Evaluation of the Clinical Performance of an Investigational Real-Time Colorectal Polyp Clinical Decision Support Device (CDSD)

Protocol # OCA 2019-GI-03

CLINICAL INVESTIGATION PLAN

Sponsored By
Olympus Corporation of the Americas (OCA)

Contact Information

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Revision History

Version Number	Release Date	Section	Change	Reason for Change
1.0	**FEB 18 2020**	**N/A**	**N/A**	**Initial Release**
2.0	**AUG 31 2020**	**Multiple**	• **Incorporate FDA feedback on Statistical Analysis Plan (sample size re-calculation, adoption of bootstrap methodology, treatment of normal tissue pathology results and recuts, additional endpoint regarding discordant unaided and aided results, etc.)** • **Minor update to exclusion criteria regarding bowel prep based on principal investigator clinical experience** • **Other minor content and administrative updates**	**Incorporated feedback from FDA Pre-submission Q181327/S003**

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Sponsor Protocol Approval Page

Haytham Gareer, MD Vice President, Clinical Affairs	DocuSigned by: Haytham Gareer B468F598C7824C3... Date: 9/2/2020 | 8:46 PM EDT
Jeremy Bolt Senior Manager, Clinical Affairs	DocuSigned by: Jeremy Bolt 524610E0399A4EB... Date: 9/2/2020 | 11:25 AM EDT

STUDY TITLE:	Evaluation of the Clinical Performance of an Investigational Real-Time Colorectal Polyp Clinical Decision Support Device (CDSD)
PROTOCOL NUMBER:	**Protocol # OCA 2019-GI-03**
VERSION NUMBER:	**2.0 (AUG 31 2020)**

We, the undersigned, have read and approve the protocol specified above and agree on its content.

Investigator Protocol Approval Page

Evaluation of the Clinical Performance of an Investigational Real-Time Colorectal Polyp Clinical Decision Support Device (CDSD)

Protocol # OCA 2019-GI-03

Protocol Version 2.0 (AUG 31 2020)

I hereby agree to participate in the above noted study sponsored by Olympus. (here in after "Study Sponsor"). I agree to conduct this investigation according to the requirements of the protocol provided by the Study Sponsor in accordance with applicable local regulations, and in accordance with the conditions imposed by the reviewing Institutional Review Board (IRB). I agree to supervise all use of the study devices and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that are submitted by me to the Study Sponsor.

I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time.

I understand this study protocol and trial results are confidential, and I agree not to disclose any such information to any person other than a representative of the Study Sponsor, the IRB/EC, or regulatory authorities without the prior written consent of the Study Sponsor.

Accepted by:

DocuSigned by:
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Principal Investigator

9/3/2020 | 11:47 AM EDT

Date

Dr. Doug Rex

Printed Name

Protocol Synopsis

Evaluation of the Clinical Performance of an Investigational Real-Time Colorectal Polyp Clinical Decision Support Device (CDSD)	
Study Objective(s)	The study objective is to establish the efficacy of the colorectal polyp CDSD in clinical use.
Planned Indication(s) for Use	The colorectal polyp Clinical Decision Support Device is intended to support authorized healthcare professionals in increasing histological prediction accuracy of physician-identified diminutive (≤ 5mm) polyps during colonoscopy for documentation and comparison with pathology. The device does not mark, highlight, or direct users' attention to a specific location in the original image. The device is not intended to replace histopathological sampling as a means of diagnosis.
Test Device	The investigational device consists of software residing on a dedicated computer enabling display of a polyp histology prediction (Adenoma or Non-Adenoma) in the Picture-in-Picture area of the endoscopic screen during colonoscopy procedures when Narrow Band Imaging (NBI) is engaged. The CDSD-aided endoscopist makes a final prediction of histology considering CDSD output.
Control Device	Unaided endoscopist prediction of polyp histology using NBI.
Study Design	Prospective, single arm, multicenter study
Planned Number of Subjects	A minimum of 2,400 subjects will be enrolled in order to obtain predictions on at least 1,918 diminutive polyps. It is anticipated that the study will take up to 6 months to complete.
Investigational Sites	Up to seven investigational sites in the USA will be utilized.
Co-Primary Endpoint(s)	Sensitivity and Specificity of CDSD-aided endoscopist predictions compared with unaided NBI prediction on the same polyp.
Additional Endpoints	1. Number, proportion, unaided NBI prediction and pathology result of diminutive polyps detected by the endoscopist and confirmed by pathology for which CDSD does not return a prediction.

	2. Sensitivity, specificity, NPV, PPV of unaided endoscopist prediction using white light compared with pathology. 3. Sensitivity, specificity, NPV, PPV of unaided endoscopist prediction using NBI compared with pathology. 4. Sensitivity, specificity, NPV, PPV of CDSD prediction compared with pathology. 5. Sensitivity, specificity, NPV, PPV of CDSD-aided endoscopist prediction compared with pathology. 6. Number, proportions and pathology results for diminutive polyps with discordant unaided predictions using NBI and aided predictions with CDSD.
Method of Assigning Subjects to Treatment	Consecutive subjects presenting for colonoscopy and meeting the pre-procedure entrance criteria will be consented and screened. Subjects meeting all the entrance criteria will be enrolled and undergo colonoscopy per the standard of care with the added use of CDSD. After detection of a polyp by the endoscopist, the user will make three histological predictions (adenoma or non-adenoma): 1) using white light 2) using NBI 3) using CDSD
Visit Schedule	1. **Screening** (*Clinic Visit*) a. Informed consent b. Pre-procedural entrance criteria 2. **Baseline** (*Clinic Visit*) a. Demographics b. Relevant medical history 3. **Procedure** (*Clinic Visit*) a. Colonoscopy procedure b. Procedural entrance criteria

	c. Unaided endoscopist prediction using white light d. Unaided endoscopist prediction using NBI and confidence level (high or low) e. CDSD prediction f. CDSD-aided endoscopist prediction and confidence level (high or low) 4. **Immediate Post Procedure Evaluation** (*Lab results only*) a. Pathological results **5. End of Study** a. End of study will be reached after final pathology results have been obtained (typically within one to two weeks of the procedure).
Study Duration	Each subject's study participation will end when the final pathology results are obtained. Study enrollment is anticipated to take up to 6 months to complete.
Key Patient Inclusion Criteria	1. ≥ 18 years of age 2. Willing and able to provide informed consent 3. Subjects undergoing colonoscopy
Key Patient Exclusion Criteria	1. Polyposis syndromes including Familial Adenomatous Polyposis Syndrome 2. Inflammatory Bowel Disease 3. Hereditary Non Polyposis Colorectal Cancer 4. Severe coagulopathy 5. Subjects scoring less than 6 on the Boston Bowel Prep Score. 6. No diminutive polyps detected during colonoscopy

