Global Prospective Case Series using a Single-Use Duodenoscope

Exalt DScope 02

E7156

CLINICAL INVESTIGATION PLAN

National Clinical Trial (NCT) Identified Number: NCT04103749

Sponsored By

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Original Release: June 27, 2019

Current Version: January 14, 2022

Revision Version	Protocol Date	Template Number and Version	Protocol Section Modified	Summary of Changes	Justification for Modification
B	August 14, 2019	AL	Contact Information, Protocol Synopsis, Section 1.2, Section 4	The list of Coordinating Principal Investigators was reduced from 7 to 2 The planned number of subjects was increased from 500 to 1000 Additional information was added to the study rationale Minor additional changes throughout	Per Investigator feedback
C	June 16, 2020	92120219, Rev/Ver C	Protocol Synopsis, Section 1.2 Study Rationale, Table 5.3-1, Section 14.1 Potential Risks and Benefits, Section 16.4 Investigator Reporting Requirements	Protocol Synopsis updated to change maximum number of sites from 20 to 40, and Altered Pancreaticobiliary Anatomy exclusion criterion removed Section 1.2 updated to reflect the commercial availability of EXALT Table 5.3-1 updated to remove Altered Pancreaticobiliary Anatomy exclusion criterion Section 14.1 updated to refer to product DFU Section 16.4 updated to reflect post-market reporting timelines Various minor terminology updates throughout	Per Investigator feedback the Altered Pancreaticobiliary Anatomy exclusion criterion was removed. Because Exalt is commercially available it can be used in patients with altered pancreaticobiliary anatomy outside of this study, and this is not listed as a contraindication in the DFU. The intent of this study is to evaluate the performance of Exalt Model D in ERCPs and other duodenoscope-based procedures. "Altered pancreaticobiliary anatomy" is not a contraindication for the use of Exalt in the approved DFU. This exclusion criterion was originally included due to questions of how well Exalt would be able to navigate tortuous GI anatomy based on insertion shaft stiffness, however

Revision Version	Protocol Date	Template Number and Version	Protocol Section Modified	Summary of Changes	Justification for Modification
					these concerns have been resolved by the clinical experience to date. Update to Clinical Study Protocol Template (Post-Market) 92120219 after FDA 510(k) clearance of the study device
D	January 14, 2022	92120219, Rev/Ver G	Cover Page; Section 3 Study Objectives and Endpoints; Section 9.1 Data Collection, Processing, and Review; Section 16 Safety Reporting	Cover page updated to include NCT Identification Number Section 3 updated to include Justification for Endpoints Section 9.1 updated to include additional paragraph to specify the changes in clinical database access after data is Hard Locked or Entry Locked Update to section 16.2 to change the Ref from MEDDEV to MDCG, and changes to the safety definitions to align with the updated guidance Update to section 16.3 to change the Ref from MEDDEV to MDCG, and changes to the AE definitions to align with the updated guidance Changes made to table 16.4-1 to align with the update guidance Various minor terminology updates throughout	Update to incorporate the changes made to the protocol template 92120219 from Ver. C to Ver. G.

Protocol Synopsis

Global Prospective Case Series using a Single-Use Duodenoscope **Exalt DScope 02** **E7156**	
Study Objective(s)	Confirm procedural performance of the Exalt™ Model D Single-Use Duodenoscope in Endoscopic Retrograde Cholangio-Pancreatography (ERCP) and other duodenoscope-based procedures
Indication(s) for Use	*Single-Use Duodenoscope* The device is intended for use with the Controller, for endoscopy and endoscopic surgery within the duodenum. *Video Imaging System Controller* The device is intended for use with a Boston Scientific endoscope for endoscopic diagnosis, treatment, and video observation.
Study Device and sizes, if applicable	Exalt™ Model D Single-Use Duodenoscope Exalt™ Controller
Study Design	Prospective case series of per standard of care ERCP procedures or other duodenoscope-based procedures
Planned Number of Subjects	Up to 1000 subjects
Planned Number of Investigational Sites	Up to 40 sites
Primary Endpoint	Ability to complete the ERCP or other duodenoscope-based procedure for the intended indication(s)
Secondary Endpoints	1. Document endoscopist rating of the Exalt single-use duodenoscope compared to marketed reusable duodenoscopes as it pertains to various design and performance related attributes

