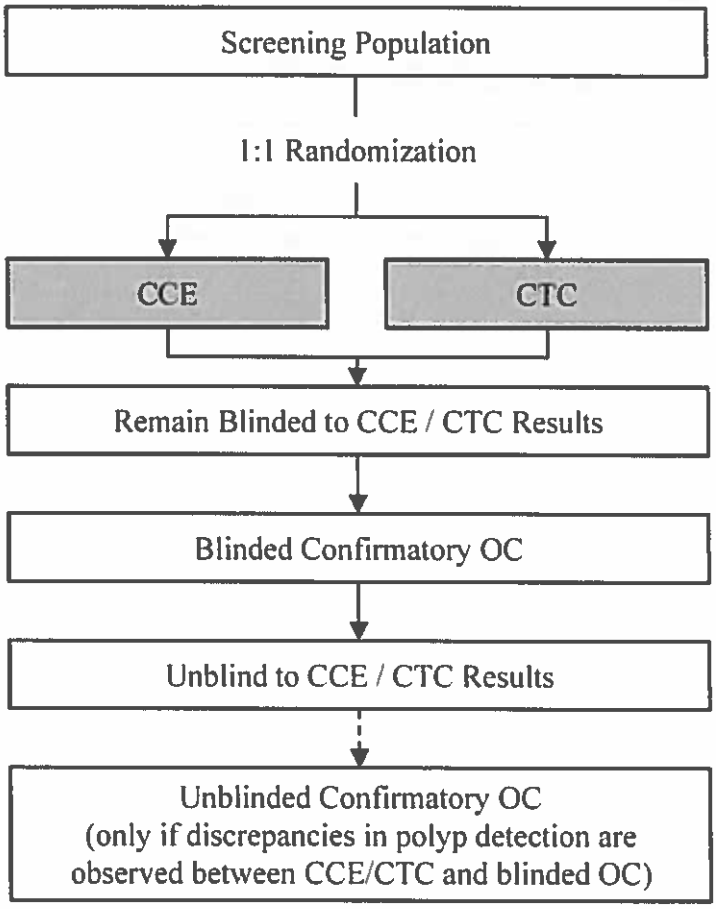
I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement. Covidien LP is an indirect wholly owned subsidiary of Medtronic plc.

Name	Signature	Date

3.0 Table of Contents

4.0 Protocol Synopsis

Background and Rationale of the Study	
Study Purpose	This trial will evaluate the efficacy of colon capsule endoscopy (CCE) versus computed tomographic colonography (CTC) in the identification of colonic polyps in a screening population.
Objective	The primary objective of this multicenter, prospective, randomized study is to assess the diagnostic yield of CCE versus CTC in a screening population.
Study Design	
Study Type	Multicenter, prospective, randomized study
Study Phase	Postmarket
Study Location	United States
Study Procedures	Study procedures are depicted in the figure below. 1. Eligible patients will be consented by the gastroenterology site, enrolled, tested for renal function using a blood test (eGFR) and 1:1 randomly assigned to one of two groups, as shown below. Subjects with GFR <45 will be discontinued from the study. 2. All subjects, whether the results are positive or negative, will undergo a confirmatory optical colonoscopy (OC) procedure within 5 weeks of the CCE ingestion or CTC procedure. The confirmatory OC will first be conducted blinded to the CCE/CTC results and then unblinded, if discrepancies in polyp detection are observed, as shown below.

	
Planned Follow-Up	Telephone follow-up will be conducted 5 – 9 days after the CCE/CTC procedure and 5 – 9 days after the OC procedure to capture any adverse events (AEs) and patient procedure preference data.
Subject Population	Screening patients who meet the eligibility criteria.
Planned # of Subjects	Incremental assessments of every 80 subjects (40 per arm) with a maximum of 320 subjects (160 per arm).
Planned study duration	Based on the number of sites and enrollment rate, study duration is expected to be up to 18 months.
Planned # of Sites	Up to 20 clinical sites in the United States

Video/Image Reading	All study analyses will be based on central reader results for both CCE and CTC. There will be 2-3 readers for each modality (CCE and CTC). All imaging will be randomly assigned among the readers. OC reports will be generated by the physician performing colonoscopies at the study site. In cases of polyp size measurement discrepancies between CCE/CTC and OC, a Clinical Events Committee (CEC) will adjudicate OC polyp size measurements.
Primary Endpoint	The primary endpoint is the diagnostic yield (proportion of subjects shown to have an actionable lesion, defined as any polyp or mass lesion ≥6 mm) by CCE as compared to CTC. Diagnostic yield of CCE/CTC will be calculated in relation to the confirmatory OC results.
Secondary Endpoints	The following accuracy measures of CCE versus CTC in the detection of polyps ≥6 mm will be assessed in relation to the confirmatory OC results and expressed on a "per subject" basis (rather than "per polyp"). • Negative predictive value (NPV) • Positive predictive value (PPV) • Sensitivity • Specificity
Additional Analyses	1. [redacted]

	6. [redacted]
Randomization	Subjects will be 1:1 randomized at the gastroenterology study site according to the procedure defined above.

Eligibility Criteria	**Inclusion Criteria** 1. Subject is between 50 and 75 years of age (for African Americans only, subject is between 45-75 years of age). 2. Subject is classified as average risk per the American Gastroenterological Association Guidelines on Colorectal Cancer (CRC) Screening: Individuals without inflammatory bowel disease, or high-risk genetic syndromes or personal history of CRC or adenomas or family history of either CRC or adenomas in a first degree relative before age 60 years. Subjects with 2 second degree relative affected with CRC are also considered average risk. 3. Subject is willing and able to participate in the study procedures and to understand and sign the informed consent. **Exclusion Criteria** 1. Subject with history of colorectal cancer or adenoma (including those identified by computed tomography [CT], optical colonoscopy, sigmoidoscopy, etc.) 2. Subject with history of negative colonoscopy within 10 years, as these subjects would be defined as not requiring screening in this timeframe. For subjects with alternative screening methods, refer to applicable guidelines. 3. Subject with currently suspected or diagnosed with hematochezia, melena, iron deficiency with or without anemia, or any other rectal bleeding, including positive fecal occult blood test of any variety. 4. Subject with any current condition believed to have an increased risk of capsule retention such as suspected or known bowel obstruction, stricture, or fistula. 5. Subject with current dysphagia or any swallowing disorder. 6. Subject with current serious medical conditions that would increase the risk associated with CCE, CTC, or colonoscopy that are so severe that screening would have no benefit. 7. Subject with a cardiac pacemaker or other implanted electromedical device. 8. Subject expected to undergo MRI examination within 7 days after ingestion of the capsule. 9. 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. 10. Subject with a diagnosis of gastroparesis or small bowel or large bowel dysmotility. 11. Subject with allergies or known contraindication to the medications or preparation agents used in the procedure as described in the relevant instructions for use.

	12. Subject has an estimated life expectancy of less than 6 months. 13. Subject is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity). 14. Subject is pregnant, suspected pregnant, or is actively breast-feeding. Females of child-bearing potential will be required to provide either a urine pregnancy test or serum pregnancy test as part of the participant's standard of care regardless of their participation in the study (except for subjects who are surgically sterile or are post-menopausal for at least two years). 15. Subject has participated in an investigational drug or device research study within 30 days of enrollment that may interfere with the subject's safety or ability to participate in this study.
Statistics	
Primary Endpoint Analysis	The primary statistical hypothesis is that the diagnostic yield (proportion of subjects having an actionable lesion, defined as any polyp or mass lesion ≥6 mm) will be noninferior for CCE compared to CTC in an average risk screening population. Diagnostic yield of CCE/CTC will be calculated in relation to the confirmatory OC results. Bayesian probability will be used to quantify strength of evidence with pre-specified interim assessments. The noninferiority margin is pre-defined as 5%. If noninferiority is proven, superiority will also be tested.
Other Analyses	All secondary endpoints will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum for continuous variables; frequency and percentage for categorical variables).
Determination of Sample Size for the Primary Endpoint	Sample size is determined based on the primary non-inferiority hypothesis under a Bayesian adaptive design. Interim assessments will be performed at every 80 subjects (40 per arm) with a maximum of 320 subjects (if needed). A noninferiority margin of 5% and an attrition rate of 10% are used.

5.0 Abbreviations and Definitions

Acronym or Term	Definition
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event
BUN	Blood Urea Nitrogen
CCE	Colon Capsule Endoscopy
CEC	Clinical Event Committee
Complete Colon Exam	Visualization of the hemorrhoidal plexus or excretion of the capsule.
CRC	Colorectal cancer
CRF	Case Report Form
CTC	Computed Tomographic Colonography
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.
DR	Data Recorder
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELS	Electrolyte Lavage Solution
FDA	United States Food and Drug Administration
FIT	Fecal Immunochemical Test
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
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	Either a principal or coordinating investigator, unless otherwise specified
IRB	Institutional Review Board
ISO	International Organization for Standardization
MITG	Minimally Invasive Therapies Group
mITT	Modified Intent-To-Treat
MRI	Magnetic Resonance Imaging
OC	Optical Colonoscopy
PEG	Polyethylene Glycol
RDC	Remote Data Capture

SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SF-ELS	Sulfate-Free Polyethylene Glycol Electrolyte Lavage Solution
USADE	Unanticipated Serious Adverse Device Effect

6.0 Introduction

6.1 Background/Justification of Investigation

Colorectal cancer is the third most common cancer and the third most common cause of cancer death in both men and women (1). Screening and early detection can significantly reduce disease-associated mortality (2). The 5-year survival rate has been reported at 90.3% when cancer is detected at a localized stage compared to 12.5% for metastasized disease (3). Recent rapid declines in the incidence of colorectal cancer have been attributed to screening, which has increased from 19.1% in 2000 to 54.5% in 2013 (1). However, it has been estimated that in 2010, only 59% of individuals aged 50 and older received colorectal cancer screening according to the recommended guidelines (4).

While optical colonoscopy (OC) is considered the gold standard for colorectal cancer screening, patient acceptance rates may be lower than recommended due to perceived discomfort. In patients unwilling or unable to undergo OC, CTC is recommended by the American Gastroenterological Society (5) and has a diagnostic yield for colorectal cancer and large polyps (≥ 10 mm) comparable to OC (6).

Colon capsule endoscopy (CCE) offers an alternative approach for visualization of the colon. The second generation PillCam® COLON 2 capsule received US Food and Drug Administration (FDA) clearance in January 2014 for detection of colon polyps in patients with an incomplete OC and in cases where a complete OC evaluation was not technically possible (7). Relative to OC, CCE provides acceptable accuracy for the detection of polyps (range 63% to 95%) with an excellent safety profile (8-14). Additional advantages of CCE include the elimination of the need for sedation, the minimally invasive and painless nature of the exam, and the ability to pursue normal daily activities immediately following the procedure. Compared to standard colonoscopy, the CCE procedure may be more readily accepted by some patients and thus increase colorectal cancer screening compliance.