Statistical Methods	
Primary Statistical Hypothesis	The co-primary effectiveness endpoint is the sensitivity and specificity of CDSD-aided endoscopist prediction.

	$Sensitivity\ (Sn) = \frac{TP}{TP + FN}$ $Specificity\ (Sp) = \frac{TN}{TN + FP}$ The hypothesis for Sensitivity is: H_{0Sn}:Sn $_{CDSD\text{-}aided} \leq$ Sn $_{CDSD\text{-}unaided}$ H_{1Sn}: Sn $_{CDSD\text{-}aided} >$ Sn $_{CDSD\text{-}unaided}$ The hypothesis for Specificity is: H_{0Sp}:Sp $_{CDSD\text{-}aided} \leq$ Sp $_{CDSD\text{-}unaided}$ H_{1Sp}:Sp $_{CDSD\text{-}aided} >$ Sp $_{CDSD\text{-}unaided}$ The overall hypothesis tested is that the CDSD-aided endoscopist predictions of polyp histology will have superior sensitivity and specificity as compared with the unaided endoscopist predictions of histology on the same polyps. H_0: H_{0Sn} or H_{0Sp} H_1: H_{1Sn} and H_{1Sp}
Statistical Test Method	Bootstrap resampling 95% confidence intervals for the difference between CDSD aided and unaided sensitivity and specificity, with bootstrap resampling performed first at the endoscopist level, then at the patient level.
Sample Size Parameters	Based on a review of the literature, without CDSD, the operator sensitivity is presumed to be 88% and the specificity is presumed to be 58% across all operators[1–6]. The operator sensitivity with CDSD is presumed to be 92% and the specificity with CDSD is presumed to be 73% across all operators based on validation testing. In order to demonstrate the primary endpoint with 80% power and one-sided significance level of 2.5% a minimum of 2400 subjects and 40 endoscopists are required. Assuming 52% of subjects will have one or more diminutive polyps[7], 1.81 diminutive polyps per subject having at least one diminutive polyp[7] and an adenoma prevalence of 58%[7] yields a minimum requirement of 1918 polyps.

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1 Introduction

Screening colonoscopy is considered the gold standard for colorectal cancer detection and prevention in the United States. Central to screening colonoscopy is the detection of adenomatous lesions. Adenomas are considered neoplastic lesions and their removal during colonoscopy is thought to disrupt the adenoma-carcinoma progression[8]. Their presence also influences the probability that an average-risk individual will develop colon cancer and so the number and size of adenomas detected during colonoscopy are a critical part of the process in calculating a patient's post-polypectomy colon cancer surveillance interval[9]. One hallmark of adenomas and advanced neoplastic lesions is their enrichment with capillaries compared with normal colon mucosa and non-neoplastic polyps[10]. Olympus' Narrow Band Imaging (NBI) is an endoscopic visualization method and adjunctive tool, cleared via 510(k) (K131780) in which broad spectrum white light illumination is filtered into bands of violet and blue light[11,12]. Preferential absorption of this light by oxy-hemoglobin in red blood cells residing in capillaries and vessels of the mucosa leads to their accentuation under NBI observation.

Over the last decade researchers have validated a handful of classification systems using NBI to accurately differentiate colorectal polyps as adenomatous or non-adenomatous based on color, presence and structure of vessels and mucosal surface patterns[13]. The NBI International Colorectal Endoscopic (NICE) Classification is one such system that was specifically created for simple characterization of diminutive (≤ 5mm) and small (< 10mm) polyps with non-magnifying endoscopes commonly available in Western nations[14] and experienced endoscopists have reached high levels of diagnostic accuracy in visual assessments relative to pathological analysis[7,15–21]. Despite this, application of NBI for real-time polyp characterization by community-level and non-expert endoscopists have yielded mixed results for performance [1,4,5,22], possibly due to variation in endoscopist skill, attention to detail or motivation.

Characterizing diminutive colorectal polyps as adenomatous and non-adenomatous, the two major classes of colorectal lesions, remains a clinical challenge for many practicing endoscopists. An adjunctive tool such as CDSD may aid in this distinction by increasing the number of accurate predictions relative to ground truth pathological analysis. The proposed study seeks to establish the effectiveness of CDSD as an adjunctive tool to assist endoscopists in the assessment of diminutive colorectal polyps.

2 Device Description

The investigational device consists of clinical decision support software (CDS) hosted on a dedicated, non-networked, medical accessory computer (the colorectal polyp Clinical Decision Support Device, hereinafter referred to as 'the Device' or 'CDSD'). The Device connects directly to the Olympus CV-190 Video Processor (non-investigational) and sits on the open bottom shelf of the medical cart while in use. See Figure 2-1 and Table 2-1 for details.