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	2. Incidence of crossover from Exalt single-use duodenoscope to reusable duodenoscope 3. Evaluation of serious adverse events (SAEs) related to the device and/or the procedure through 30 days after the ERCP or duodenoscope-based procedure
Follow-up Schedule	• Screening/Baseline • Index Procedure • 72-hr Follow-Up Visit • 30 day Follow-Up Visit
Participant Duration	The study duration for each subject is expected to be approximately 1 month
Inclusion Criteria	1. 18 years or older 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study 3. Scheduled for a clinically indicated ERCP or other duodenoscope-based procedure
Exclusion Criteria	1. Potentially vulnerable subjects, including, but not limited to pregnant women 2. Subjects for whom endoscopic techniques are contraindicated 3. Subjects who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor 4. Investigator discretion
Statistical Methods	
Statistical Hypothesis	A statistical hypothesis is not required for this study as it is a case series of per standard of practice ERCP or other duodenoscope-based procedures

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1. Introduction

1.1. *Background*

Flexible endoscopes are used globally for the diagnosis and treatment of diseases of the GI tract. These delicate instruments are used in Endoscopic Retrograde Cholangiopancreatography (ERCP) procedures, which are performed with side viewing endoscopes (duodenoscopes) that to date are all reusable devices.[1] Given their reusability, these instruments must be reprocessed through high level disinfection (HLD) in order to prevent the spread of nosocomial infections[2], although different levels of disinfection may be produced depending on disinfection method, device modification, and staff adherence to disinfection protocols.[1,3-5]

In recent years there have been an increased number of nosocomial infection outbreaks traced to contaminated duodenoscopes used during ERCP procedures in many states throughout the US and Europe.[3,6-8] Organisms involved in these recent outbreaks include Carbapenem-resistant Enterobacteriaceae (CRE), including *Escherichia coli*, and *Klebsiella pneumoniae*.[6] Unfortunately, some of the cases linked to these outbreaks have proven to be fatal.[8] Typically, infections discovered post-ERCP procedures vary between 2%-4%[9], but it is unclear whether these infections are caused by contaminated duodenoscopes or the procedure.[6]

The gastrointestinal tract is a highly contaminated environment, and the intricate tip design and long, narrow working channels of modern duodenoscopes render them extremely difficult, if not impossible, to adequately clean.[10] Even strict adherence to all HLD procedures results in a non-zero, although minimal, level of potentially infectious microbes.[10] This remains a large problem, and neither manufacturers or regulatory bodies, such as the FDA, were providing guidance for this. While these cases reported in the hospitals listed above occurred in 2012, several other cases emerged globally, and months later the FDA stated that they were warning manufacturers, monitoring, and providing closer surveillance in an effort to prevent further infections associated with contaminated duodenoscopes.[11] The FDA mandated the three duodenoscope manufacturers in the US, Olympus, Pentax, and Fujifilm, conduct post-market surveillance studies to evaluate the rate of duodenoscope contamination with viable microorganisms after standard HLD in actual practice. While the studies assumed a <0.4% contamination rate, the study revealed 5.4% of duodenoscopes interrogated for these studies remained contaminated with high concern microorganisms including *E. coli* and *Pseudomonas aeruginosa*.[12]

1.2. *Study Rationale*

Conventional reusable duodenoscopes have been identified as the source of multiple cases of fatal and non-fatal nosocomial infections throughout the US and Europe, despite adherence to duodenoscope sterilization and reprocessing guidelines. In some cases, the infectious organisms were later identified as belonging to a family of bacteria that has a high level of resistance to conventional antibiotics, known as CRE. The Exalt™ Model D Single-Use

Duodenoscope is the first single-use disposable duodenoscope available on the open market, which does not need to be sterilized or reprocessed because they are only used for a single patient in one case before they are disposed of. The availability of this device may save patient lives by removing a potential source of infection and save the healthcare system money used to treat the infections and to reprocess the devices.