Studies have shown that CCE may have a higher sensitivity and patient acceptance than CTC. In one study (12), the accuracy of CCE and CTC (relative to unblinded OC) were compared in 50 subjects with positive results from the fecal occult blood test (iFOBT-positive). Sensitivity (88.2% CCE vs. 88.2% CTC), specificity (87.8% CCE vs. 84.8% CTC), positive likelihood ratio (PLR; 3.75 CCE vs. 3.0 CTC), and negative likelihood ratio (NLR, 0.06 CCE vs. 0.07 CTC) were all similar between the study arms. However, 78% of subjects reported that they favored CCE over CTC due to the bloating and mild pain perceived during CTC.

A second study compared CCE to CTC in subjects with incomplete colonoscopy and found that CCE resulted in a twofold increase in the diagnostic yield of clinically relevant colorectal cancer compared to CTC (15). When using colonoscopy of positive cases as the gold standard, the diagnostic yield of CCE to detect positive polyps ≥6mm was 24.5% compared to 12.2% for CTC. Similarly, for colonoscopy-confirmed polyps ≥10mm, the diagnostic yield of CCE was 5.1% compared to 3.1% for CTC.

While the studies above have compared CCE versus CTC in iFOBT-positive subjects and those with prior incomplete colonoscopy, the efficacy of CCE versus CTC in the identification of colonic polyps has not yet been evaluated in a screening population. The primary objective of this multicenter, prospective, randomized study is to assess the diagnostic yield of CCE versus CTC in average risk patients without a personal or family history of CRC or adenomas, inflammatory bowel disease, or high-risk genetic syndromes.

6.2 Report of Prior Investigations

Table 1 describes the results of 14 published and 2 unpublished original clinical research studies of the PillCam® COLON 2 Capsule endoscopy system for the detection of colonic polyps in both symptomatic patients with known or suspected colonic disease and asymptomatic patients undergoing colon cancer screening (8-22). This table does not include studies conducted specifically to assess CCE for the evaluation of ulcerative colitis, Crohn's Disease, or obscure gastrointestinal bleeding.

These studies demonstrate that CCE sensitivity for polyps compares favorably with OC and CTC for colorectal cancer screening and diagnosis (Table 1).

Table 1. Prior Clinical Studies of CCE with the PillCam® COLON 2 Capsule for the Detection of Colonic Polyps

Study	Title	Design	Compar-ator	Subjects	Effectiveness Results	Safety Results
Published Studies						
Adler et al., 2014 (22)	Second-generation colon capsule endoscopy is feasible in the out-of-clinic setting	Prospective, Noncomparative, Multicenter	None	41 patients with known or suspected colonic disease	Diagnostic Yield: • Lesions ≥6mm: 24% (10/41)	Adverse Events: • None
Adrian-de-Ganzo et al., 2015 (16)	Uptake of Colon Capsule Endoscopy vs Colonoscopy for Screening Relatives of Patients with Colorectal Cancer	Prospective, Randomized, Comparative	Optical colonoscopy (OC)	329 asymptomatic first-degree relatives of patients with colorectal cancer	Diagnostic Yield: • CCE: 11.7% (14/120 • OC: 11.5% (13/113 • P=0.96	Major complications: • None Minor complications: • Abdominal discomfort: 2.2% CCE vs. 3.7% OC
Baltes et al. 2014 (abstract) (18)	PillCam Colon 2 After Incomplete Colonoscopy - a Prospective Multi-Center Study	Prospective, Multicenter, Single-Arm	None	74 patients with prior incomplete colonoscopy	Diagnostic Yield: • 49% (36/74) Polyps located in segments not reached by OC: 75% (27/36)	Complications: • None reported
Busegeanu et al, 2014 (19)	A series of images of digestive cancers using PillCam COLON2 video capsule endoscopy	Single-Center Case Series	None	7 patients with highly suspicious lesions following incomplete colonoscopy or refusal of colonoscopy	Diagnostic Yield: • 100% (7/7)	Major complications: • None reported Minor complications: • None reported
Eliakim et al., 2009 (8)	Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy	Prospective, Comparative, Multicenter (MA200)	OC	104 patients with known or suspected colonic disease	Polyps ≥6mm • Diagnostic yield OC: 19% • Diagnostic yield CCE: 36% • Sensitivity of CCE: 89% • Specificity of CCE: 76% Polyps ≥10mm • Diagnostic yield OC: 8% • Diagnostic yield CCE: 17% • Sensitivity of CCE: 88% • Specificity of CCE: 89%	Adverse Events: • None

Table 1. Prior Clinical Studies of CCE with the PillCam® COLON 2 Capsule for the Detection of Colonic Polyps

Study	Title	Design	Compar-ator	Subjects	Effectiveness Results	Safety Results
Hagel et al., 2014 (9)	Colon capsule endoscopy: detection of colonic polyps compared with conventional colonoscopy and visualization of extracolonic pathologies	Prospective, Comparative, Single-Center	OC	24 patients with known or suspected colonic disease	Per-polyp analysis: • CCE sensitivity: 90.9% • CCE specificity: 67.6% • CCE PPV: 93.0% • CCE NPV: 71.4% Diagnostic Yield (per patient): • OC: 69.6% • CCE: 60.8%	Adverse events: • None Minor complications: • Headache: 1 patient
Holleran et al., 2014 (10)	Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology	Prospective, Comparative, Single-Center	OC	62 FIT-positive colorectal cancer screening patients	Per-polyp analysis: • CCE sensitivity: 95% • CCE specificity: 65% • CCE PPV: 79% • CCE NPV: 90% Diagnostic Yield (per patient): • OC: 58% • CCE: 69%	Adverse events: • None
Negreanu et al., 2013 (20)	PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy	Prospective, Noncomparative, Single-Center	None	70 colorectal cancer risk patients, unable or unwilling to perform colonoscopy	Diagnostic Yield (per patient): • Any size: 34% (23/67) • Polyps >6mm: 5 pts • ≥3 polyps: 10 pts • Multiple colonic angioma: 2 • Colon cancer: 4 pts • New Crohn's disease: 1 pt • Radiation enterisis: 1 pt • Insignificant lesions: 19 pts	Complications: • None
Nogales et al. 2013 (abstract) (21)	Utility of Colon Capsule Endoscopy after an Incomplete Colonoscopy: Multicentric Spanish Study	Prospective, Noncomparative	None	96 patients with prior incomplete colonoscopy	Diagnostic Yield (per patient): • New lesions: 60% (58 pts) • Polyps: 41 pts • Diverticula: 8 pts • Neoplasia: 2 pts • Solitary ulcers: 2 pts	Complications: • None reported

Table 1. Prior Clinical Studies of CCE with the PillCam® COLON 2 Capsule for the Detection of Colonic Polyps

Study	Title	Design	Compar-ator	Subjects	Effectiveness Results	Safety Results
Rex et al. 2015 (11)	Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population	Prospective, Comparative, Multicenter, (MA204)	OC	695 asymptomatic patients scheduled for colorectal cancer screening	Polyps ≥6mm • Diagnostic yield OC: 28% • Sensitivity of CCE: 81% • Specificity of CCE: 93% Polyps ≥10mm • Diagnostic yield OC: 11% • Sensitivity of CCE: 80% • Specificity of CCE: 97%	Major complications: • None associated with CCE • Hospitalization for abdominal pain: 1 pt Minor complications: • Nonserious events related to bowel prep (vomiting, nausea, headache, etc): 11%
Rondonotti et al., 2014 (12)	Accuracy of capsule colonoscopy and computed tomographic colonography in individuals with positive results from the fecal occult blood test	Prospective, Comparative, Single-Center	CTC and OC	50 FIT-positive CRC screening patients	CCE Results: • Sensitivity: 88.2% • Specificity: 87.8% • PLR: 3.75 • NLR: 0.06 CTC Results: • Sensitivity: 88.2% • Specificity: 84.8% • PLR: 3.0 • NLR: 0.07	Adverse events: • CCE: None associated with procedure or prep • CTC: Significant pain: 2 pts Minor complications: • CCE: Difficulty swallowing capsule: 2 pts • CTC: Mild, self-limiting abdominal pain: 10 pts
Saito et al., 2015 (13)	Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study	Prospective, Comparative, Multicenter	OC	72 patients referred for OC because of personal history of polyps ≥6 mm or any other colon lesion requiring endoscopic or surgical treatment	CCE Sensitivity: • Per patient: 94% • Per polyp: 86.6%	Adverse events: • None Minor complications: • Mild vomiting: 1 pt

Table 1. Prior Clinical Studies of CCE with the PillCam® COLON 2 Capsule for the Detection of Colonic Polyps

Study	Title	Design	Compar-ator	Subjects	Effectiveness Results	Safety Results
Spada et al., 2011 (14)	Second-generation colon capsule endoscopy compared with colonoscopy	Prospective, Comparative, Multicenter (MA201)	OC	117 patients with known or suspected colonic disease	Polyps ≥6mm • Diagnostic yield OC: 41.3% • Sensitivity of CCE: 84% • Specificity of CCE: 64% Polyps ≥10mm • Diagnostic yield OC: 29.3% • Sensitivity of CCE: 88% • Specificity of CCE: 95%	Serious Adverse events: • None related to CCE • Colon perforation after polypectomy: 1 pt Mild/Moderate Adverse Events: • Prep-related vomiting, nausea, etc: 5 pts • Fatigue due to long capsule procedure: 2 pts • Severe abdominal pain during OC: 1 pt
Spada et al. 2015 (15)	Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial	Prospective, Comparative, Multicenter	CTC	100 patients with prior incomplete colonoscopy	Ability to detect OC Positive Cases: Polyps ≥6mm • CCE Diagnostic Yield: 24.5% • CTC Diagnostic Yield: 12.2% • Relative sensitivity of CCE versus CTC: 2.0 • CCE PPV: 96% • CTC PPV: 85.7% Polyps ≥10mm • CCE Diagnostic Yield: 5.1% • CTC Diagnostic Yield: 3.1% • Relative sensitivity of CCE versus CTC: 1.7 • CCE PPV: 83.3% • CTC PPV: 100%	Serious Adverse events: • None related to CCE or CTC • Post-procedure pain and lypothymia due to air insufflation in one patient. Mild Adverse Events: • Fatigue: CCE, 1 pt • Events related to colon preparation: nausea (11), vomiting (7), headache (6), abdominal pain (3), vertigo (1).