Figure 2-1: System Overview

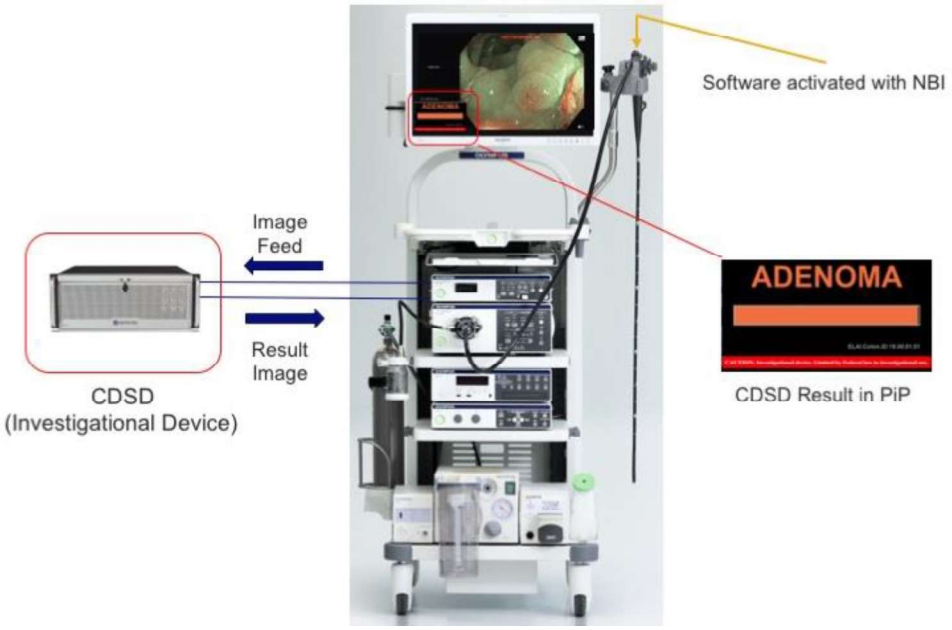


Table 2-1: CDSD Hardware Specification

Dimensions	18.75" wide x 8.0" high x 20.5" deep
Processor	Intel i7
Memory	16GB DDR4
Hard Drive	Solid State Drive, Enterprise Grade
GPU	nVidia Quadro P4000
Capture Card	HD-SDI input/output
USB Ports	2x Front/ 4x Rear
Operating System	Windows 10 IOT, 64 bit

The Device connects to the Olympus CV-190 Video Processor through two HD-SDI cables, enabling the receipt of the endoscopic signal from the CV-190, and sending of the Device's output to the CV-190 for display in the Picture-in-Picture (PiP) region of the endoscopic monitor.

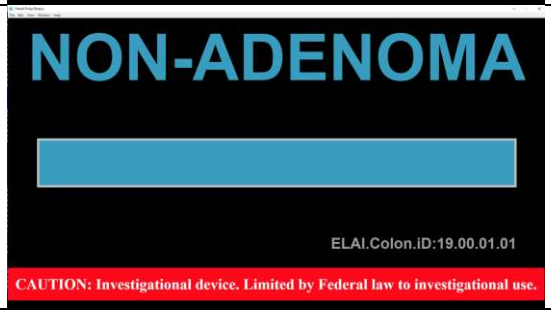
The software composing the Device contains two modules:

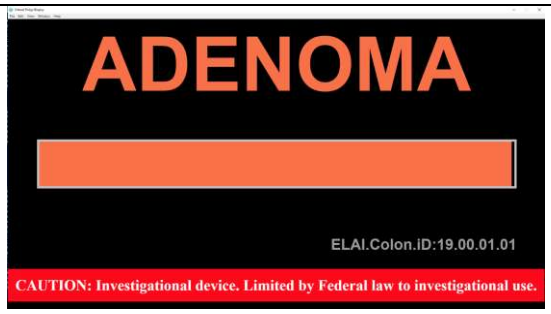
- User Interface module (the "UI module"), and
- Artificial Intelligence module (the "AI module").

2.1.1 User Interface Module

The CDS continuously receives the raw (unfiltered) endoscopic video stream from the CV-190 video processor, and integrates the data from the AI module into the final information displayed by the UI module. This information is presented as both a text output and progress bar in the PiP region of the monitor alongside the raw video output. The presented text output is either 'non-adenoma', 'adenoma' or no text is displayed where model prediction repeatability is not achieved, too variable over consecutive frames or no polyp is present in the video stream that is identifiable to the AI module. The progress bar illustrates model prediction repeatability and is color-coded to identify suspected adenoma/non-adenoma. Figure 2-2 depicts these different outputs.

Figure 2-2: Graphical User Interface of CDSD

Empty Bar • NBI is not engaged, OR • NBI is engaged but the software cannot classify the polyp or no polyp is present	
Filling Bar • The software is classifying a polyp	
Result: Non-Adenoma • The software has repeatedly classified the suspected polyp and has returned a result of Non-Adenoma.	

Result: Adenoma • The software has repeatedly classified the suspected polyp and has returned a result of Adenoma.	

The information of the investigational device does not obfuscate the primary endoscopic video on the monitor, nor does it mark, highlight, or direct users' attention to a specific location on the endoscopic video. The investigational device's output is clearly identified as 'Investigational Device' (refer to Figure 2-2) to ensure the endoscopist does not mistake it for the primary endoscopic video.

2.1.2 **Artificial Intelligence Module**

The AI module is composed of a static AI model, trained on raw endoscopic videos (video recordings) originating from unaltered recordings of colorectal polyps, specifically of diminutive polyps (≤5 mm) with proven pathology. The AI module takes raw endoscopic data as input (full frame, no segmentation), and outputs two data streams:

(1) Classification of video frames into white light mode versus Olympus CV-190 NBI mode, and
(2) Classification of endoscopic images of the NBI class (only) into 'adenoma' and 'non-adenoma'.

Information from the AI module is presented to the operator, via the User Interface module described in section 2.1.1 only when the Olympus CV-190 processor is engaged in the NBI mode by the operator.

The investigational Device connects to and is used with the Olympus EVIS EXERA III, which includes the CV-190 Video Processor (CV-190). The EVIS EXERA III system was last cleared via 510(k) K131780. During the clinical study, the EVIS EXERA III system will be used within its cleared indication for use.

Further, table 2-2 provides a complete listing of non-investigational devices needed or recommended for use in the clinical study.