In April-May 2019, 60 patients were prospectively enrolled in a consecutive ERCP case series using the Exalt™ Model D Single-Use Duodenoscope. The primary endpoint of this study was the ability to complete the ERCP or other duodenoscope-based procedure for the intended indication(s). All 60 (100%) ERCPs were completed, 58 (97%) using the single-use duodenoscope only, and 2 (3%) with crossover to a reusable duodenoscope.

2. Study Device Description

The Exalt™ Model D Single-Use Duodenoscope is a sterile, single-use endoscope that facilitates access to the duodenum, delivery of accessories, and live video when connected to an Exalt™ Controller.

The Exalt™ Controller is an electronic device that:

- Receives video signals from a Boston Scientific single-use endoscope,
- Processes the video signals,
- Outputs video images to a video monitor, and
- Outputs electrical signal(s) that interface with external image capture systems.

The Controller also controls the light transmitted by the tip of the single-use endoscope to illuminate the area of interest within the anatomy. Buttons on the Controller's front panel enable the user to control the brightness level of the light.

To use the Controller, connect it to a video monitor with a video cable and then connect a Boston Scientific single-use endoscope to the Controller. The Controller provides direct visualization during an endoscopic procedure.

The Controller interfaces with external media capture equipment via the Controller's rear panel connectors. Image capture is initiated via a button on the Boston Scientific single-use endoscope. The Controller sends a signal to the video monitor notifying the user that an image capture has been initiated. Directions for use for the Exalt™ Model D Single-Use Duodenoscope and Exalt™ Controller will be supplied separately to the investigational site in a regulatory binder. Investigators will use the device in accordance with the supplied directions and their institutional standard of care.

3. Study Objectives and Endpoints

Table 3-1: Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary Endpoints		
To confirm procedural performance of the Exalt™ Model D Single-Use Duodenoscope in Endoscopic Retrograde Cholangio-Pancreatography (ERCP) and other duodenoscope-based procedures	The primary endpoint is the ability to complete the ERCP procedures for the intended indication(s).	Completion of ERCP and other duodenoscope based procedures is the standard measurement of the performance of a duodenoscope. This endpoint will indicate that these procedures can be achieved with the Exalt duodenoscope.
Secondary Endpoints		
To confirm procedural performance of the Exalt™ Model D Single-Use Duodenoscope in Endoscopic Retrograde Cholangio-Pancreatography (ERCP) and other duodenoscope-based procedures	The following will be recorded as secondary endpoints during index procedure through follow-up: 1. Document endoscopist rating of the Exalt single-use duodenoscope compared to marketed reusable duodenoscopes as it pertains to various design and performance related attributes. 2. Incidence of crossover from Exalt single-use duodenoscope to reusable duodenoscope. 3. Evaluation of serious adverse events (SAEs) related to the device and/or the procedure through 30 days after the ERCP or other duodenoscope based procedures	1. Endoscopist rating of the study device provide a subjective evaluation of the device performance by intended users. 2. The ability to complete the index procedure with the Exalt duodenoscope is an important indicator of the performance of the device. 3. Serious adverse events are being collected at 30 days in order to detect any event with a late onset and to document the safety profile of the study device.

4. Study Design

This is a prospective, multi-center case series of standard of care ERCP procedures and other duodenoscope-based procedures with up to 1000 subjects. This study represents the post-market clinical development stage of the study device according to ISO 14155. The endoscopist will use the Exalt single-use duodenoscope in place of the reusable duodenoscope normally used in the endoscopy unit at their own discretion.

4.1. *Justification for the Study Design*

The study is designed to demonstrate that physicians are able to complete standard of care ERCP procedures and other duodenoscope-based procedures with the Exalt Model D single-use duodenoscope. The Exalt duodenoscope is designed to perform similarly to conventional marketed reusable duodenoscopes.

5. Subject Selection

5.1. *Study Population and Eligibility*

All inclusion and exclusion criteria below must be verified during screening.

5.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 5-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 5.3) is met.