Table 1. Prior Clinical Studies of CCE with the PillCam® COLON 2 Capsule for the Detection of Colonic Polyps

Study	Title	Design	Compar-ator	Subjects	Effectiveness Results	Safety Results
Unpublished Studies						
Morgan, Rex, et al. (manuscript in preparation)	Evaluation of PillCam® COLON 2 in Visualization of the Colon	MA202 / NCT01087528	OC	51 patients with known or suspected colonic disease	Polyps ≥6mm • Sensitivity of CCE: 85.7% • Specificity of CCE: 73.5% Polyps ≥10mm • Sensitivity of CCE: 100% • Specificity of CCE: 90.5%	Serious Adverse Events: • None related to CCE or procedures
Burch, Kashyap, Kastenberg, Pound, Rex, Romeo (enrolling)	A Multicenter, Consecutive, Randomized Study to Optimize the Bowel Preparation Regimen for the PillCam® COLON 2 Capsule Endoscopy Procedure	MA205 / NCT02481219	Comparison of 2 bowel preparation regimens	125 average-risk subjects undergoing CCE without optical colonoscopy	Enrollment in progress	Enrollment in progress

In addition, in a meta-analysis (23) of 5 studies (8-10, 12, 14) including symptomatic patients or those with high risk of colon cancer, the pooled sensitivity and specificity of CCE for the detection of colorectal polyps were 87% and 76%, respectively, for polyps ≥6 mm and 89% and 91%, respectively, for polyps ≥10 mm. Adverse events (AEs) were very low; 3.9% of patients experienced mild to moderate AEs related to the bowel preparation (headache, nausea, vomiting, abdominal pain, fatigue). Capsule retention was reported in 3 patients (0.8%).

7.0 Identification and Description of Investigational Device

The PillCam® COLON 2 Capsule endoscopy system (manufactured by Given Imaging LTD, Medtronic, Yoqneam, Israel) will be used in this evaluation.

The PillCam® COLON 2 Capsule endoscopy system is comprised of four main subsystems: (1) an ingestible PillCam® COLON 2 capsule; (2) PillCam Recorder; (3) RAPID® software; and (4) Given® Workstation. The PillCam® COLON 2 Capsule endoscopy system includes a new capsule design (PillCam COLON 2), PillCam Recorder (DR3), and a new version of the RAPID® Software (RAPID® 8.3). Modifications were also made to the PillCam® COLON 2 capsule's field of view, effective frame rate, image quality and capsule power management. Changes designed to increase system simplicity and make the management of subjects easier were added as well. For example, the PillCam® COLON 2 includes the RAPID® software which is designed to assess polyp size and an audio-visual guidance system integrated into the PillCam Recorder that is intended to help guide the subject through the procedure. The new PillCam® Endoscopy system with the PillCam® COLON 2 capsule is fully compliant with all safety and radio standards and regulations similar to the currently marketed capsule endoscopy systems.

PillCam® COLON 2 capsule is ingested by the patient after bowel preparation, with a sip of water.

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

7.1 PillCam® COLON 2 Capsule

PillCam® COLON 2 has been designed to achieve more complete coverage of the colonic mucosal surfaces. Improvements 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)

7.2 Given® 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 Investigator Brochure.

7.3 GIVEN® Workstation

The Workstation is a modified standard personal computer that is intended for reviewing the RAPID® 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.

8.0 Study Design

This is a multicenter, prospective, randomized study to evaluate the efficacy of CCE versus CTC in the identification of colonic polyps in a screening population.

Subjects will be enrolled at up to 20 clinical sites in the United States. Subjects who meet the eligibility criteria will be screened by the gastroenterology site for study participation at a baseline visit which will also include a blood test for renal function (eGFR), and will be evaluated on the randomized procedure day (CCE versus CTC) and again on the day of both the blinded and unblinded OC procedures. Telephone follow-ups will be conducted 5 – 9 days after the CCE/CTC procedure and 5 – 9 days after the unblinded OC procedure to assess subject well-being and capture any AEs, regardless of relationship to the CCE, CTC, or OC procedures. On the second follow-up call after the OC procedure, subjects will be requested to answer procedure preference questions (sample questionnaires are included in Appendix D).

All CCE RAPID® videos and CTC images will be evaluated by local and central readers. All study analyses will be based on central reader results for both CCE and CTC. Two sets of central readers will be utilized, one set for reading of the CCE RAPID® videos and one set for reading the CTC studies. Both groups of readers will be experts in the reading process for their respective procedures. Readers will provide a report of their findings to the sponsor within 2 weeks of capsule ingestion or CTC procedure in order to allow subjects to return within 5 weeks capsule ingestion or CTC procedure to undergo confirmatory OC. The first OC procedure will be performed with the clinician blinded to the CCE or CTC results. Immediately following this blinded procedure, the clinician will review the CCE or CTC results report provided by the sponsor from the central readers, and a second unblinded OC procedure will be performed if there are discrepancies between the CCE/CTC findings and OC.

Colonoscopy must not be performed by the same person who conducts the local CCE reading, or anyone who has reviewed CCE/CTC results for that subject.

In cases of polyp size measurement discrepancies between CCE/CTC and OC, a Clinical Events Committee (CEC) will adjudicate OC polyp size measurements. Bowel preparation regimens for all three procedure types will be standardized across sites and are described in detail in the Appendix.

8.1 Study Objective

The primary objective of this multicenter, prospective, randomized study is to assess the diagnostic yield of CCE versus CTC in a screening population.

8.2 Primary Effectiveness Endpoint

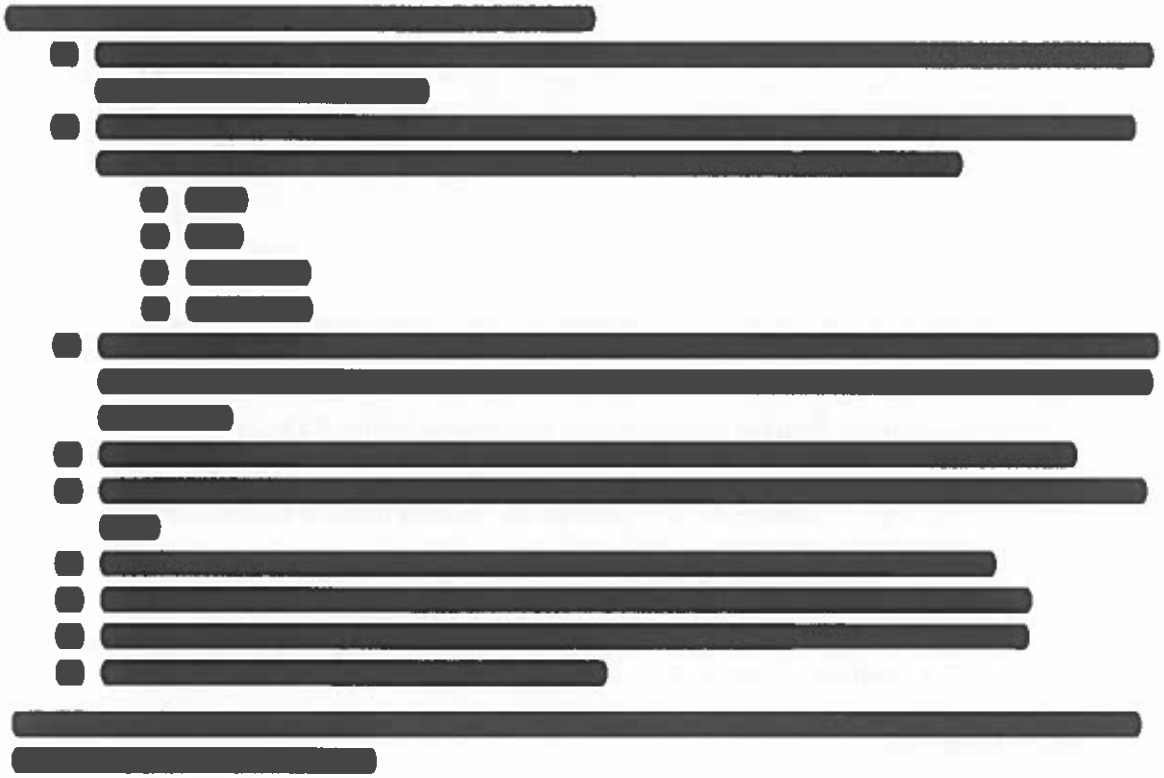
The primary effectiveness endpoint is the diagnostic yield (proportion of subjects shown to have an actionable lesion, defined as any polyp or mass lesion ≥6 mm) by capsule colon endoscopy as compared to computed tomographic colonography. Diagnostic yield of CCE and CTC will be calculated in relation to the confirmatory OC results.

8.3 Secondary Effectiveness Endpoints

The following accuracy measures of CCE versus CTC in the detection of polyps ≥6 mm will be assessed in relation to the confirmatory OC results and expressed on a "per subject" basis (rather than "per polyp").

- Negative predictive value (NPV)
- Positive predictive value (PPV)
- Sensitivity
- Specificity

8.4 Additional Analyses



8.5 Safety Endpoints

AEs will be reported by number, severity, timing, and relationship to the study procedures (imaging modality, colonoscopy), as described in Sections 11.7 and 11.8. The recording of adverse events for all

enrolled subjects will begin with the start of the CCE/CTC bowel preparation and end with the OC Follow-up call. All AEs will be captured, regardless of severity or relationship to the procedure.

8.6 Qualifications and Training

8.6.1 Site Principal Investigator (Gastroenterologist)

A gastroenterologist at each site, either performing the capsule or colonoscopy procedure, will be designated as the Site Principal Investigator for that site. There will be only one Principal Investigator for each site. All subject consent and randomization will be conducted by the Site Principal Investigator (gastroenterologist).

Board-certified gastroenterologists in accordance with medical and hospital guidelines will be considered for participation as site investigators in this study. Physicians in training (residents, fellows) and physician assistants may assist the Study Investigator in any aspect of the procedure as per standard procedures and practices at his/her institution and provided that they are experienced with the use of the PillCam® CCE system. CCE Local readers will be trained on capsule reading in accordance with the e-learning program and will be required to complete this training session with a score above 80%.

Each Investigator participating in the clinical trial and the associated clinical study staff will receive training on the clinical protocol. This includes training on AE reporting, case report form (CRF) completion, and Good Clinical Practice (GCP), as well as the device and system (including procedural use, device characteristics, shelf life and storage requirements, warnings, precautions, and contraindications).

8.6.2 CCE Central Reader Qualifications

Central readers will be experienced gastroenterologists trained to read PillCam® COLON 2 RAPID® videos. The central readers are independent physicians and are not site investigators.

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® COLON 2 RAPID® videos. The training will include RAPID® 8.3 software and RAPID® videos evaluation training.

8.6.3 Radiologists

Radiologists associated with each site will collaborate with the site principal investigator (gastroenterologist) to conduct the CTC examination. The radiologist can be assigned from a remote site. Experience and training are required in order to accurately perform CTC examinations, as defined in the ACR-SAR-SCBT-MR Practice Parameter for the Performance of Computed Tomography Colonography in Adults, Section III, Qualifications and Responsibilities of Personnel (23). In accordance with the practice parameters, radiologists meeting the qualifications will have, "substantial knowledge of radiation biology, the physics of CT scanning, the principles of CT image acquisition and postprocessing, including the use of diagnostic workstations, and the design of CT protocols, including rate and timing of contrast administration. The physician also will have substantial experience in CT interpretation, including CT of extracolonic structures that will be included on the CTC examination." Education regarding patient preparation, bowel insufflation, and CT image acquisition as well as formal hands-on training are also required in accordance with the practice parameters, including "the interpretation, reporting, and/or supervised review of at least 50 endoscopically confirmed CTC cases." The CTC exam sites will also be

expected to possess expertise in patient preparation, bowel insufflation, and CT image acquisition. Refer to the ACR-SAR-SCBT-MR Practice Parameters for additional details (23).