Table 2-2: Non-Investigation Devices Required/Recommended

Device *	**Manufacturer**	**Description**	**Required or Recommended**
CV-190	Olympus	Endoscopic video processor	Required
CLV-190	Olympus	Endoscopic light source	Required
OEV-262	Olympus	Endoscopic video monitor	Recommended
One or more of the following colonoscopes:			
CF-HQ190L	Olympus	Colonoscope	Required
PCF-H190(D)L	Olympus	Colonoscope	Required

3 Study Objectives

The study objective is to establish the efficacy of the colorectal polyp CDSD in clinical use.

4 Study Endpoints

Co-Primary Endpoint:

Sensitivity and Specificity of CDSD-aided endoscopist predictions compared with unaided prediction on the same polyp.

Secondary Endpoints:

1. Number, proportion unaided NBI prediction and pathology result of diminutive polyps detected by the endoscopist and confirmed by pathology for which CDSD does not return a prediction.
2. Sensitivity, specificity, NPV, PPV of unaided endoscopist prediction using white light.
3. Sensitivity, specificity, NPV, PPV of unaided endoscopist prediction using NBI.
4. Sensitivity, specificity, NPV, PPV of CDSD prediction.
5. Sensitivity, specificity, NPV, PPV of CDSD-aided endoscopist prediction.
6. Number, proportions and pathology results for diminutive polyps with discordant unaided predictions using NBI and aided predictions with CDSD.

5 Study Design

The study shall be a prospective, single arm, multicenter study. Endoscopists comprising a range of clinical experience will be invited to participate in the study at each site. All

participating endoscopists will receive an overview of the NICE classification to guide their unaided and CDSD-aided assessments as well as instruction on the use of CDSD.

For each participating endoscopist, consecutive subjects presenting for colonoscopy and meeting the pre-procedure entrance criteria will be consented and screened. Consented subjects meeting all the entrance criteria will be enrolled and undergo colonoscopy per the standard of care with the added use of CDSD. CDSD-unaided and CDSD-aided predictions will be compared with the ground truth of histopathology. Presuming at least 40 endoscopists participate, each endoscopist will make approximately 60 predictions on diminutive polyps through the course of the study.

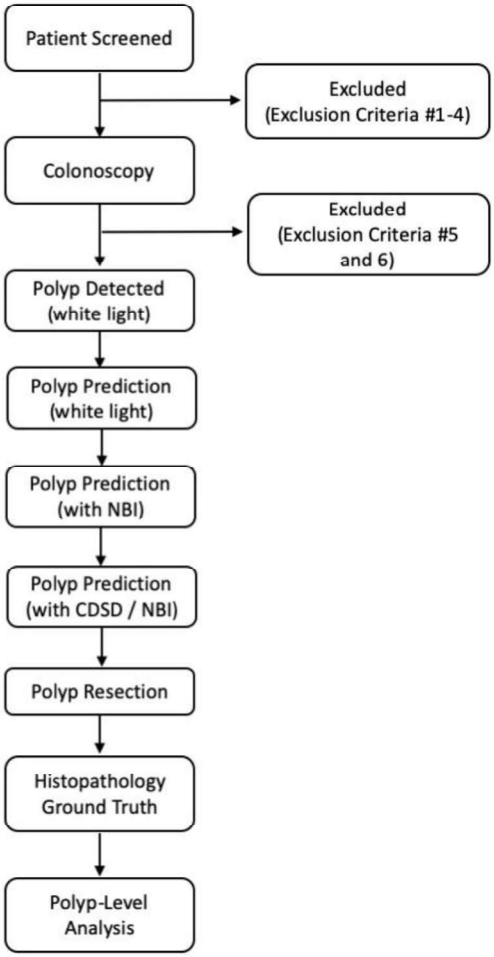


Figure 5-1: Procedure Flow

During the procedure, the endoscopist will insert the colonoscope to the cecum as per standard of care. Examination will be under white light illumination. Typically during withdrawal, but also during insertion at the discretion of the endoscopist, identified lesions

will have their location, size and shape documented. The endoscopist will inspect the lesions and estimate the size of lesion (diameter in mm) using a device such as the tip of a biopsy forceps or snare catheter tip as is common practice. Diminutive size is defined as a diameter ≤5mm. For diminutive polyps, an initial histology prediction will be made in white light as 'Adenoma' or 'Non-adenoma' based on the endoscopist's experience and training. NBI will be engaged and the endoscope tip will be steadied with the lesion centered. The endoscopist will be blinded to the CDSD result. The endoscopist will make a second prediction of polyp histology as 'Adenoma' or 'Non-adenoma' using NICE classification criteria (see Figure 5-1). NICE Type 1 will be defined as Non-Adenoma and NICE Type 2 will be defined as Adenoma. The endoscopist must make a prediction and is not permitted to render an 'unsure' or 'don't know' prediction. The endoscopist will state their level of confidence in the prediction. [1,15,16,23]. See Table 5-1 for a description of the NICE classification and criteria used to predict diminutive polyp histology.

Table 5-1: NBI International Colorectal Endoscopic (NICE) Classification

NICE Classification	Type 1	Type 2
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structures surrounded by brown vessels
Predicted Histology (Human or CDSD)	Non-Adenoma	Adenoma

After making their prediction using NBI alone, the endoscopist or coordinator will enable PiP to allow the endoscopist to observe the CDSD result. The CDSD result shall be recorded as 1) Adenoma, 2) Non-adenoma, or 3) No prediction after system stabilization. The endoscopist considers their initial prediction and the output of the device to make a final combined prediction of polyp histology as 'Adenoma' or 'Non-adenoma'. The endoscopist will make a determination of their confidence in their prediction as either 'high' or 'low'. If CDSD does not return a prediction this does not indicate that no polyp is present. More likely, this output is due to the module not being able to make a clear adenoma/non-adenoma assessment based on the training the model has received. Based on software validation testing, this is expected to occur in approximately 11-16% of the polyps. In cases that this occurs, the result will be recorded as "no prediction". In this scenario, the endoscopist will make a final prediction without the aid of CDSD.

Polyps will be biopsied or resected as per the standard of care and placed in a separate specimen jar or polyp trap chamber and uniquely labeled as per standard procedure. The exam will continue and the steps above are repeated for each identified diminutive lesion. At the end of the procedure, polyp specimens are sent to pathology for review. The pathologist is blinded to the endoscopist predictions and CDSD prediction.

The diagnosis will be rendered by the pathologist, who is blinded to the endoscopists' polyp characterization, and the pathology report will be reviewed by the endoscopist. A CDSD-aided or CDSD-unaided prediction of Adenoma will be rendered as a True Positive when the pathological diagnosis is 'conventional adenoma' (a.k.a. tubular adenoma), tubulovillous adenoma, villous adenoma, traditional serrated adenoma (TSA), adenoma with high grade dysplasia or cancer. A CDSD-aided or unaided prediction of non-adenoma will be rendered as a True Negative when the pathological diagnosis is hyperplastic polyp, sessile serrated polyp (SSP), inflammatory polyp, lymphoid aggregate/follicle, granulation tissue or normal colonic mucosa. Diminutive polyps that are lost following resection or destroyed during pathology prior to diagnosis will be excluded from the analysis due to lack of ground truth pathology results.

In cases where the CDSD-aided endoscopist prediction and the pathology result differs, a recut and reanalysis of the tissue block will be conducted. In such cases, the second successful pathology reading will be recorded and used as the histopathological ground truth.

5.1 *Scale and Duration*

A minimum of 2,400 subjects will be enrolled in order to obtain predictions on at least 1,918 diminutive polyps. It is anticipated that the study will take up to 6 months to complete.

5.2 *Treatment Assignment*

For each participating endoscopist, consecutive subjects presenting for colonoscopy and meeting the pre-procedure entrance criteria will be consented and screened. Subjects meeting all the entrance criteria will be enrolled and undergo colonoscopy according to the standard of care with the added use of CDSD.

During the procedure, subjects found to meet any of the exclusion criteria will be excluded from the study. CDSD will be applied to all endoscopist-identified diminutive polyps in all subjects. Pathology will be blinded to all predictions. See Figure 5-1 for details.

5.2.1 **Target Lesions**

Diminutive (≤5mm) colorectal polyps identified during colonoscopy will be considered target lesions.

5.3 *Justification for the Study Design*

This study design was chosen to follow current standard of care endoscopy procedures with the exception of introduction of CDSD as part of the physician's decision algorithm. Pathology remains the gold standard methodology for diagnosis in this study. The study aims to demonstrate that CDSD is capable of increasing the sensitivity and specificity of endoscopist predictions for diminutive polyp histology. The single arm design was chosen to evaluate the incremental improvement in predictive accuracy relative to the standard of care while controlling for variability in polyp presentation by using a matched pair design. Inclusion of endoscopists comprising a range of experience is intended to reflect real-life clinical practice and potential increased benefit to non-expert users. Blinding allows for independence of assessments, and comparison of results without bias.

6 Subject Selection

6.1 *Study Population and Eligibility*

Subjects who provide informed consent and meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in this study.

6.2 *Entrance Criteria*

6.2.1 Inclusion Criteria

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical study, provided no exclusion criterion is met.

1. ≥ 18 years of age
2. Willing and able to provide informed consent
3. Subject scheduled for colonoscopy

6.2.2 Exclusion Criteria

Subjects who meet any one of the following criteria will be excluded from this clinical study.

1. Polyposis syndromes including Familial Adenomatous Polyposis (FAP) Syndrome
2. Inflammatory Bowel Disease (IBD)
3. Hereditary Non Polyposis Colorectal Cancer (HNPCC)
4. Severe coagulopathy
5. Subjects with a cumulative score of 6 or less on the Boston Bowel Prep Score
6. No diminutive polyps detected during colonoscopy

7 Subject Accountability

7.1 *Point of Enrollment*

Existing family history and other standard-of-care screening tests and questions may be used to determine subject eligibility for recruitment prior to the colonoscopy procedure. Following signing of the informed consent form (ICF), subjects will be defined as being enrolled in the study, however; subjects may subsequently be excluded from the study based on findings during the procedure consistent with exclusion criteria listed in Section 6. Consented subjects who fail the procedural entrance criteria will be considered screening failures, and the reason for exclusion will be recorded. Subjects who meet all entrance criteria including those evaluated during the colonoscopy procedure will be considered the Intent to Treat (ITT) population for this study.

8 Study Methods

8.1 *Data Collection*

Table 8-1: Data Collection Schedule

Procedure/Assessment	Screening / Enrollment	Procedure	Post- procedure (Lab results only)
Informed consent	X		
Inclusion / Exclusion	X	X	
Demographics	X		
Medical history	X		
Colonoscopy / CDSD		X	
Pathology assessment			X
Follow-up pathology assessment			X (as needed)
Device deficiencies assessment		X	

X: Required Procedure/Assessment

8.2 *Informed Consent*

All subjects taking part in this clinical study must undergo the informed consent process. Subjects must be allowed adequate time to review the consent, raise questions, and make a voluntary decision to participate in the clinical study. Each subject must sign and date the IRB approved ICF before any clinical study-related procedures are performed. A copy of signed ICF will be provided to the subject for his/her records. A subject's participation in the clinical study begins with the signing and dating of the ICF.

8.2.1 Post-Consent Eligibility Validation

Exclusion criteria such as poor bowel prep and absence of diminutive polyps will not be known until after the start of the procedure. Consented subjects who fail exclusion criteria during the procedure will be considered screening failures and excluded from the statistical analysis.

8.3 *Screening/Enrollment*

Consecutive subjects presenting for colonoscopy will be considered for participation. Existing family history and other standard-of-care screening tests and questions may be used to determine subject eligibility for recruitment prior to the colonoscopy procedure. Subjects meeting the pre-procedural entrance criteria will be consented prior to the colonoscopy procedure. Demographic and relevant medical history data will be collected. Subjects may still be excluded from the study during the colonoscopy procedure assessment if they no longer meet entrance criteria.

8.4 *Colonoscopy Procedure*

The colonoscopy procedure will proceed as per standard of care with the exception of use of CDSD. The following information will be collected during this visit:

- Colonoscopy indication
- Endoscopist
- Colonoscope model used
- Procedure date
- Length of procedure (scope in to scope out) including cecal intubation time and withdrawal time
- Procedural entrance criteria
- Unaided physician prediction using white light
- Unaided physician prediction and confidence level using NBI
- CDSD prediction
- CDSD aided physician prediction and confidence level
- Number, size, shape and location of all identified polyps

8.5 *Post-Procedure*

Lab results will be collected for all specimens sent to pathology, including secondary lab results in cases where a recut/re-analysis of specimen is requested by the endoscopist and

performed. Diagnosis based on pathology will be recorded as well as prescribed surveillance interval.

8.6 *Study Completion*

An individual subject's participation in the study shall conclude following the end of the procedure. Data collection shall end following review of the pathology report for any specimens resected or biopsied during the procedure. In cases where pathology re-evaluation is requested, data collection shall end once all subsequent pathology re-evaluations are complete and secondary pathology reports are reviewed by the investigators.

8.7 *Source Documents*

Source documents are the subject records maintained at the study site. In most cases, the source documents will be the physician's or hospital's subject chart. In some cases, the source documents may be electronic. In both cases, the information captured in the CRF must match the information in the chart or electronic source document. The Investigator agrees to make source documents (hard copy or electronic) available for monitoring by the Sponsor and/or their representatives.

8.8 *Local Laboratory Documentation*

Local laboratories for the clinical sites will be used as per standard practice. Appropriate certifications and documentation records will be collected for the study file.

9 Statistical Considerations

9.1 *Endpoints*

9.1.1 Primary Endpoint

The co-primary effectiveness endpoint is the sensitivity and specificity of CDSD-aided endoscopist prediction.

$$Sensitivity\ (Sn) = \frac{TP}{TP + FN} \quad Specificity\ (Sp) = \frac{TN}{TN + FP}$$

9.1.1.1 Hypotheses

A 2x2 table for accuracy of paired predictions with NBI is constructed for both adenomas (Sn, histology reference standard positive) and non-adenomas (Sp, histology reference standard negative) (Tables 9-1 and 9-2).

Table 9-1: Sample 2x2 Table for Paired Adenoma Predictions with NBI (Reference Standard Positive)

		CDSD-unaided Prediction		
		Positive	Negative	Total
CDSD-aided Prediction	Positive	a	b	a+b
	Negative	c	d	c+d
	Total	a+c	b+d	a+b+c+d

Table 9-2: Sample 2x2 Table for Paired Non-Adenoma Predictions with NBI (Reference Standard Negative)

		CDSD-unaided Prediction		
		Positive	Negative	Total
CDSD-aided Prediction	Positive	m	n	m+n
	Negative	p	q	p+q
	Total	m+p	n+q	m+n+p+q

In order to test the effect of CDSD, individual hypotheses for sensitivity and specificity will be evaluated based on 2x2 tables of paired predictions for adenomas and non-adenomas, respectively. The hypothesis for Sensitivity is:

H_{0Sn}: $Sn_{\text{CDSD-aided}} \leq Sn_{\text{CDSD-unaided}}$ or $\frac{(a+b)}{(a+b+c+d)} \leq \frac{(a+c)}{(a+b+c+d)}$

H_{1Sn}: $Sn_{\text{CDSD-aided}} > Sn_{\text{CDSD-unaided}}$ or $\frac{(a+b)}{(a+b+c+d)} > \frac{(a+c)}{(a+b+c+d)}$

The hypothesis for Specificity is:

H_{0Sp}: $Sp_{\text{CDSD-aided}} \leq Sp_{\text{CDSD-unaided}}$ or $\frac{(p+q)}{(m+n+p+q)} \leq \frac{(n+q)}{(m+n+p+q)}$

H_{1Sp}: $Sp_{\text{CDSD-aided}} > Sp_{\text{CDSD-unaided}}$ or $\frac{(p+q)}{(m+n+p+q)} > \frac{(n+q)}{(m+n+p+q)}$

The overall hypothesis tested is that the CDSD-aided endoscopist predictions of polyp histology will have superior sensitivity and specificity as compared with the unaided endoscopist predictions of histology on the same polyps.

H_0: H_{0Sn} or H_{0Sp}

H_1: H_{1Sn} and H_{1sp}

9.1.1.2 Sample Size

In order to demonstrate the primary endpoint with 80% power and one-sided significance level of 2.5% a minimum of 40 endoscopists and approximately 2400 subjects are required. Assuming 85% of subjects have adequate bowel preparation, 52% of subjects with adequate bowel preparation have one or more diminutive polyps, 1.81 diminutive polyps per subject having at least one diminutive polyp and a 58% adenoma prevalence[7] yields a minimum requirement of 1918 polyps.

9.1.1.3 Statistical Methods

The 95% confidence intervals for the differences between CDSD-aided and CDSD-unaided sensitivity and specificity are estimated using bootstrap resampling with resampling performed first at the endoscopist level and then at the patient level. The null hypothesis is rejected if both lower bounds of the confidence intervals are greater than 0.

$Sn_{CDSD\text{-}aided} - Sn_{CDSD\text{-}unaided} > 0$

$Sp_{CDSD\text{-}aided} - Sp_{CDSD\text{-}unaided} > 0$

The assumptions of the statistical model used to establish the sample size are:

1. There are at a minimum 40 endoscopists participating in the study and each endoscopist makes approximately 60 predictions,
2. For each endoscope (CF-HQ190 and PCF-H190) and for each class of diminutive polyp (adenoma and non-adenoma) there is an intra-cluster correlation coefficient of 0.05 for predictions made by the same endoscopist[5],
3. There is no correlation between an operator's sensitivity and specificity,
4. There is no correlation between predictions made by the same operator across endoscope models (CF-HQ190 and PCF-H190),
5. The distribution of adenomas and non-adenomas within subjects with more than one diminutive polyp was modelled and is described in the statistical analysis plan,
6. The values from the range of possible values for the discordant pairs (b, c, n and p) that are used to calculate sample size are reported in Tables 9-3, 9-4, 9-5 and 9-6),
7. Without CDSD, the operator sensitivity is presumed to be 88% and the specificity is presumed to be 58% across all operators for all colonoscopes[1–6]. The operator sensitivity with CDSD is presumed to be 92% and specificity with CDSD is presumed to be 75% across all operators when using the CF-HQ190 colonoscope (benchtop testing data). The operator sensitivity with CDSD is presumed to be 91% and the specificity with CDSD is presumed to be 72% across all operators when using the PCF-H190 colonoscope (benchtop testing data). Combined, the operator

sensitivity with CDSD is presumed to be 92% and the specificity with CDSD is presumed to be 73% across all operators,

8. The prediction rate for CDSD with CF-HQ190 is 89% and the prediction rate for CDSD with the PCF-H190 is 84% (benchtop testing data),
9. The proportion of subjects examined with the PCF-H190 will be 50%,
10. The proportion of subjects that present with adequate bowel preparation will be 85%[24], the proportion of patients with diminutive polyps will be 52%[7], there will be 1.81 diminutive polyps per subject having diminutive polyps[7], the overall prevalence of adenomas will be 58%[7],
11. The proportion of predictions with and without CDSD that will be assessed as normal tissue by pathology is estimated to be approximately 15%.

A simulation analysis was performed in which a dataset is generated at each step following the assumptions above. To account for intra-cluster correlation at the endoscopist level, for each endoscope and each class of diminutive polyps, the proportions of accurate and non-accurate predicions are sampled following a Dirichlet distribution, as described in Gönen[25]. At each simulation step, bootstrap resampling based 95% confidence intervals for the differences between CDSD-aided and CDSD-unaided sensitivity and specificity are calculated. Bootstrap resampling is performed first at the endoscopist level and then at the patient level. The power is calculated as the number of simulation steps where the lower bound of both confidence intervals is greater than 0.

Table 9-3: Assumptions for Proportions of Predictions for Adenomas (Sensitivity, Reference Standard Positive) with CF-HQ190

		CDSD-unaided Prediction		
		Positive	Negative	Total
CDSD-aided Prediction	Positive	0.8411	0.0859	0.9270
	Negative	0.0365	0.0365	0.073
	Total	0.8776	0.1224	1.00

Table 9-4: Assumptions for Proportions of Predictions for Adenomas (Sensitivity, Reference Standard Positive) with PCF-H190

		CDSD-unaided Prediction		
		Positive	Negative	Total
CDSD-aided Prediction	Positive	0.8301	0.0749	0.905
	Negative	0.0475	0.0475	0.095
	Total	0.8776	0.1224	1.00

Table 9-5: Assumptions for Proportions of Predictions for Non-Adenomas (Specificity, Reference Standard Negative) with CF-HQ190

		CDSD-unaided Prediction		
		Positive	Negative	Total
CDSD-aided Prediction	Positive	0.124	0.124	0.248
	Negative	0.299	0.453	0.752
	Total	0.423	0.577	1.00

Table 9-6: Assumptions for Proportions of Predictions for Non-Adenomas (Specificity, Reference Standard Negative) with PCF-H190

		CDSD-unaided Prediction		
		Positive	Negative	Total
CDSD-aided Prediction	Positive	0.1415	0.1415	0.283
	Negative	0.2815	0.4355	0.717
	Total	0.423	0.577	1.00

9.1.2 Secondary Endpoints

1. Number, proportion, unaided NBI prediction and pathology result of diminutive polyps detected by the endoscopist and confirmed by pathology for which CDSD does not return a prediction.
2. Sensitivity, specificity, NPV, PPV of unaided endoscopist prediction using white light compared with pathology.
3. Sensitivity, specificity, NPV, PPV of unaided endoscopist prediction using NBI compared with pathology.
4. Sensitivity, specificity, NPV, PPV of CDSD prediction compared with pathology.
5. Sensitivity, specificity NPV, PPV of CDSD-aided endoscopist prediction compared with pathology.
6. Number, proportions and pathology results for diminutive polyps with discordant unaided predictions using NBI and aided predictions with CDSD.

9.2 *General Statistical Methods*

9.2.1 Analysis Sets

Intention to Treat (ITT) analysis will be performed on all subjects meeting the entrance criteria. The primary endpoint will be assessed by ITT analysis on polyp level data.

9.2.2 Subgroup Analyses

Subgroup analyses of interest include impact of colonoscopy indication, impact of colonoscope used, impact of endoscopist confidence on sensitivity and specificity, impact of endoscopist experience on level of confidence in prediction, impact of endoscopist experience on frequency with which CDSD returns a result (i.e. influence of endoscope handling) and agreement with pathology as well as unaided and CDSD aided performance segmented by Paris Classification. Additional subgroup analyses may be performed as appropriate.

9.2.3 Additional Analyses

In cases where the CDSD-aided endoscopist prediction and the pathology result differs, a recut and reanalysis of the tissue block will be conducted. In such cases, the second successful pathology reading will be recorded and used as the histopathological ground truth.

10 Data Management

10.1 *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data collection system (EDC). The clinical database will reside on a production server hosted by the EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

10.2 *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of

the product. These documents will be retained for a longer period of time by agreement with Olympus or in compliance with other local regulations.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and Olympus must receive written notification of this custodial change. Sites are required to inform Olympus in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

11 Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. IRB approval of the revised protocol must be obtained prior to implementation.

12 Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor. Sites may also be required to report deviations to the IRB, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

13 Device/Equipment Accountability

The study Devices/equipment shall be securely maintained, controlled, and used only in this clinical study.

The sponsor shall keep records to document the physical location of all study Devices/equipment from shipment of study Devices from Olympus or designated facility/equipment to the investigation sites until return or disposal.

Records shall be kept by clinical sites to document the physical location and conditions of storage of all study Devices/equipment.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the study Devices/equipment, which shall include the following:

- Date of receipt
- Identification of each study Device/piece of equipment (batch number, serial number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date of return (and number) of unused, expired, or malfunctioning study Devices/equipment, if applicable.

14 Compliance

14.1 *Statement of Compliance*

This study will be conducted in accordance with 21 CFR 812 and 814.20 part 56 and part 50, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB has been obtained. Any additional requirements imposed by the IRB shall be followed, if appropriate.

14.2 *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Trial Agreement, the clinical investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Trial Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.

- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report to Sponsor, and assess every observed device deficiency.
- Maintain the device accountability records and control of the Device, ensuring that the study Device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

14.2.1 **Delegation of Authority**

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3 ***Institutional Review Board***

The protocol and informed consent document must have the approval of a properly constituted committee ("Institutional Review Board") responsible for approving clinical

trials. The signed IRB approval letter must identify the documents approved (i.e., list the Investigator's name, the protocol title, and date of approval, and informed consent document). A copy of the approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB approval and renewals will be obtained throughout the duration of the study as required by IRB requirements. Copies of the Investigator's reports and the IRB continuance of approval must be provided to the sponsor.

14.4 *Sponsor Responsibilities*

All information and data sent to Olympus concerning subjects or their participation in this study will be considered confidential by Olympus. Only authorized Olympus personnel or an Olympus representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by Olympus for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Olympus will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Olympus may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

14.4.1 **Role of Olympus Representatives**

Olympus personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during procedures. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of Olympus equipment/devices.

In addition, Olympus personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

14.5 *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by Olympus for subjects in the study will be obtained.

15 Monitoring

On site and/or remote monitoring may be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the Sponsor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by Olympus personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by Olympus or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

16 Potential Risks and Benefits

16.1 *Risks Associated with the Study Device(s)*

The study Device has no interaction with the subject, therefore there is no risk of Device-related adverse events. The study Device may fail to operate and/or show a prediction, however, in these cases the procedure and post-procedure care will proceed as per standard practice. It is anticipated that the use of CDSD may slightly lengthen the procedure time but it is not expected to have significant impact on the subject.

16.2 *Anticipated Benefits*

Subjects may receive no benefit from participation in this study. It is possible that in some cases, pathological results may be reconsidered based on CDSD prediction, in which case adenoma may be diagnosed when it otherwise might not have been.

16.3 *Risk to Benefit Rationale*

There is no risk to subjects from participation in this study, with the exception of potential loss of confidentiality. Appropriate measures will be taken by the clinical sites and Sponsor to ensure confidentiality is protected including de-identification of study data collected and reported by the Sponsor. Given that use of the CDSD does not present new risks for the subjects, and may provide potential benefit, the risk ratio is considered to be acceptable.

17 Safety Reporting

17.1 *Reportable Events by investigational site to Olympus*

The CDSD is a minimal risk adjunctive tool to be used in conjunction with standard colonoscopy. As CDSD has no interaction with the subject, adverse events are not

anticipated to occur in the study and no safety reporting will be required. Any device deficiencies will be recorded as per section 17.2 below.

17.2 *Olympus Device Deficiencies*

All Device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to Olympus within 3 days of the clinical site becoming aware of the event. If possible, the Device(s) should be returned to Olympus for analysis. Instructions for returning the study Device(s) will be provided. If it is not possible to return the Device, the investigator should document why the Device was not returned and the final disposition of the Device. Device failures and malfunctions should also be documented in the subject's medical record.

18 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study Devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, IRB approval, FDA requirements, as applicable. The ICF must be accepted by Olympus or its delegate (e.g. CRO), and approved by the site's IRB, or central IRB, if applicable.

Olympus will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB. Any modification requires acceptance from Olympus prior to use of the form. The ICF must be in a language understandable to the subject and if needed, Olympus will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,

- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported to the IRB and FDA as required.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. Acceptance by Olympus is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

19 Suspension or Termination

19.1 *Premature Termination of the Study*

Olympus reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRB, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

19.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Olympus to suspend or discontinue development of the Device.

19.2 *Termination of Study Participation by the Investigator or Withdrawal of IRB Approval*

Any investigator, or IRB may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Olympus. Investigators, associated

IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

19.3 *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Olympus. The IRB and regulatory authorities, as applicable, will be notified.

In the event an IRB terminates participation in the study, participating investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Olympus.

19.4 *Criteria for Suspending/Terminating a Study Site*

Olympus reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 1 month after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study Devices and testing equipment, as applicable, will be returned to Olympus. The IRB and regulatory authorities, as applicable, will be notified.

20 Publication Policy

Olympus requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a Olympus study or its results. Olympus will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Olympus adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, Olympus personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- Olympus involvement in publication preparation should be discussed with the Coordinating Principal Investigator(s) at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

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21.1 *Abbreviations*

Abbreviations are shown in Table 21-1.

Table 21-1: Abbreviations

Abbreviation/Acronym	Term
AI	Artificial Intelligence
CDSD	Clinical Decision Support Device
CFR	Code of Federal Regulations
CRF/eCRF	Case Report Form / Electronic Case Report Form
CRO	Contract Research Organization
EDC	Electronic Data Collection
FAP	Familial Adenomatous Polyposis
FDA	Food & Drug Administration
GCP	Good Clinical Practice
HCP	Health Care Professional
HNPCC	Hereditary Non Polyposis Colorectal Cancer
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention To Treat
OCA	Olympus Corporation of the Americas
NBI	Narrow Band Imaging
NICE	NBI International Colorectal Endoscopic [Classification]
NPV	Negative Predictive Value
PiP	Picture-in-Picture
PPV	Positive Predictive Value
SSP	Sessile Serrated Polyp
TN	True Negative (as confirmed by pathology)
TP	True Positive (as confirmed by pathology)
UI	User Interface
WHO	World Health Organization