Table 5-1: Inclusion Criteria

Inclusion Criteria	1. 18 years or older 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study 3. Schedule for a clinically indicated ERCP or other duodenoscope-based procedure

5.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 5-2) cannot be included in this study or will be excluded from this clinical study.

Table 5-2: Exclusion Criteria

Exclusion Criteria	1. Potentially vulnerable subjects, including, but not limited to pregnant women 2. Subjects for whom endoscopic techniques are contraindicated 3. Subjects who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor 4. Investigator discretion

6. Subject Accountability

6.1. *Point of Enrollment*

Subjects will be considered enrolled into the study at the time of the study-specific informed consent form (ICF) execution. Subjects who have signed informed consent but do not undergo the study procedure are considered screen failures. Screen failures will be recorded in the Electronic Data Capture (EDC) by each study site and will not count toward total study enrollment.

In the case it is determined that the subject failed to meet the inclusion/exclusion criteria after the subject has agreed to participate in the study and has signed the informed consent, the study personnel will complete the Screening form and the End of Study form.

6.2. *Withdrawal*

Subjects will participate in the study voluntarily and may withdraw at any time without prejudice to further treatment. All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to study device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Applicable case report forms up to the point of subject withdrawal, including an End of Study form must be completed. Unless the withdrawal is due to a Serious Adverse Event, additional subject data will not be collected after the point at which the subject has been withdrawn or withdraws consent from the study. Data collected up to the point of withdrawal may be used by the investigators as permitted in the ICF.

6.3. *Lost to Follow-Up*

A subject will be considered lost to follow-up if he/she fails to return for their scheduled follow-up visits and is unable to be contacted by the study site staff after at least three documented attempts, at which point an End of Study form should be completed. Before a participant is deemed lost to follow up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods).

These contact attempts should be documented in the participant's medical record or study file.

6.4. *End-of-Study Definition*

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred.

Subjects will be followed through 30 days post index procedure. At study completion, an End of Study form will be completed. The end of study is defined as completion of the last visit or a reason for the last study visit not having been completed has been determined by the investigator or designee. If the last follow-up visit was not completed, the investigator will note the reason on the study completion form (e.g. subject withdrawn by investigator, subject withdrew consent, lost to follow-up, AE, death, etc.).

7. Study Methods

7.1. *Data Collection*

The data collection schedule is shown in Table 7-1.

Table 7-1: Data Collection Schedule

Procedure/Assessment	Screening	Baseline	Index Procedure	Follow-up Visits	
				72-hour visit (-1, +2 Days) Office/ Telephone	Day 30 visit (± 3 Days) Office/ Telephone
Informed consent process, including informed consent signature date	X				
Demographics, Medical History		X			
Index Procedure			X		
Maneuvers			X		
Exalt Evaluation			X		
Device Event Assessment			X		
Adverse Event Assessment			X	X	X
End of Study					X

X=required

7.2. *Study Candidate Screening*

Subjects who are clinically indicated for an ERCP or other duodenoscope-based procedure and meet the listed eligibility criteria may be screened for trial enrollment. All patients who are considered for enrollment but not enrolled will be recorded.

7.2.1. Strategies for Recruitment and Retention

All patients under the care of a study investigator during the enrollment period of a site will be considered for recruitment.

7.3. *Informed Consent*

Data collection and/or study procedure will not occur prior to the subject signing the ICF. Patients will be considered enrolled in the study once they sign the informed consent. Once a subject is considered enrolled in the study, baseline information may be obtained.

7.4. *Baseline*

Baseline information will include the following data points: age at time of consent, gender, and relevant medical history.

7.5. *Index Procedure*

During the index procedure, the endoscopist or designated member of study staff will record: start and stop times of procedure, scope information, whether certain types of medicine were administered, and any activities completed or attempted during the procedure, regardless of original intent. Any ensuing device events will be recorded and reported.

After the ERCP procedure has been completed, the endoscopist will rate their experience using the Exalt device during the index procedure.

7.6. *72 hour (-1 day, + 2 days) and 30 day (± 3 days) Assessments*

All enrolled subjects will be seen in person or evaluated via telephone to screen for any post-procedure adverse events, and to evaluate the resolution of any previously noted adverse events or sequelae, as applicable.