ACR-SAR-SCBT-MR Practice Parameter certification is required prior to reading CTC study cases.

Each radiologist participating in the clinical trial and the associated clinical study staff will receive training on the clinical protocol.

8.6.4 CTC Central Reader Qualifications

CTC central readers will be expected to possess the following expertise, in accordance with the ACR-SAR-SCBT-MR Practice Parameter for the Performance of Computed Tomography Colonography in Adults, Section III, Qualifications and Responsibilities of Personnel (23). ACR-SAR-SCBT-MR Practice Parameter certification is required prior to reading CTC study cases.

1. Formal hands-on interactive training using dedicated CTC software, including the interpretation, reporting, and/or supervised review of at least 50 endoscopically confirmed CTC cases using primary 2D and/or primary 3D search with application of routine problem-solving techniques. Ideally this collection of training cases will be chosen to demonstrate the gamut of appearances of colonic polyps and cancer and CTC interpretation pitfalls. Additionally, the cases should include examinations performed for a variety of indications (e.g., screening, symptomatic, incomplete colonoscopy with subsequent validation) and acquisition techniques (e.g., with and without fluid tagging and intravenous contrast).
2. A total of 50 cases every 2 years should be reviewed to maintain skills in CTC.

In addition to the above criteria, central readers will be required to have interpreted at least 500 prior CTC studies.

8.7 Subject Selection and 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 appropriate IRB of the respective clinical site. Enrollment of up to 320 subjects is planned. Interim analyses will be performed every 80 subjects (40 per arm) to reassess sample size based on a Bayesian adaptive design.

Subjects' participation in the study will last approximately 5–6 weeks, including bowel preparation, CCE or CTC, both blinded and unblinded OC procedures, and follow-up 5-9 days post-OC procedure via telephone.

Subjects who meet all inclusion criteria, but no exclusion criteria, will be eligible for participation in the study.

8.7.1 Inclusion Criteria

1. Subject is between 50 and 75 years of age (for African Americans only, subject is between 45-75 years of age).
2. Subject is classified as average risk per the American Gastroenterological Association Guidelines on Colorectal Cancer Screening: Individuals without inflammatory bowel disease, or high-risk genetic syndromes or personal history of CRC or adenomas or family history of either CRC or

adenomas in a first degree relative before age 60 years. Subjects with 2 second degree relative affected with colorectal cancer are also considered average risk.

3. Subject is willing and able to participate in the study procedures and to understand and sign the informed consent.

8.7.2 Exclusion Criteria

1. Subject with history of colorectal cancer or adenoma (including those identified by computed tomography [CT], optical colonoscopy, sigmoidoscopy, etc.).
2. Subject with history of negative colonoscopy within 10 years, as these subjects would be defined as not requiring screening in this timeframe. For subjects with alternative screening methods, refer to applicable guidelines.
3. Subject with currently suspected or diagnosed with hematochezia, melena, iron deficiency with or without anemia, or any other rectal bleeding, including positive fecal occult blood test of any variety.
4. Subject with any current condition believed to have an increased risk of capsule retention such as suspected or known bowel obstruction, stricture, or fistula.
5. Subject with current dysphagia or any swallowing disorder.
6. Subject with current serious medical conditions that would increase the risk associated with CCE, CTC, or colonoscopy that are so severe that screening would have no benefit.
7. Subject with a cardiac pacemaker or other implanted electromedical device.
8. Subject expected to undergo MRI examination within 7 days after ingestion of the capsule.
9. 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.
10. Subject with current known gastrointestinal motility disorders.
11. Subject with allergies or known contraindication to the medications or preparation agents used in the procedure as described in the relevant instructions for use.
12. Subject has an estimated life expectancy of less than 6 months.
13. Subject is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity).
14. Subject is pregnant, suspected pregnant, or is actively breast-feeding. Females of child-bearing potential will be required to provide either a urine pregnancy test or serum pregnancy test as part of the participant's standard of care regardless of their participation in the study (except for subjects who are surgically sterile or are post-menopausal for at least two years).
15. Subject has participated in an investigational drug or device research study within 30 days of enrollment that may interfere with the subject's safety or ability to participate in this study.

8.8 Withdrawal of Subjects

Subjects may withdraw from the study at their own request or at the request of their legally acceptable representative. 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 investigational procedures
- Subject noncompliant with visits
- At the specific reasonable request of the study sponsor

The sponsor must be informed of each withdrawal case. The reason for withdrawal must be recorded in the CRF and in the subject file.

8.9 Procedures to Minimize Bias

A 1:1 randomization will be employed to minimize bias relative to the comparison of the two study arms. In addition, RAPID® videos and CTC images will be randomly distributed among the central readers.

In addition, the confirmatory OC will be conducted first blinded to the CCE/CTC results and then unblinded.

8.10 Study Procedures

8.10.1 Study Flow

Study procedures are depicted in the figure below. Subjects will undergo be a blood test for renal function and will then be 1:1 randomly assigned to undergo either CCE or CTC. Subjects with eGFR < 45 may be discontinued from the study upon physician discretion, since eGFR value < 45 will be problematic for the CTC procedure, but not for the CCE procedure.

All subjects will undergo a confirmatory OC procedure within 5 weeks of the CCE or CTC procedure. The confirmatory OC will be conducted first blinded to the CCE/CTC results and then unblinded, if there are discrepancies in results, as shown below.

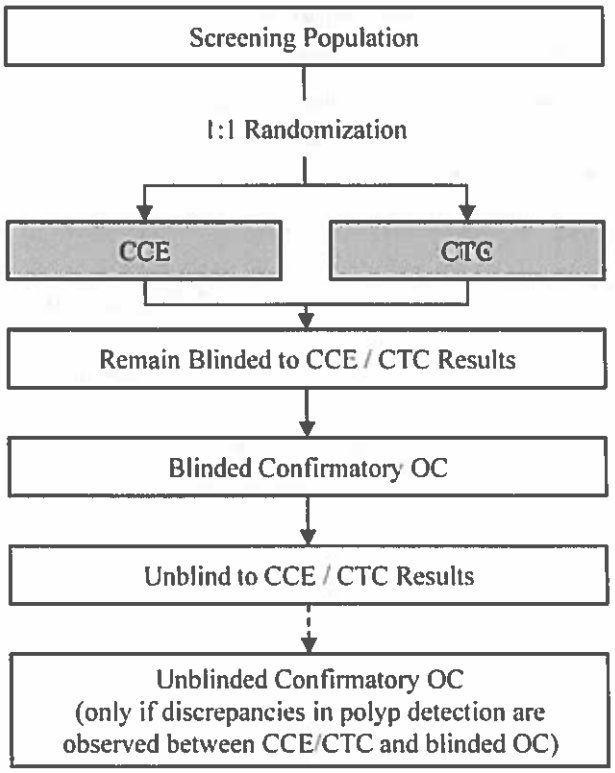


Figure 1. Study Flow Chart

8.10.2 Screening and Informed Consent

A screening/baseline visit will be performed within 30 days prior to the scheduled CCE or CTC procedure to assess preoperative eligibility. In the event that the screening and eligibility assessment takes place more than 30 days prior to the planned randomized procedure (CCE or CTC) date, the investigator should contact the subject prior to the procedure date to assure there is no change in the subject's medical condition. All potential subjects who meet all of the inclusion criteria, but none of the exclusion criteria, will be invited to participate in the study.

At the screening visit, subjects will be approached to obtain written informed consent prior to any study specific procedures being performed. 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 an IRB-approved ICF. Subjects will be informed that their participation in this study is voluntary and they may refuse to participate or discontinue from the study at any time. Subjects will be given the opportunity to ask the investigator questions so that they are adequately informed about the research. A copy of the signed informed consent must be provided to the subject and the informed consent process will be documented in source documents.

If new information becomes available that may affect a subject's decision to continue to take part in the study, this information will be discussed with the subject by the investigator.

Once eligibility is confirmed and informed consent has been signed, the subject's baseline condition will be assessed to include: renal function assessment, date of birth, gender, height, weight, waist circumference, cigarette smoking history and prior abdominal surgery.

- Relevant medical history will be assessed based on clinical condition categorized by category codes specified in the case report form.
- Documentation will occur of previous GI procedures, such as OC and CTC, including number, date, and results from the last procedure.
- Female subjects will be assessed for childbearing potential, and if they do have childbearing potential, they will undergo a urine pregnancy 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. Additional urine pregnancy test will be performed during visit 2, prior to capsule ingestion or CTC.
- All subjects will be tested for renal function using a blood test (eGFR)

8.10.3 Randomization

Subjects will be randomized in a 1:1 ratio to receive screening by either CCE (using the PillCam® endoscopy system with PillCam® COLON 2 capsule) or CTC. The study will utilize randomization in blocks in order to allocate subjects into two arms:

- Group 1: CCE
- Group 2: CTC

Randomization will occur at the screening visit at the gastroenterology site, after eligibility has been confirmed and signed informed consent has been obtained. Due to the nature of the test and control screening procedures, neither the subject nor the investigator will be blinded to the assigned study arm.

8.10.4 Screen Failures

A subject is considered enrolled in the study when the ICF is signed. Only subjects who received study-assigned procedures will be followed. Any subject who is determined to be ineligible for study participation prior to undergoing the randomized (CCE or CTC) procedure, will be considered a screen failure. The reason for the screen failure will be clearly captured on the applicable CRFs.

8.10.5 Randomized Procedure (CCE or CTC)

Detailed procedures for the bowel preparation and conduct of the randomized CCE or CTC procedures are included in Appendix A (CCE procedure instructions) and Appendix B (CTC procedure instructions).

Subjects will be instructed to follow a detailed colon preparation regimen prior to and during the randomized CCE or CTC procedure. With the exception of Gastrografin, all colon preparation products will be standard colon cleansing products approved by the FDA and are detailed in Appendices A and B.

8.11 Image Reading

All CCE RAPID® videos and CTC images will be evaluated by local and central readers. For CCE studies at the local site, there will be one individual performing colonoscopy and another reading the video. For CCE studies and CTC images, local readers will perform the evaluationat the same time frame as reading performed by central readers.

All study analyses will be based the results of two sets of central readers, one set for reading of the CCE RAPID® videos and one set for reading the CTC images. All 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 for each video or image. Videos/images will be randomly distributed among the readers.

All study analyses will be based on the results of the central readers and the findings of the central readers are final.

Readers will provide a report of their findings to the sponsor within 2 weeks of capsule ingestion or the CTC procedure in order to allow subjects to return within 5 weeks of capsule ingestion or the CTC procedure to undergo the OC procedure.

Detailed reader instructions are included in Appendix A4 (CCE reader instructions) and Appendix B4 (CTC reader instructions).

8.11.1 OC Procedure

All subjects will undergo a confirmatory OC procedure within 5 weeks of the randomized CCE or CTC procedure. The confirmatory OC will be conducted once or twice, depending on findings compared to CCE or CTC, if discrepancies between results exist. For the first (blinded) OC procedure, the operator must be blinded to both the central reader results and any local reader reports of the randomized CCE/CTC results. After the blinded OC procedure, the operator will read the central reader results for CCE/CTC. If CCE/CTC results are not congruent to the blinded OC procedure results, an unblinded OC procedure will be performed to verify polyp presence. Instructions for the bowel preparation and conduct of the OC procedure are provided in Appendix C.

Diagnostic yield of CCE/CTC will be calculated in relation to the confirmatory OC results. See Appendix D for details on polyp-matching algorithm.

8.11.2 Study Assessments Table

Table 2. Study Schedule

	Screening (Visit 1; -30 days)	CCE or CTC Procedure (Visit 2; Day 0)	Follow-Up via Telephone (5 – 9 days after Visit 2)	OC-Blinded, then OC-Unblinded (Visit 3) (Within 5 weeks of Visit 2)	Follow-Up via Telephone (5 – 9 days after Visit 3)
Informed consent	X				
Preoperative eligibility criteria	X				

Table 2. Study Schedule

	Screening (Visit 1; -30 days)	CCE or CTC Procedure (Visit 2; Day 0)	Follow-Up via Telephone (5 – 9 days after Visit 2)	OC-Blinded, then OC-Unblinded (Visit 3) (Within 5 weeks of Visit 2)	Follow-Up via Telephone (5 – 9 days after Visit 3)
Demographics	X				
Medical/surgical history	X				
Height and weight	X				
Pregnancy test[a]	X	X			
Randomization	X				
Blood test for renal function (GFR)	X				
Effectiveness endpoints		X		X	
Adverse events		X	X	X	X
Subject procedure preference					X
Study exit					X

a. Pregnancy test to be administered to females of reproductive age who have not undergone previous sterilization or hysterectomy procedures. 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. Additional urine pregnancy test will be performed during Visit 2, prior to capsule ingestion or CTC.

9.0 Statistical Analysis

9.1 Sample Size Determination

The sample size is estimated based on the primary non-inferiority hypothesis under a Bayesian adaptive design. Interim assessments will be performed at every 80 subjects (40 per arm) with a maximum of 320 subjects (160 per arm). Early success will be claimed if the pre-defined success criterion is met.

The following parameter assumptions are used in the estimation, based on prior literature (15).

- Predicted CCE diagnostic yield: 25%
- Predicted CTC diagnostic yield: 15%
- Noninferiority hypothesis with a 5% margin
- Accounting for approximately 10% attrition

With the assumptions, a total of 320 subjects (160 per arm) with interim assessments at every 80 subjects (40 per arm) will provide more than 80% power to test the primary hypothesis at the significance level of 5%.

Note that the expected sample size will be smaller than 320 with the adaptive Bayesian design since an early interim claim for success is possible. Additionally, if non-inferiority is proven, superiority will also be tested (which is not statistically powered at 80%).

9.2 Primary Hypothesis Analysis

The primary statistical hypothesis is that the diagnostic yield (proportion of subjects having an actionable lesion, defined as any polyp or mass lesion ≥6 mm) will be noninferior for CCE compared to CTC in a screening population, that is, H_0: $p_1 \leq p_0 - \delta$ versus H_a: $p_1 > p_0 - \delta$ where p_1 and p_0 are the diagnostic yield rates for CCE and CTC respectively. The non-inferiority margin (δ) is pre-defined to be 5%.

The probability of $(p_0 - p_1 < \delta)$ will be computed from the posterior distribution of the difference $(p_0 - p_1)$. Should the posterior probability $\Pr(p_0 - p_1 < \delta \mid Data)$ be at least 98% at the interim or 96% at the final analysis, then the null non-inferiority hypothesis will be rejected, and non-inferiority of CCE to CTC will be claimed. The probabilities of 98% (interim) and 96% (final) are chosen to ensure the false positive rate (type I-like error) is well controlled.

If the non-inferiority of CCE to CTC is established with respective to the diagnostic yield, a superiority test will also be performed. The null superiority hypothesis is H_0: $p_1 \leq p_0$, and the alternative superiority hypothesis is H_a: $p_1 > p_0$. The probability of $(p_1 > p_0)$ will be computed from the posterior distribution of the difference $(p_1 > p_0)$. If the posterior probability $\Pr(p_1 > p_0 \mid Data)$ is at least 98% (interim) or 96% (final), then the null superiority hypothesis will be rejected and superiority of CCE to CTC will be claimed.

If the interim non-inferiority analysis does not meet the pre-defined success criteria, there will be no early claim for success and the study will continue until completion.

9.3 Effectiveness Analyses

All effectiveness variables will be summarized using descriptive statistics. The difference between treatment groups in catogrical variables will be tested using two-sided Chi-square test or Fisher's exact test as appropriate. The difference between treatment groups in continuous variables will be tested using two-sided t-test or non-parametric Wilcoxon rank sum test as appropriate.

- Sensitivity, specificity, NPV, and PPV for the detection of polyps ≥6 mm and ≥10 mm (per subject) relative to the confirmatory OC exam
- [redacted]

9.4 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 11.8.

AEs 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 11.8. Comparisons between treatments of the proportions of subjects experiencing at least one AE, at least one SAE, at least one CCE/CTC device/procedure related AE, and at least one colonscopy procedure related AE will be made using Chi-square test or Fisher's exact test as appropriate.

9.5 Analysis Populations

The primary effectiveness analysis will be based on all randomized subjects without major protocol deviations (defined to be protocol violations that may have a significant impact on subject outcomes) and who don't meet any of the following criteria:

1. Subject withdraws
2. Capsules remained in the stomach or small bowel during the entire procedure
3. Optical colonoscopy could not be done
4. System technical failure

A confirmatory effectiveness analysis will be conducted on a modified intent-to-treat (mITT) population, including all randomized subjects with CTC or CCE. In the unlikely event that a subject receives the incorrect procedure, the subject will be included in the analysis using the procedure that is actually received. All other effectiveness endpoints will be analyzed based on the mITT population. Safety evaluation will be based on all study subjects accordingly to procedures actually received.

9.6 Interim Analyses

Interim analyses are planned after each 80 subjects (40 per arm) have completed the primary endpoint, until 320 total subjects or the non-inferiority for the primary endpoint is met (whichever occurs first).

Additionally, sample size re-assessments will be carried out during interim analyses. The conditional power will be calculated to determine if a sample size adjustment is necessary. There will not be necessary to adjust the alpha level if the conditional power is greater than 50% (i.e., within the promising zone). If the chance of success is too low (i.e. <10%), *early stopping for futility may be considered.*

10.0 Risk/Benefit Analysis

CCE is well-tolerated by patients. As show in Table 1 in Section 6.2, no serious CCE-related AEs have been reported in 14 clinical studies (8-21). Most AEs are self-limiting, mild/moderate, effects of the bowel preparation regimen (nausea, vomiting, diarrhea, abdominal pain, headache, and vertigo). A full description of all reported AEs is included in the Risk Assessment Report, Post-Market Vigilance, and in the product Instructions for Use and Users Guide. This includes difficulty and/or inability to swallow the capsule, asymptomatic capsule retention, and nausea/vomiting. Patients also reported fatigue during the procedure due to the long prep and recording time.

11.0 Adverse Events and Complications

Adverse events will be collected at the start of the CCE/CTC bowel preparation and end with the OC Follow-up call (5-9 days after the unblinded OC procedure). During the course of the study the following AEs and serious adverse events (SAEs) will be collected:

- All adverse events related to the CCE, CTC and or OC procedures
- All retained capsules greater than 14 days
- All perforations
- All device deficiencies that may lead to a SAE
- All adverse events that meet serious adverse event definition in Section 11.2
- All deaths

11.1 Adverse Event

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 investigational medical device. This definition includes events related to the investigational medical device or the comparator and the procedures involved. For users or other persons, this definition is restricted to events related to the investigational medical device.

AEs will be collected and documented until 5 – 9 days after the OC procedure, at which point the subject will be contacted by telephone, and will then be considered to have reached the end of the study.

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

See Sections 11.10 and 11.11 for recording and reporting of AEs.

11.2 Serious Adverse Event

A serious adverse event (SAE) is one that:

a) led to death,
b) led to serious deterioration in the health of the subject that either resulted in

1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or

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

NOTE: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a SAE.

Some important medical events, although they may not result in death, be life-threatening, or require hospitalization may still be considered SAEs when, based upon appropriate medical judgment, they are felt to jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life threatening means that the subject was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This does not include an AE that, if more severe, might have caused death.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

11.3 Adverse Device Effect (ADE)

An Adverse Device Effect (ADE) is an occurrence related to or caused by the investigational device, procedure or comparator that is not serious. This includes use error or intentional abnormal use of the device. In addition inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the device are also included.

In the case of an ADE, OC should be postponed until the ADE is resolved and per physician discretion.

11.4 Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect (SADE) is an adverse device effect, comparator, or procedure that has resulted in any of the consequences characteristic of a serious adverse event and is serious, but is not unanticipated.

11.5 Unaticipated Serious Adverse Device Effect (USADE)

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

11.6 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.

11.7 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.

11.8 Adverse Event Relationship Classification

AE relationship to study procedures will be reported for 3 procedure types:

1. CCE (including capsule and/or sensors)
2. CTC Exam
3. Colonoscopy Exam

For each of the 3 procedure types above, relationship will be categorized as:

- *Not Related*: No relationship between the AE and the administration of any study procedure and a known relationship to other etiologies such as concomitant medications, non-study procedures, or the subject's clinical state.
- *Related:* An AE that follows a plausible temporal sequence from administration of a study procedure and follows a known response pattern to a study procedure. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- *Impossible to Determine:* Given the information available, sequence and timing of events, it is impossible to determine the relationship of the AE with the study procedure.

11.9 Adverse Event Outcome Classification

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

- *Resolved:* The event has fully resolved at the end of the study.
- *Resolved with sequelae*: The event has resolved, but retained pathological conditions resulting from the prior disease or injury.
- *Continuing:* The event is ongoing at the end of the study.
- *Death:* This event is determined to be the cause of death.

11.10 Adverse Event Recording

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. Adverse events will be monitored from the start of the CCE/CTC bowel preparation and end with the OC follow up call

For purposes of the TOPAZ protocol, the following occurrences are considered to be expected observations following bowel preparation (vomiting, nausea, headache, dizziness, gagging, hemorrhoidal bleeding, bloating, rash, abdominal pain, syncope, tinnitus, chest burning, chills, and flu-like symptoms) and will not be considered reportable AEs, as long as the event is not defined as a SAE. Adverse Events should be reported to MDT study team within 10 working days.