7.7. *Study Completion*

Subjects will be followed for 30 days (± 3 days) post index procedure. Subjects will continue to receive care from their doctor as they normally would. At study completion, an End of Study form will be completed, indicating whether the subject completed the study. If the last follow-up visit was not completed, the reason will be noted on the study completion form (e.g. subject withdrawn by investigator, subject withdrew consent, lost to follow-up, AE, death, etc.).

7.8. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified

(i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

8. Statistical Considerations

8.1. *Statistical Hypothesis and sample size justification*

A statistical hypothesis is not required for this study as it is a case series of per standard of practice ERCP or other duodenoscope-based procedures.

8.2. *General Statistical Methods*

8.2.1. Analysis Sets

Enrolled Cohort

A subject is considered enrolled after signing the study-specific ICF. Subjects who sign the ICF, but subsequently do not meet one or more of the eligibility criteria provided in Section 5.2and Section 5.3 will be considered screen failures and excluded from the study.

Intent-to-Treat Cohort (ITT)

This cohort consists of enrolled subjects who meet all eligibility criteria and are planned to have an ERCP or other duodenoscope based procedure using Exalt duodenoscope.

Treated Cohort

The treated cohort is a subset of the ITT subjects who have an ERCP or other duodenoscope based procedure using the Exalt duodenoscope.

8.3. *Data Analyses*

All statistical analyses will be done using The SAS System software, version 8 or higher (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

8.3.1. Baseline Data

Subject demographics and clinical history will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency statistics for discrete variables.

8.3.2. Procedure Data

Procedure data including qualitative evaluation will be collected and reported using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency statistics for discrete variables.

8.3.3. Post-Procedure Data

Post-procedure information will be collected as detailed in the Table 7.1-1. Data Schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency statistics for discrete variables.

8.3.4. Interim Analyses

No formal interim analyses are planned for this study.

9. Data Management

9.1. *Data Collection, Processing, and Review*

Subject data will be recorded in the Medidata Rave limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata. 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 Rave 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 Medidata EDC system for site response. Site staff will be responsible for resolving queries in the database.

All access to the clinical database will be changed to “Read only” after all data is either “Hard Locked” or “Entry Locked”. Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the “Database Locked” or Decommissioned and all database access revoked.

9.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. 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 BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

10. 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/EC/REB, and the regulatory authority if applicable 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.

Deviations from the investigational plan, with the reason for the deviation must be documented and reported to the sponsor via EDC. Sites may also be required to report deviations to the IRB/EC/REB, and the local regulatory authority, per local guidelines and national/government regulations.

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

11. Commercial Device/Equipment Accountability

The study devices/equipment owned by Boston Scientific shall be securely maintained, controlled, and used only in this clinical study. The Inventory Management Record will be used to track subjects and study device allocations during the study for study devices not labeled investigational. Equipment owned by Boston Scientific shall be returned in the condition in which it was provided, reasonable wear and tear excepted.

12. Device/Equipment Accountability for Products Labeled Investigational

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. The Device Accountability Log will be used to track subjects and device allocations during the study for study devices labeled investigational. Equipment shall be returned in the condition in which it was provided, reasonable wear and tear excepted.

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

Records shall be kept by the site 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 or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the study device/piece of equipment was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning study devices/equipment, if applicable.

13. Compliance

13.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator. This study will be conducted in accordance with European Medical Device Regulation, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC/REB and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

13.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study 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/EC/REB, 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 Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page (if applicable) and 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, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain 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; 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/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject’s participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).

- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the study device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- 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.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

13.2.1. Delegation of Responsibility

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, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

13.3. *Institutional Review Board/ Ethics Committee*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC/REB and/or competent authority (CA) 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 study product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF. Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

13.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. 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 BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

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.

13.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed. Support may include, but is not limited to, HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

Typical tasks may include the following:

- Provide instructions for the safe return of products. For potentially hazardous items, provide specialized instructions and materials, as applicable.

- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed form
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

In addition, BSC 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

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

13.5. *Insurance*

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

14. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor 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 BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

The study may also be subject to a quality assurance audit by BSC 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.

15. Potential Risks and Benefits

15.1. *Instructions for Use*

Please refer to the Instructions for Use for an overview of anticipated (device) effects, and risks associated to the study device(s).

15.2. *Risks Associated with Participation in the Clinical Study*

Risk associated with participation in the Clinical Study are similar to that of an ERCP with standard duodenoscope. Participation in the trial may be time consuming.

15.3. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

15.4. *Anticipated Benefits*

Recent literature has identified an outbreak with carbapenem-resistant Enterobacteriaceae (CRE).[3-8] That endoscopic transmission of infection can be prevented by strict adherence to disinfection protocols has been challenged with no clearly identified protocol to reduce this risk.[13] Use of a Single-Use Duodenoscope would alleviate the need for high level disinfection of the standard Duodenoscope, thereby reducing the risk of infection transmission between patients.

15.5. *Risk to Benefit Rationale*

Based on collected reports in literature to-date, the risk-to-benefit ratio is within reason for foreseeable risks. However, literature reports do not always capture all side effects. Observation and follow-up of patients is required as outlined in the protocol.

16. Safety Reporting

16.1. *Reportable Events by Investigational Site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Non-Serious Adverse Events
- All Serious Adverse Events
- All Study Device Deficiencies

- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 16-1 for AE definitions).

Refer to Section 15 for the known risks associated with the study device(s).

16.2. *Definitions and Classification*

Adverse event definitions are provided in Table 16-1. Administrative edits were made on the safety definitions from ISO 14155 and EU 2017/745 for clarification purposes.

Table 16-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.

Table 16-1: Safety Definitions

Term	Definition
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, user or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Table 16-1: Safety Definitions

Term	Definition
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet other SAE criteria.

16.3. *Relationship to Study Device(s) and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to the study device, and/or study procedure. See criteria in Table 16-2:

Table 16-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the study device or the procedures related to the use of the study device; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

Table 16-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause,
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

16.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 16-3.

Table 16-3: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, MDCG 2020-10/1)	**Communication Timeline post-market studies** (EU MDR 2017/745, MDCG 2020-10/1 MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study	• Within 1 business day of first becoming aware of the event • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.	• At request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study	• Within 10 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor	• When documentation is available. • Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations.

Table 16-3: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, MDCG 2020-10/1)	**Communication Timeline post-market studies** (EU MDR 2017/745, MDCG 2020-10/1 MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
		• Reporting required through the end of the study	• Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event, as requested by sponsor.	• When documentation is available • Upon request of sponsor.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to, malfunctions use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Study Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Complete eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study	• Within 3 calendar days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of sponsor	• Upon request of sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. recommend within 10 business days) after becoming aware of the information • Reporting required through end of study • At sponsor request	• Adverse Device Effects (or other key events of interest, e.g., Heart Failure): In a timely manner but not later than 30 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 30 business days after becoming aware of the information • Reporting required through end of study • Upon request of sponsor
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.		

Table 16-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies (21 CFR Part 812, MDCG 2020-10/1)	Communication Timeline post-market studies (EU MDR 2017/745, MDCG 2020-10/1 MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

16.5. *Device Deficiencies*

Device deficiencies for the Devices under study (i.e. the study device) will be documented and reported to BSC. If possible, the device(s) under study should be returned to BSC for analysis. Instructions for returning the study device(s) will be provided in site initiation visit slides. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF.

16.6. *Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs/ECs/REBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

17. 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, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO) and approved by the site's IRB/EC/REB, or central IRB, if applicable.

Boston Scientific 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/EC/REB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB 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 by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC/REB), as appropriate.

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/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised

ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

18. Committees

18.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations team include health care providers with expertise and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

There will be no other committees (e.g., Clinical Events Committee, Data Monitoring Committee, Independent Data Reviewer, Morbidity and Mortality Events Committee, etc.) used in this study.

19. Suspension or Termination

19.1 Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs/REBs, 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:

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development/ marketing of the device.