The potential serious adverse events associated with the use of the device:

- include delayed or no excretion of the capsule, per IFU: Capsule retention is defined as having a capsule remain in the digestive tract for more than two weeks.
- aspiration,
- obstruction,
- perforation, and mucosal injury or bleeding.
- In some instance, intervention is required to remove the capsule.

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.

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

11.11 Adverse Event Reporting

Please refer to the table below for a list of the minimum AE reporting requirements for investigators. If local regulations or IRB 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 and SADEs, the Principal Clinical Research Specialist or medical monitor may be contacted by phone; this will not serve as a substitute for proper reporting in RDC.

Investigator AE Reporting Requirements

Type	Report to	Reporting Timeframe (from time of learning of event)
Adverse Event (AE)	IRB/EC	Per IRB reporting requirements
	Sponsor	Within 10 working days
Serious Adverse Event (SAE)	Sponsor	Within 10 working days
	IRB/EC	Per IRB reporting requirements
Adverse Device Effect (ADE),	Sponsor	Within 10 working days
	IRB/EC	Per IRB reporting requirements

Serious Adverse Device Effect (SADE) and Unanticipated Serious Adverse Device Effect (USADE)		
Device Deficiency	Sponsor (technical support)	Within 10 working days
	IRB/EC	If SAE occurs due to the device deficiency, within 10 days and per IRB reporting requirements
Device Related AE/SAE	Sponsor	Within 10 days

All events will be reviewed by Medtronic safety officer or designee to determine any reporting obligations to the IRB.

12.0 Device Deficiencies

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

PillCam® COLON 2 Capsule endoscopy system device deficiencies will be documented on the appropriate device deficiency eCRF, and the device should be returned to Medtronic for analysis, if possible. Instructions for returning the investigational 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.

13.0 Ethics and Compliance

13.1 Statement 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. The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirements (1CFR 11, 21 CFR 50, 21 CFR 54, 21 CFR 56, 21 CFR 803, 21 CFR 812).

This may include an inspection by Medtronic representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/Medtronic representatives, and must allow direct access to source documents to the Regulatory Authority/Medtronic representatives. Regulatory Authority approvals/authorizations/notifications,where required, will also be in place and fully documented prior to study start.

13.2 Protocol Compliance

No changes to the protocol will be permitted without the written approval from Medtronic and the IRB. The investigator must notify Medtronic and the reviewing IRB of any deviation from the Investigational Plan 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 Plan. If these changes or deviations affect the scientific soundness of the Plan or the rights, safety, or welfare of human subjects the IRB will also be notified. All other deviations will be reported per the site's IRB deviation policy. Should any deviations from the Investigational Plan 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.

13.3 Institutional Review Board (IRB)

Documented approval from the appropriate Institutional Review Board (IRB) will be obtained for all participating centers prior to study start, according to ICH GCP, local laws, regulations, and organization. When necessary, an extension, amendment, or renewal of the IRB approval must be obtained. The IRB must supply to the sponsor a list of the IRB membership and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

13.4 Medical Monitor

The Sponsor will utilize a Medtronic Medical Monitor to provide a medical review and adjudication in case requested by the safety officer or clinical study manager. Upon request by the safety officer or clinical study manager, the Medical Monitor will adjudicate relevant AEs in the Oracle RDC system (adjudication CRF). The Medical Monitor will not be affiliated with an investigative center.

During the review of AEs, the Medical Monitor will not be blinded to the randomized assignment or investigational site.

13.5 Subject Informed Consent

A core information and consent form will be provided. Prior to the beginning of the trial, the investigator must have the IRB written approval/favorable opinion of the written ICF and any other written information to be provided to subjects. The written approval of the IRB together with the approved subject information/ICFs must be filed in the study files.

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s), and must adhere to GCP and to the ethical principles originating in the Declaration of Helsinki. Written informed consent must be obtained before any study specific procedure takes place. Participation in the trial and date of informed consent given by the subject should be documented appropriately in the subject files.

13.6 Insurance

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.

13.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will be kept confidential. Only the subject number and initials will be recorded in the CRF, and if the subject name appears on any other document, it must be obliterated. In cases were the local law does not allow using the subject initials 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 trial are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects' records to be identified.

13.8 Use of Data and Publications

The Medtronic-MITG 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. 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).

14.0 Monitoring Procedures

Site visits will be conducted by an authorized Medtronic representative to inspect study data, subjects' medical records, and CRFs in accordance with appropriate FDA regulations 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 CRFs, IRB decisions, and Investigator, 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. The accuracy and quality of the data obtained from the investigator and maintained by Medtronic will be confirmed through a structured program of clinical field auditing and internal review detailed in the monitoring plan. 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.

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 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, 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.

15.0 Data Collection and Processing

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.

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 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.

In cases of polyp size measurement discrepancies between CCE/CTC and OC, a Clinical Events Committee (CEC) will adjudicate OC polyp size measurements.

Manual and/or automatic queries will be created in the Oracle remote 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.

16.0 Study Supplies and Device Accountability

16.1 Indication

The PillCam® COLON 2 capsule endoscopy system is intended to provide visualization of the colon. It may be used for detection of colon polyps in patients after an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible. In addition, it is intended for detection of colon polyps in patients with evidence of gastrointestinal bleeding of lower GI origin. This applies only to patients with major risks for colonoscopy or moderate sedation, but who could tolerate colonoscopy and moderate sedation in the event a clinically significant colon abnormality was identified on capsule endoscopy.

16.2 Contraindications

PillCam® COLON 2 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-ingestion testing and profile.
- In patients with cardiac pacemakers or other implanted electromedical devices.
- In patients with dysphagia or other swallowing disorders.

16.3 Packaging and Storage

PillCam® COLON 2 capsule should be stored in a dry place, at a temperature below 25°C (81°F) and away from magnetic sources. To prevent capsule activation, PillCam® COLON 2 capsule should be kept in the box until use.

Even if stored in its original container and according to recommendations, PillCam® COLON 2 capsule should not be used past the expiration date.

16.4 Inventory Control

The Sponsor will initiate shipment of equipment to the site upon receipt of all required documents (e.g., IRB approval, local regulatory authorities' approval if applicable). 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.

For each dispensed capsule, the following information should be recorded: the subject study number and the capsule ID number.

At the termination of the study, all unused study material must be returned with the corresponding documentation as directed by Medtronic.

17.0 General Information

17.1 Study Contact Information

Questions regarding safety or medical procedures should be directed to Medical Affairs. All other questions should be directed to Clinical Affairs.

Clinical Affairs	Medical Affairs
Hilla Debby Director, Clinical & Regulatory Given Imaging LTD Medtronic POB 258, 20692 Yoqneam, Israel 2 Hacarmel St. New Industrial POB 258 20692 Yoqneam, Israel Phone: +972 (4) 909-7774 [redacted] Fax: +972 (73) 250-1533 Email: Hilla.Debby@medtronic.com	Robin Price MD PhD Director of Global Medical Affairs Given Imaging LTD Medtronic 540 Oakmead Parkway Sunnyvale, CA 94085 [redacted] Email: Robin.O.Price@medtronic.com Ari Bergwerk MD Medical Advisor, Medical Affairs Given Imaging LTD Medtronic New Industrial Park POB 298, 20698 Yoqneam, Israel Phone +972 (4) 909-7822 [redacted] Fax +972 (73) 250-1537 Email: Ari.Bergwerk@medtronic.com

17.2 Retention of Records

The investigator 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, the clinical trial agreement, the Investigator Agreement, investigational device accountability records, individual subject records, and signed informed consent forms. Subject files and other source data must be kept for a period of not less than 2 years after the date on which this investigation is terminated or completed. All data and documents should be made available if requested by relevant authorities.

17.3 Study Completion/Termination of Study

Medtronic reserves the right to discontinue the study at any stage, with suitable written notice to all investigators, all reviewing IRB, and FDA.

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.

Any USADE will be investigated immediately and, if the sponsor determines that unreasonable risk to subjects is possible, the study will be terminated and all regulating authorities and participating investigators will be notified.

18.0 References

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19.0 Appendix A – CCE Procedure Instructions

The purpose of this multicenter, prospective, randomized study is to compare the diagnostic yield, accuracy, and safety of colon capsule endoscopy (CCE) and computed tomographic colonography (CTC) in the identification of colonic polyps in a screening population.

This appendix includes instructions for the CCE randomized procedure in 4 parts:

- Appendix A1 – CCE Bowel Preparation
- Appendix A2 – CCE Subject Instructions Form
- Appendix A3 – CCE Procedure Instructions
- Appendix A4 – CCE Image Reading Instructions
- Appendix A5 – CCE Bowel Cleansing Scale

19.1 Appendix A1 – CCE Bowel Preparation Instructions

Subjects will be instructed to follow a detailed dietary and colon preparation regimen prior to and during the CCE procedure day. With the exception of Gastrografin, all colon preparation products will be standard colon cleansing products approved by the FDA.

If necessary, capsule position will be monitored to ensure adequate booster administration. Subjects will keep a timed diary of key preparation steps and bowel activity, including capsule excretion. Subjects will be allowed to leave the unit only after the second boost was adminstered if the capsule is not yet excreted. Subjects leaving before excretion will be instructed to disconnect the recorder at excretion or 12 hours after capsule ingestion (whichever comes first).

Colon Preparation Procedure for Subjects Randomized to the CCE arm

Two Days Prior to the Procedure Day	**Instructions**
All Day	Drink at least 10 glasses of liquid
Bedtime	Four Senna tablets
The Day Before the Procedure Day	
Meals	Clear liquid diet all day
7:00pm – 9:00pm	2 liters sulfate-free PEG electrolyte lavage solution (such as ELS; NuLYTELY, Braintree Laboratories, Braintree, MA), one 8-10 oz. cup every 10-15 minutes.
Procedure Day	
Meals	None until 2 hours after suppository
45-75 min prior to capsule ingestion	2 liters sulfate-free PEG-ELS
	Capsule Ingestion
1 hour after capsule ingestion	Prokinetics (only if capsule is in stomach >1 hr.): 10 mg Metoclopromide (Reglan/Pramin) or 250 mg oral Erythromycin
First Boost: After capsule entry into small bowel	3 oz. SUPREP* plus 60 ml Gastrografin
Second Boost: 3 hrs. after first boost, only if capsule not excreted	3 oz. SUPREP* plus 30 ml Gastrografin
Suppository: 2 hrs. after second boost, only if capsule not excreted	10 mg Bisacodyl
2 hrs. after suppository	Standard full meal

*Diluted in water per subject instructions form

19.2 Appendix A2 – CCE Subject Instructions Form

During the PillCam® COLON 2 procedure subjects will be asked to use a Subject Instructions Form to document their activities during the bowel preparation and colon 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 CRF entries.

See attached document, "TOPAZ CCE Subject Instructions"

19.3 Appendix A3 – CCE 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 A2) and the subject will complete the bowel preparation procedure as detailed in Appendix A1.

The subject's last bowel movement should be clear prior to beginning the CCE exam.

Between 45 and 75 minutes after the final PEG ingestion, the subject will swallow the PillCam® COLON Capsule with a cup of water.

Throughout the CCE 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.

The PillCam Recorder will be disconnected either upon capsule excretion or DR alert "End of Procedure" (whichever comes first). If subject cannot be monitored for the entire procedure duration in the clinic, the subject may leave the clinic after administering the second boost while still connected to the system. The subject will be requested to disconnect the system at home upon one of the following: capsule excretion, "End of Procedure" alert or 12 hours from ingestion, whichever comes first, and send it back to the clinic the following day. The PillCam Recorder may also be removed in case of procedure failure.

Throughout the CCE procedure, the subject will be instructed to notify the study physician if experiencing abdominal pain, headache, vomiting, or any other unexpected symptoms.

19.4 Appendix A4 – CCE Image Reading Instructions

Step 1: Clinical Site Sends CCE Raw Data to the Sponsor

Following the completion of the CCE procedure, the raw data and RAPID® video will be downloaded from the DR3 to the Given® workstation. A copy of the RAPID® raw data and video should be sent within **3 working days** to the sponsor who will forward it to the central reader for evaluation.

Step 2: Sponsor Sends CCE Raw Data to the Central Reader

The sponsor should send the following information to the randomly assigned reader for each video with **2 working days** of receipt from the site:

- RAPID video
- Procedure date
- Subject code (initials and number)

Step 3: Image Reading by Local and Central Readers

For each RAPID® video, the central reader will evaluate the following:

1. Adequacy of colon preparation for each colorectal segment (cecum, ascending, transverse, descending/sigmoid, and rectum) and for the overall colon using a validated system, as shown in Appendix A5. This information should be recorded in the CRF.
2. For CCE-detected polyps, tumors or lesions, the following information shall be documented as a video thumbnail (selected image within the video) and recorded in the CRF.
    - Location (cecum, ascending, transverse, descending/sigmoid, and rectum)
    - RAPID® time
    - Polyp size in millimeters. Size must be measured using the Polyp Size Estimation SW utility that will be provided as part of the RAPID® software.

    Location in the colon will be estimated using visible landmarks, particularly the cecal landmarks and the anus, and the RAPID program, which displays the approximate position of the capsule in the abdominal-pelvic cavity. Capsule time to reach the cecum, the hepatic and splenic flexures, and time to exit the rectum will also be measured by the software.

    Readers will trace the longest visible dimension of the polyp using a function within the software, which will automatically calculate the length. Readers will save all findings as photographs and detailed descriptions, and deliver to the sponsor within 2 weeks of reading.

    All CCE local and central reading will be conducted in accordance with the sponsor's RAPID®8.3 software and RAPID® videos evaluation training.

    Colonoscopy must not be performed by the same person who conducts the local reading.

Step 4: Reader Sends CCE Results to the Sponsor

All findings will be saved as thumbnails, with detailed description of each finding, to create a detailed GRML file. Central readers will provide a report of their findings to the sponsor within 2 weeks of capsule ingestion in order to allow subjects to return within 5 weeks capsule ingestion procedure to

undergo confirmatory OC. The central readers will be required to return the following items to the sponsor:

- Signed RAPID® report
- GRML file
- Case Report Form (CRF)

Step 5: Sponsor Sends CCE Results back to the Site

Upon receipt, the sponsor will send the signed RAPID report, the signed cleansing evaluation form, and the case report form to a designated person at the relevant site. Local reader results will be read within 2 weeks and kept at the subject binder until confirmatory OC. The results will not be disclosed to the physician performing the colonoscopy until after the blinded colonoscopy is complete.

The GRML file will be provided to the relevant site upon specific request.

19.5 Appendix A5 – CCE Bowel Cleansing Scale

Cleansing Level Scale for Colon 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.

20.0 Appendix B – CTC Procedure Instructions

The purpose of this multicenter, prospective, randomized study is to compare the diagnostic yield, accuracy, and safety of colon capsule endoscopy (CCE) and computed tomographic colonography (CTC) in the identification of colonic polyps in a screening population.

This appendix includes instructions for the CTC randomized procedure in 4 parts:

- Appendix B1 – CTC Bowel Preparation
- Appendix B2 – CTC Subject Instructions Form
- Appendix B3 – CTC Procedure Instructions
- Appendix B4 – CTC Image Reading Instructions
- Appendix B5 – CTC Bowel Cleansing, Distension, and Tagging Scale

20.1 Appendix B1 – CTC Bowel Preparation

Bowel preparation for CTC will follow the regimen below and includes stool tagging, laxative purgation, and fluid tagging.

Magnesium Citrate Colon Preparation Procedure for Subjects Randomized to the CTC Arm

Three Days Prior to the Procedure Day	Instructions
All Day	Low-residue diet
Two Days Prior to the Procedure Day	
All Day	Low-residue diet
The Day Before Procedure Day	
Meals	Clear liquid diet all day
Before 11am	Two 5 mg bisacodyl tablets plus 8 ounces of clear liquid
2pm	One bottle (296 ml) magnesium citrate followed by 6 cups of clear liquids
5pm	225 mL liquid barium sulfate suspension One bottle (296 ml) magnesium citrate followed by 6 cups of clear liquids
8pm	50 mL bottle of Omnipaque (iohexol) 350 mgI/mL mixed in 8 oz. clear liquid
Midnight	No food or water
Procedure Day	
Meals	None until after procedure

Adapted from: UW Health. Health Facts for You: Getting Ready for Your Virtual Colonoscopy (Routine VC Prep) [cited 2015 August 11]. Available from: http://www.uwhealth.org/healthfacts/diagnostic-tests/7560.html

20.2 Appendix B2 – CTC Subject Instructions Form

Subjects randomized to the CTC arm will be provided with a subject instructions form that details the bowel preparation procedure described above. This form will be used to document the subject's adherence to the procedure steps and will also serve as source data for CRF entries.

See attached document, "TOPAZ CTC Subject Instructions"

20.3 Appendix B3 – CTC Procedure Instructions

The subjects last bowel movement should be clear prior to beginning the CTC exam.

The CTC procedure and study interpretation will be conducted in accordance with the ACR–SAR–SCBT-MR Practice Parameter for the Performance of CT Colonography in Adults (Available from: http://www.acr.org/quality-safety/standards-guidelines/practice-guidelines-by-modality/ct) and other published literature (Johnson et al. N Engl J Med 2008;359:1207-17).

CTC examinations will occur at designated facilities with expertise in CTC procedures. ACR-SAR-SCBT-MR Practice Parameter certification is required prior to reading CTC study cases.

For CTC, colon insufflation will be performed with the subject in the lateral decubitus or supine position after placement of a catheter tip (with a retention balloon) in the rectum using an automated CO_2 insufflator. The colon will be insufflated to a set pressure, which will likely require at least 2 liters of CO_2.

The catheter will be left in the rectum, and, with the subject in the supine position, a CT scout image will be taken to confirm adequate colon distention. If adequate bowel distention is not achieved, additional air will be insufflated into the colon.

After scanning the subject in the supine position, the subject will be placed in the prone position, and additional CO_2 will be administered. Subsequently, CT will be performed with the subject in the prone position. If a prone position is not possible for the subject, a right lateral decubitus position is preferred for optimal gas and fluid redistribution.

A low-dose technique without IV contrast administration or glucagon will be utilized.

Specific CT parameters include:

- 16 slice or greater MDCT
- Collimation: 0.5–1.0 mm
- Reconstructed slice thicknesses: 1–1.25 mm
- Reconstruction interval: 0.8 mm
- Pitch: 0.98–1.5
- Matrix: 512 × 512
- Field-of-view: to fit the subject
- 50 effective mAs
- Peak voltage: 120 kV
- Each series should be obtained in end expiration to minimize pressure effects of inflated lungs on the transverse colon

*In case different CT machines are used, manufacture recommended protocol should be followed.

20.4 Appendix B4 – CTC Image Reading Instructions

Step 1: CTC Site Conducts CTC Exam

Step 2: CTC Radiologist Sends CTC Raw Data to the Sponsor

The site conducting the CTC should transfer the CTC DICOM file to the sponsor **within 3 working days** of the CTC exam.

Step 3: Sponsor Sends the CTC Raw Data Files to the Central Reader

Central readers will be experienced, independent physicians trained to read CTC who are not site investigators. For each case, the reader should receive the following information **within 2 working days** of receipt from the CTC site:

- CTC DICOM file
- Procedure date
- Subject code (initials and number).

Step 4: CTC Exam Reading

All CTC studies will first be read by local readers (radiologists) at the site conducting the CTC exam using their standard software. Workstations utilized for CTC interpretation should be able to display 2D and 3D data as well as prone and supine data side-by-side for interactive interrogation. The software should also allow the interpreting physician to change the window width and level settings interactively and in real time. Extracolonic structures will be documented at the time of the review of the colon.

For each CTC exam, local and central readers will evaluate the following:

1. Adequacy of colon preparation, distention, and fecal tagging for each colorectal segment (cecum, ascending, transverse, descending/sigmoid, and rectum) and for the overall colon using a validated system, as shown in Appendix B5. This information should be recorded in the CRF.
2. For detected polyps, tumors or lesions, the following information shall be documented as representative image (selected image within the file) and recorded in the CRF.
    - Location (cecum, ascending, transverse, descending/sigmoid, and rectum)
    - Distance in cm from the anus
    - Polyp size in millimeters.

Step 5: Reader Sends CTC Results to the Sponsor

Analysis of CTC data by the central readers is to be performed using 3D software. The central readers will be required to read the CTC images in a timely manner (within 2 weeks) and send back to the sponsor the following items:

- Signed CTC report
- DICOM file
- Case Report Form (CRF)

Step 6: Sponsor Sends CTC Results back to the Site

Upon receipt, the sponsor will send the signed CTC report and the case report form to a designated person at the relevant site. Local reader results will be read within 2 weeks and kept at the subject binder until

confirmatory OC. The results will not be disclosed to the physician performing the colonoscopy until after the blinded colonoscopy is complete.

20.5 Appendix B5 – CTC Bowel Cleansing, Distension, and Tagging Scale

Quality of bowel preparation for CTC will be evaluated on the basis of colon cleanliness, distension, and fecal tagging in accordance with prior publications (Fletcher, AJR Am J Roentgenol 2013; 201:787–794).

The colon will be divided into five segments: cecum, ascending, treansverse, descending/sigmoid, and rectum. For all evaluations, the worst section of a segment will be used to define the segmental score. Per segment scores will be averaged for overall scores of distention, fluid, and stool (quantity and size) scores. If one of the overall distention, fluid, or stool scores is considered inadequate, then the exam prep will be considered inadequate.

Residual Fluid and Stool Grading

Rating		Description
0	Adequate	0% of the lumen filled with residual fluid or stool
1		<33% of the lumen filled with residual fluid or stool
2	Inadequate	33% of the lumen filled with residual fluid or stool both prone and supine
3		>33% of the lumen filled with residual fluid or stool both prone and supine

Adapted from Fletcher, AJR Am J Roentgenol 2013; 201:787–794

Stool Size Grading

Rating		Description
0	Adequate	No stool
1		Stool ≤5 mm (could miss polyps < 5mm)
2	Inadequate	Stool 6–9 mm (could miss polyps 5-9 mm)
3		Stool ≥10 mm (could miss poloyps ≥10mm)

Adapted from Fletcher, AJR Am J Roentgenol 2013; 201:787–794

Segmental Distention Grading

Rating		Description
0	Adequate	>90% of estimated maximal distention
1		75–90% of estimated maximal distention
2	Inadequate	50–74% of estimated maximal distention
3		<50% of maximal distention

Adapted from Fletcher, AJR Am J Roentgenol 2013; 201:787–794

21.0 Appendix C – Optical Colonoscopy (OC) Procedure Instructions

The purpose of this multicenter, prospective, randomized study is to compare the diagnostic yield, accuracy, and safety of colon capsule endoscopy (CCE) and computed tomographic colonography (CTC) in the identification of colonic polyps in a screening population.

All subjects will undergo a confirmatory optical colonoscopy (OC) procedure within 5 weeks of the CCE ingestion or CTC procedure. The confirmatory OC will first be conducted blinded to the CCE/CTC results and then unblinded, if discrepancies in polyp detection are observed, as shown below.

Diagnostic yield of CCE/CTC will be calculated in relation to the confirmatory OC results.

This appendix includes instructions for the OC randomized procedure in 4 parts:

- Appendix C1 – OC Bowel Preparation
- Appendix C2 – OC Subject Instructions Form
- Appendix C3 – OC Procedure Instructions
- Appendix C4 – OC Bowel Cleansing Scale

21.1 Appendix C1 – OC Bowel Preparation

The OC bowel preparation is a standard bowel prep utilized in current medical practice and will include administration of Senna tablets, a clear liquid diet and administration of a purgative sulfate-free polyethylene glycol electrolyte lavage (SF-ELS) solution (e.g., NuLYTELY) divided into two doses: the first dose on the evening before the exam and the 2nd dose on the morning of the exam day (the 2nd dose may be consumed at the clinic or home, per physician discretion).

Colon Preparation Procedure for Optical Colonoscopy

Two Days Prior to the Procedure Day	**Instructions**
All Day	Drink at least 10 glasses of liquid
Bedtime	Four Senna tablets
The Day Before the Procedure Day	
Meals	Clear liquid diet all day
7:00pm – 9:00pm	2 liters sulfate-free PEG electrolyte lavage solution (such as ELS; NuLYTELY, Braintree Laboratories, Braintree, MA), one 8-10 oz. cup every 10-15 minutes.
Procedure Day	
12am to completion of optical colonoscopy procedure	None until after procedure
7am to approx. 8:30am	2 liters sulfate-free PEG electrolyte lavage solution (such as ELS; NuLYTELY, Braintree Laboratories, Braintree, MA), one 8-10 oz. cup every 10-15 minutes.
Per physician discretion	Conduct optical colonoscopy

21.2 Appendix C2 – OC Subject Instructions Form

During the OC bowel preparation procedure, subjects will be asked to use a Subject Instructions Form 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 CRF entries.

See attached document, "TOPAZ OC Subject Instructions"

21.3 Appendix C3 – OC Procedure Instructions

The confirmatory OC will first be conducted blinded to the CCE/CTC results and then unblinded, if discrepancies in polyp detection are observed, as shown below. For the blinded OC procedure, the colonoscopist will be kept blinded to the CCE or CTC results until the OC procedure visualizes the entire colon. After the blinded colonoscopy, the colonoscopist will review the RAPID or CTC report with the CCE or CTC results. If results are not congruent, a second colonoscopy will be performed.

For both the blinded and unblinded OC studies:

- Study GI endoscopists (not the same GI physician that performs the local reading) will be trained by the sponsor on polyp size estimation using study designated biopsy forceps (Radial Jaw 4, by Boston Scientific), to confirm homogeneous methods between all participating study centers.
- The OC examination will be recorded electronically and sent to the sponsor. Only the subject study ID and initials should appear in the recorded video either by inserting the initials to the recording machine or by including a snapshot of the subject's initials written on a piece of paper at the beginning of the procedure. The withdrawal time will need to be at least 6 minutes as per common practice.
- Size measurement for every polyp using the reference forceps will be documented in a picture (i.e., open study forceps will be placed as close as possible to the polyp, on maximum linear dimension, while it is being photographed).
- All OC still pictures will be saved in a digital format (.tif or .bmp). Quality copies of the pictures taken during OC will be provided to the study sponsor with the OC report.
- These videos and pictures will be archived by the sponsor and may be used in future analyses to, for example, provide further information about observed lesions, to assess study quality, or add further information regarding comparisons between colonoscopy and capsule findings.

For each OC procedure the following information will be collected:

- Adequacy of colon preparation for each colorectal segment (cecum, ascending, transverse, descending/sigmoid, and rectum) and for the overall colon using a validated system, as shown in Appendix C4. This information should be recorded in the CRF.
- Colonoscopy report
- The following information will be collected and documented for each polyp detected:
    - Location: Colon segment (i.e., cecum, ascending, transverse, descending/sigmoid, and rectum)
    - Polyp size: Size must be measured by reference using the designated biopsy forceps (Radial Jaw 4, Boston Scientific)
    - Histology Report High Definition still pictures of the polyp with the reference forceps at the location
    - For unblinding procedure - Findings Confirmation Case Report Form

Note: Findings from the initial blinded OC will be documented separately from the unblinded OC on separate CRFs.

21.4 Appendix C4 – OC Bowel Cleansing Scale

Cleansing Level Scale for Optical Colonoscopy

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.

22.0 Appendix D – Patient Procedure Preference Sample Questionnaires

The purpose of this multicenter, prospective, randomized study is to compare the diagnostic yield, accuracy, and safety of colon capsule endoscopy (CCE) and computed tomographic colonography (CTC) in the identification of colonic polyps in a screening population.

This appendix includes patient procedure preference sample questionnaires that may be used in the study. Data for patient procedure preference will be collected over the phone 5-9 days after the OC procedure.

- Appendix D1 – CTC versus OC Procedure Preference Sample Questionnaire
- Appendix D2 – CCE versus OC Procedure Preference Sample Questionnaire

22.1 Appendix D1 – CTC versus OC Procedure Preference Sample Questionnaire

Was subject follow-up performed?	☐No ☐Yes
If Yes, date of follow-up	(dd-MMM-yyyy)
Which procedure would you prefer to have in the future?	☐ CTC Procedure ☐ Optical Colonoscopy

Why do you prefer this procedure? (choose 2-3 that apply)

- ☐ No time off work required if completed outside of a clinical trial
- ☐ No need for someone to drive me
- ☐ Prefer to be sedated for tube insertion
- ☐ No need to be put to sleep
- ☐ No need for an IV
- ☐ Less bowel prep required
- ☐ Less invasive
- ☐ Less discomfort (specify):
  - ☐ Air pushed into colon was uncomfortable
  - ☐ Other
- ☐ Less embarrassing
- ☐ Exam took less time
- ☐ More familiar with it
- ☐ No need to drink chalky solution
- ☐ Can collect tissue (biopsy) at same time
- ☐ No radiation
- ☐ Finds more polyps
- ☐ Safer
- ☐ Standard screening procedure
- ☐ Cutting edge technology

Comment

22.2 Appendix D2 – CCE versus OC Procedure Preference Sample Questionnaire

Was subject follow-up performed?	☐No ☐Yes
If Yes, date of follow-up	_____ (dd-MMM-yyyy)
Which procedure would you prefer to have in the future?	☐ CCE Procedure ☐ Optical Colonoscopy

Why do you prefer this procedure? (choose 2-3 that apply)

- ☐ No time off work required if completed outside of a clinical trial
- ☐ No need for someone to drive me
- ☐ No need to be put to sleep
- ☐ No need for an IV
- ☐ Less bowel prep required
- ☐ Can move around during procedure
- ☐ Less invasive
- ☐ Less embarrassing
- ☐ Exam took less time
- ☐ More familiar with it
- ☐ No need to drink chalky solution
- ☐ Can collect tissue (biopsy) at same time
- ☐ Finds more polyps
- ☐ Safer
- ☐ Standard screening procedure
- ☐ Cutting edge technology

Comment _____

23.0 Appendix E – Matching Algorithm

To address inherent uncertainties in the comparison of polyp localizations and sizes, a polyp-matching algorithm will be used to determine the agreement between CCE/CTC and OC. The first step of this procedure is to identify all polyps ≥6mm detected by any method (OC, CCE, or CTC). The polyp with the largest estimated diameter of either OC or CCE/CTC will be referred to as the 'reference' polyp. The colon segment location (cecum, ascending, transverse, descending/sigmoid, or rectum) of the reference polyp will be determined and recorded. The largest polyp identified using the other method within the same or an immediately adjacent segment location of the "reference" polyp will be used to determine agreement based on a size matching algorithm. If there were two polyps of equal size that were "the largest" and located in different segments of the colon, then the location and size matching algorithm will be repeated for each of these reference polyps to determine agreement of CCE/CTC with OC.

For a given polyp to be considered a match between CCE/CTC and OC, it has to be assessed within 50% (plus or minus) of the size of the largest estimate of the two studies (CCE and OC or CTC and OC) and must appear within the same or immediately adjacent colon segments.

For example, if CCE detected a 10 mm polyp, the ±50% range would be 5-15 mm. If colonoscopy detected a 6 mm polyp (±50% range = 3-9mm) in the same or immediately adjacent segment, the 2 polyps would be considered a match (CCE true positive) because the two ranges overlap.

The "reference" polyp size will then be used to assign the polyp to the following groups: ≥6 mm, and/or ≥10 mm in size. For each subject, the CCE/CTC evaluation will be classified into one of four categories of agreement relative to OC, as shown in Table 3.

Table 3. Polyp Matching Accuracy Assessment

	Findings of blinded or unblinded colonoscopy	
Findings of CCE or CTC	Positive	Negative
Positive	**True positive (A)** Polyps ≥6mm: Polyp matching exists and "reference" polyp size is ≥6 mm Polyps ≥10mm: Polyp matching exists and "reference" polyp size is ≥10 mm	**False positive (B)** Polyps ≥6mm: No polyp matching and CCE/CTC is ≥6 mm Polyps ≥10mm: No polyp matching and CCE/CTC polyp is ≥10 mm
Negative	**False negative (C)** Polyps ≥6mm: No polyp matching and OC polyp is ≥6 mm Polyps ≥10mm: No polyp matching and OC polyp is ≥10 mm	**True negative (D)** Polyps ≥6mm: All reported polyps are <6 mm Polyps ≥10mm: All reported polyps are <6 mm, or Polyp matching exists and "reference" polyp size is <10 mm

The accuracy measures will be calculated based on the matched results, including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Additionally, sensitivity analyses including varying matching sizes and using OC as the reference will be performed to assess the robustness of the results.