19.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC /REB Approval

Any investigator or associated IRB/EC/REB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs/REBs, 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 Boston Scientific. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/EC/REB terminates participation in the study, participating investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and study product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

19.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific 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 12 months 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 BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

20. Study Registration and Results

20.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

20.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

20.3. *Publication Policy*

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific 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, BSC 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.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

21. Reimbursement and Compensation for Subjects

21.1. *Compensation for Subject's Health Injury*

Boston Scientific will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

22. Bibliography

1. Baron TH, Kozarek RA, Carr-Locke DL. ERCP. 3rd ed. Philadelphia: Elsevier; c2019. Chapter 5, Duodenoscope Reprocessing; p. 44-48.

2. Funk S.E., Reaven N.L. High-level endoscope disinfection processes in emerging economies: financial impact of manual process versus automated endoscope reprocessing. Journal of Hospital Infection 2014, 86, 250-254.
3. Epstein L, Hunter JC, Arwady MA, Tsai V, Stein L, Gribogiannis M, et al. New Delhi metallo-β-lactamase-producing carbapenem-resistant Escherichia coli associated with exposure to duodenoscopes. JAMA. 2014;312:1447–1455.
4. Verfaillie CJ, Bruno MJ, Voor in ’ t Holt AF, Buijs JG, Poley JW, Loeve AJ, et al. Withdrawal of a novel-design duodenoscope ends outbreak of a VIM-2-producing Pseudomonas aeruginosa. Endoscopy. 2015;47:493–502.
5. Wendorf KA, Kay M, Baliga C, Weissman SJ, Gluck M, Verma P, et al. Endoscopic retrograde cholangiopancreatography-associated AmpC Escherichia coli outbreak. Infect Control Hosp Epidemiol. 2015;36:634–642.
6. Rauwers AW, Voor in ‘t holt AF, Buijs JG, de Groot W, Hansen BE, Bruno MJ, Vos MC. High prevalence rate of digestive tract bacteria in duodenoscopes: a nationwide study. GUT. 2018;0,1-9.
7. Alrabaa SF, Nguyen P, Sanderson R, Baluch A, Sandin RL, Kelker D, et al. Early identification and control of carbapenemase-producing Klebsiella pneumoniae, originating from contaminated endoscopic equipment. Am J Infect Control. 2013;41:562–564.
8. Murray P. Preventable tragedies: superbugs and how ineffective monitoring of medical device safety fails patients. Health, Education, Labor, and Pensions Committee, US Senate: Washington, DC; 2016.
9. Koleva J, Peters FT, van de Mei HC, Degener JE. Transmission of infection by flexible gastrointestinal endoscopy and bronchoscopy. Clin Microbiol Rev. 2013;26(2):231-254.
10. Rutala WA, Weber DJ. Gastrointestinal Endoscopes: A Need to Shift From Disinfection to Sterilization? JAMA. 2014;312(14):1405–1406. doi:10.1001/jama.2014.12559.
11. FDA. FDA warns duodenoscope manufacturers about failure to comply with required postmarket surveillance studies to assess contamination risk. 2018 Mar 9. Available from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm600388.htm
12. FDA. FDA Continues to Remind Facilities of the Importance of Following Duodenoscope Reprocessing Instructions: FDA Safety Communication. 2019 Apr 12. Available from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm600388.htm
13. Kohli DR, Grys TE, Pannala R. Eliminating Duodenoscope-Associated Transmission of Carbapenem-Resistant Enterobacteriaceae (CRE): In Search of an Optimal Strategy. Dig Dis Sci. 2017;62(11):2961-2963.

23. Abbreviations and Definitions

23.1. *Abbreviations*

Abbreviations are shown in Table 23-1.

Table 23-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
CA	Competent Authority
CRE	Carbapenem-resistant Enterobacteriaceae
CRF	Case Report Form
CRO	Contract Research Organization
EC	Ethics Committee
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
EDC	Electronic Data Capture
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HCP	Health Care Personnel
HLD	High Level Disinfection
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-Treat
REB	Research Ethics Board
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect