Prospective, Multi-Center, All-Comer MANTIS Endoscopic Clipping Study

MANTIS Clip Study

E7170

CLINICAL INVESTIGATION PLAN

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
Ver. B	**12Oct2022**	**90702637 Ver AQ**	**None**	**No changes to content**	**Protocol not initially stored in BSC Document Repository (WindChill) as trainable document. Upreved only to allow BSC employees to assign and complete training.**
Ver. C	**17Feb2023**	**90702637 Ver AQ**	**2, 6, 7, 8, 9, 11, 12, 16, 19, 20**	**Changes to Initial and Continued Enrollment Cohort and associated sections**	**Modified objective to include evaluation of the procedural and clinical merit of specific attributes and expand enrollment to countries where the device is not yet approved**
Ver. D	**24Jul2023**	**90702637 Ver AQ**	**2, 6, 8**	**Change to Study Design and Objective to include consecutive enrollment**	**Modified to clarify that there will be consecutive enrollment**

2. Protocol Synopsis

MANTIS Clip Study	
Objectives	Initial Cohort To document performance of the MANTIS™ Clip in all indications for endoscopic clipping. Continued Enrollment Cohort To evaluate the procedural and clinical merit in consecutive cases in which at least one MANTIS clip is selected, of specific attributes of the MANTIS™ Clips, including but not limited to the ability of this new endoscopic clipping device: o to provide prophylaxis to reduce the risk of delayed bleeding post lesion resection o to close post mucosal resections/polypectomy ulcers, post submucosal dissection ulcers, or mucosal incisions made in conjunction with endoscopic myotomy procedures o to close lumenal perforations, fistulas, or leaks o to close perforations after full thickness resection of lesions in the gastrointestinal (GI) tract
Indications for Use	Resolution™ Clip family is indicated for clip placement within the GI tract for the purpose of: 1. Endoscopic marking 2. Hemostasis for: o Mucosal/sub-mucosal defects < 3 cm o Bleeding ulcers o Arteries < 2 mm o Polyps < 1.5 cm in diameter o Diverticula in the colon o Prophylactic clipping to reduce the risk of delayed bleeding post lesion resection 3. Anchoring to affix jejunal feeding tubes to the wall of the small bowel 4. As a supplementary method, closure of GI tract luminal perforations < 20 mm that can be treated conservatively

MANTIS Clip Study	
Study Device	MANTIS™ is a clip in the Resolution 360 Clip product family.
Study Procedure	The portion of the endoscopic procedure where the MANTIS™ Clip is used for hemostasis, closure, anchoring or marking.
Study Design	Prospective, multi-center, open label, consecutive enrollment • Group A: Hemostasis • Group B: Closure • Group C: Anchoring • Group D: Endoscopic Marking • Group E: Other
Number of Subjects and Sites	• Initial Cohort: Up to 50 cases • Continued Enrollment Cohort: 240 cases • Up to 15 sites globally
Primary Effectiveness Endpoint	Initial Cohort Ability to complete the indication for the use of endoscopic clipping Continued Enrollment Cohort Clinical success defined as, where applicable, o Absence of delayed bleeding o Sustained closure of the targeted leasion up to 30 days after the endoscopic clipping procedure
Primary Safety Endpoint	Rate of serious adverse events (SAEs) related to the MANTIS™ clip or the endoscopic study portion of the procedure. NOTE: If providing hemostasis to an active bleed requires possible additional hemostasis after the index study procedure for management of bleeding SAEs within 7 days[36] of the index study procedure, then such bleeding SAEs are not counted for the Primary Safety Endpoint.
Additional Endpoints	1. Technical success at placement defined as ability to deploy the endoscopic clips in satisfactory position. 2. Ability to anchor device, mobilize the tissue, and approximate defect edges for secured closure. (Group B only).

MANTIS Clip Study	
	3. Post procedural bleeding, defined as a severe bleeding event that required hospitalization, a blood transfusion (>5 units), or another invasive intervention (angiographic or surgery) within 30 days after the study clip placement. 4. For active bleeding hemostasis cases only a. Rate of patients requiring additional modalities of hemostasis. b. Report of hemostasis of active bleeding 7 days after the index study procedure, defined as ability to stop the active bleed at the time of the study procedure and/or with additional clipping procedures to provide hemostasis of continued or recurrent bleeding within 7 days of the index study procedure
Follow-up Schedule	• Baseline • Procedure • 30 day follow up (both Initial and Continued Enrollment Cohort)
Study Duration	Enrollment is expected to be completed in approximately 12 months; therefore the total study duration is estimated to be approximately 13 months as Subjects will be on the study for up to 30 days.
Key Inclusion Criteria	1. Subject indicated for endoscopic clipping per local standard of practice. 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study. NOTE: Hemostasis and closure can be needed in the setting of complications such as perforations or acute bleeding that are typically rare and sometimes emergent. In such circumstances consenting the patient before the procedure is not feasible and consent shall be obtained from the patient after the procedure but before any study data is collected.
Key Exclusion Criteria	1. Subjects who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor. 2. Subjects who the investigator deems at risk for study device or procedure related complications per the Instructions for Use (IFU), where commercially available or the Investigator Brochure (IB) for countries where the study device is not approved.

MANTIS Clip Study	
Statistical Methods	Initial cohort: No hypotheses will be tested, only observational, summary statistics will be performed. Continued enrollment cohort: A systematic literature search was conducted on PubMed and Embase from January 1, 2016 to September 2022 to identify studies that evaluated the safety and effectiveness of an endoscopic clip device for closing various types of incisions, lesions, or defects in the gastrointestinal tract resulting from endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), polypectomy of polyps or adenomas, perforations, and fistulas. The primary objective of the search strategy was to identify studies that examined the closure of large mucosal defects by endoscopic clipping. Twenty studies were identified through a post-market literature review activity were included to the analysis with a total of 2257 patients. We hypothesize that the **clinical success rate** of MANTIS™ clip will be greater than the performance goal of **89%** with expected clinical success rate of **94%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect: • 20 publications representing 2257 patients: 93.9% (95% CI 88.6%-97.6%) We hypothesize that the **serious adverse event (SAE) rate** related to MANTIS™ clip or the endoscopic clipping portion of the procedure will be lower than the performance goal of **19%** with expected related SAE rate of **10%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect: • 9 publications representing 1019 patients: 9.8% (95% CI 3.7%-18.5%) Using an exact test with an alpha level of 0.05, **240 subjects** enrolled will provide at least 80% power for the performance and safety metrics. These tests will only be performed for cases in the continued enrollment cohort.

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4. Introduction

4.1. *Background*

The endoscopic clip, endoclip or hemoclip, was first introduced by Hayashi for the treatment of gastrointestinal (GI) bleeding in Japan in 1975.[1] Over the past decades, the hemostatic clips technology has evolved and it has become the standard of care for gastrointestinal bleeding. Endoscopic clips achieve gastrointestinal hemostasis by clamping the vessel and/or approximating the edges of the lesion, producing mechanical compression without causing tissue injury.[2, 3]

Gastrointestinal bleeding (GIB) is one of the major causes of emergency hospital admission. In the United States, GIB accounted for more than 500,000 hospitalizations and consumed nearly US$5 billion in 2014.[4] GIB is usually categorized according to its anatomic location as either upper GIB (UGIB) or lower GIB (LGIB). Acute UGIB may originate in the esophagus, stomach, and duodenum. The common causes of acute UGIB are peptic ulcer disease including from the use of aspirin and other non-steroidal anti-inflammatory drugs, variceal hemorrhage, Mallory-Weiss tear and neoplasms including gastric cancers. Other relatively common causes include esophagitis, erosive gastritis/duodenitis, vascular ectasias and Dieulafoy's lesion.[5] Among 16%-20% of acute UGIB cases, more than one endoscopic diagnosis may be identified as the cause of GIB. Acute UGIB is a common condition worldwide that has an estimated annual incidence of 40-150 cases per 100,000 population, frequently leads to hospital admission, and has significant associated morbidity and mortality, especially in the elderly.[6] LGIB is defined as bleeding that emanates from a source distal to the ligament of Treitz. LGIB is approximately one-fifth as common as UGIB and accounts for approximately 20 to 30 hospitalizations per 100,000 adults per year. The incidence of LGIB increases substantially with age, presumably due to the high incidence of diverticulosis and vascular disease in this group. Prognosis in LGIB varies and given that most acute LGIB is self-limited, outcomes are typically favorable. However, the mortality associated with LGIB is generally considered to be less than 5% and when it occurs, is often a result of comorbid condition.[7]

UGIB usually presents with hematemesis and/or melena. Hematochezia usually indicates bleeding from the lower GI tract but can occasionally be the presentation for a briskly bleeding upper gastrointestinal source. Variceal hemorrhage is life threatening and should be a major consideration in diagnosis as it accounts for up to 30% of all cases of acute UGIB and up to 90% in patients with liver cirrhosis. LGIB classically presents with hematochezia, however bleeding from the right colon or the small intestine can present with melena. Bleeding from the left side of the colon tends to present bright red in color, whereas bleeding from the right side of the colon often appears dark or maroon-colored and may be mixed with stool.[5]

Following the publication of Hayashi et al, Binmoeller KF et al popularized the endoclip use in 1993 by conducting an uncontrolled study to evaluate performance of an improved metallic clip (Olympus hemoclip) for the endoscopic treatment of nonvariceal GIB.[8] Initial designs were cumbersome and performed inconsistently. Improvements appeared in the mid-1990s from the Olympus Company with the introduction of a reloadable clip. It was reusable rotatable device that required manually reloading a disposable clip onto a small hook at the end of a metal cable running through a plastic sheath. Followed by the pre-loaded QuickClip in 2002

and rotatable QuickClip2 in 2005. The preloaded version is easier and faster to use, especially in the setting of a bleeding lesion. Cook's TriClip and Boston Scientific's Resolution clip both were launched in 2003. At the end of 2010, a new type of clip, developed by Ovesco Endoscopy AG as an over-the-scope-clip device and commonly known as the bear claw, was introduced. Its design was fundamentally different from through-the-scope devices in that the clip is held on the outside of the tip of the endoscope until it is released, by a deployment much like a band-ligation handle.[9, 10] A new clip by Cook Medical was introduced on a limited basis in the United States in 2011. The Instinct Endoscopic Hemoclip has similarities and differences from its predecessors. It has two arms with anchoring teeth and nitinol strips for added strength, controlled 360-degree bidirectional rotation, no plastic sheath, can be opened and closed multiple times and has a very simple, one-directional deployment mechanism. Resolution 360™ Clip was launched by Boston Scientific Corporation, and CE marked in December 2016 with the features such as controlled 360-degree bidirectional rotation, radiopacity and MR conditional.

This overtime improvement in design and performance of endoclip devices resulted in use of hemostatic clips for variety of GIB conditions such as prevention of bleeding from ulcers[11], Mallory Weiss tears [12], Dieulafoy's lesion[13], polypectomy sites[14], varices[15-17], and diverticulae[18]; to close mucosal defects resulting from endoscopic mucosal resection[19], hemostasis of GI fistula[20]; and perforations of the esophagus[21], stomach[22], and colon[23]. Clips have also been used to secure feeding tubes[24], esophageal stents, and manometry catheters to the GI wall. Endoscopic clipping using the currently available devices appears effective and safe.[25-33]

4.2. *Study Rationale*

The MANTIS Clip is designed to be delivered Through-The-Scope (TTS) and has features intended to optimize ability to close mucosal/submucosal defects by anchoring the device, mobilizing the tissue, and approximating defect edges for secure closure. This clinical study aims to document in a prospective manner the use of the MANTIS TTS clip and the impact of its enhanced capabilities when used for hemostasis, closure, anchoring and marking. Compared to prior endoscopic clips in the Resolution 360 Platform the MANTIS™ clip has newly designed jaws which have increased jaw thickness and modified teeth geometry aimed to provide enhanced tissue grasping capabilities.

This study will prospectively document the performance of the MANTIS clip when used per standard of practice. It is designed to be a multicenter study to assure broad representation of use of the MANTIS clip.

5. Device Description

5.1. *Device Under Study*

The MANTIS™ clip, which is manufactured by Boston Scientific Corporation is a Through-The-Scope (TTS) device that leverages all features and advantages on the delivery system and the deployment system from the Resolution 360 product family.

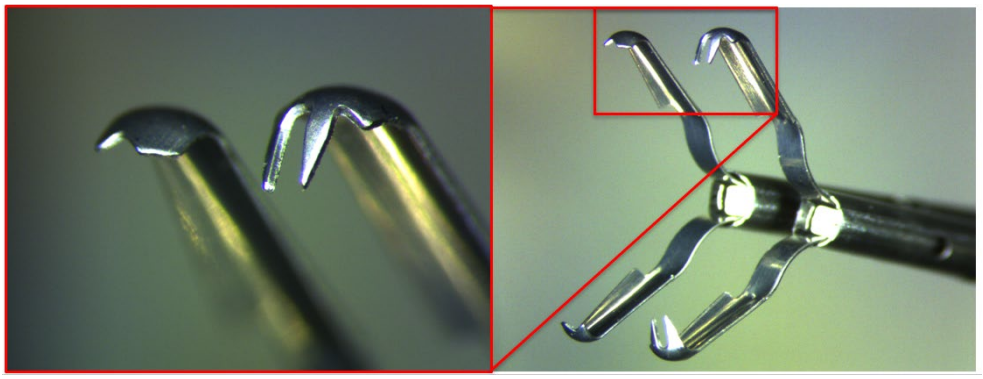
The MANTIS Clip is indicated for clip placement within the Gastrointestinal (GI) tract for the purpose of Endoscopic marking, Hemostasis for: Mucosal/sub-mucosal defects < 3 cm, Bleeding ulcers, Arteries < 2 mm, Polyps < 1.5 cm in diameter, Diverticula in the colon, Prophylactic clipping to reduce the risk of delayed bleeding post lesion resection, Anchoring to affix jejunal feeding tubes to the wall of the small bowel, and as a supplementary method, closure of GI tract luminal perforations < 20 mm that can be treated conservatively.

The MANTIS clip consists of a radiopaque, single-use clip with an 11mm clip opening, pre-loaded on a flexible, rotatable delivery system. The clip is designed to be compatible with forward viewing endoscopes with working channels equal to or greater than 2.8 mm.

The radiopaque MANTIS clip is engineered to enable opening and closing no more than five times prior to deployment, aiding in repositioning of the clip at the lesion site. Re-opening, closing and rotation capability may be limited by clinical circumstances and patient anatomy, among other factors.

Study devices are labeled on the box and inner pouch and include information not limited to name of legal manufacturer, device name and dimensions, lot number and expiration date. Device labeling will be provided in local language(s) as per national regulations. For a detailed description of each device, please reference the Instructions for Use (IFU) included in each device package where commercially available or the Investigator Brochure (IB) for countries where the study device is not approved.

Figure 1. Jaw geometry comparison (full and augmented view) Resolution 360 (left) vs MANTIS™ clip (Right)



6. Study Objectives

Initial Cohort:
To document performance of the MANTIS™ Clip in all indications for endoscopic clipping.

Continued Enrollment Cohort:

To evaluate the procedural and clinical merit in consecutive cases in which at least one MANTIS clip is selected, of specific attributes of the MANTIS™ Clips, including but not limited to the ability of this new endoscopic clipping device:

- to provide prophylaxis to reduce the risk of delayed bleeding post lesion resection
- to close post mucosal resections/polypectomy ulcers, post submucosal dissection ulcers, or mucosal incisions made in conjunction with endoscopic myotomy procedures
- to close lumenal perforations, fistulas, or leaks
- to close perforations after full thickness resection of lesions in the gastrointestinal (GI) tract

7. Study Endpoints

7.1. *Primary effectiveness endpoints*

Initial Cohort

Ability to complete the indication for the use of endoscopic clipping

Continued Enrollment Cohort

Clinical success defined as, where applicable,

- Absence of delayed bleeding
- Sustained closure of the targeted leasion (up to 30 days after the endoscopic clipping procedure)

7.2. *Primary Safety endpoint*

Rate of serious adverse events (SAEs) related to the MANTIS™ clip or the endoscopic study portion of the procedure.
NOTE: If providing hemostasis to an active bleeding in Group A requires possible additional hemostasis after the index study procedure for management of bleeding SAEs within 7 days of the index study procedure, then such bleeding SAEs are not counted for the Primary Safety Endpoint.

Additional endpoints:

- Technical success at placement defined as ability to deploy the endoscopic clips in satisfactory position.
- Ability to anchor device, mobilize the tissue, and approximate defect edges for a secured closure.
- Post procedural bleeding, defined as a severe bleeding event that required hospitalization, a blood transfusion (>5 units) , or another invasive intervention (angiographic or surgical) within 30 days after completion of the study clip placement procedure.

- For active bleeding hemostasis cases only
    - Rate of patients requiring additional modalities of hemostasis.
    - Report of hemostasis of active bleeding 7 days after the index study procedure, and/or with additional clipping procedures to provide hemostasis of continued or recurrent bleeding within 7 days of the index study procedure

8. Study Design

Prospective, multi-center, multi-national, open label, consecutive enrollment. The population will be split up into 5 groups, namely:

- Group A: Hemostasis
- Group B: Closure
- Group C: Anchoring
- Group D: Endoscopic Marking
- Group E: Other

8.1 Scale and Duration

Scope of the series:

- **Initial Cohort:**
    - Up to 50 cases
- **Continued Enrollment Cohort:**
    - Up to 240 cases not including Initial Cohort
- Up to 15 sites

The study duration for each subject is expected to be approximately 1 month. Enrollment is expected to be completed in approximately 18 months per cohort.

Study visits:

- Screening/Enrollment and Baseline: Informed consent process, including informed consent signature date
- Procedure
- 30-day follow-up Telephone Interview

8.2 Justification for the Study Design

The study is designed to demonstrate that physicians are able to complete standard of care procedures using of a new endoscopic clipping device when used for hemostasis, closure, anchoring and marking.

9 Subject Selection

9.1 Inclusion Criteria

Subjects who meet all of the following criteria (see Table 9.1-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.2) is met.

Table 9.1-1: Inclusion Criteria

Inclusion Criteria	1. Subject indicated for endoscopic clipping per local standard of practice. 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study NOTE: Hemostasis and closure can be needed in the setting of complications such as perforations or acute bleeding that are typically rare and sometimes emergent. In such circumstances consenting the patient before the procedure is not feasible and consent shall be obtained from the patient after the procedure but before any study data is collected.

9.2 Exclusion Criteria

Subjects who meet any one of the following criteria (Table 9.2-1) cannot be included in this study or will be excluded from this clinical study. No vulnerable populations will be enrolled in this study per the local standard of care at the institution/IRB.

Table 9.2-1: Exclusion Criteria

Exclusion Criteria	1. Subjects who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor 2. Subjects who the investigator deems at risk for study device or procedure related complications per the Instructions for Use (IFU) where commercially available or the Investigator Brochure (IB) for countries where the study device is not approved.

10 Subject Accountability

10.1 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) system 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.

10.2 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.

10.3 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.

10.4 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.)

11 Study Methods

11.1 Data Collection

The data collection schedule is shown in Table 10-1.1.

Table 10-1.1: Data Collection Schedule

Procedure/Assessment	Screening	Baseline	Study Procedure	30 Days (± 5 days) Follow Up
Informed consent process, including informed consent signature date	X			
Demographics, Medical History		X		
Procedure			X	
Device Deficiency Assessment			X	X
Adverse Event Assessment			X	X
End of Study			X	X

X=required

11.2 Study Candidate Screening

No study-specific data will be collected until after the subject has signed an Informed Consent Form (ICF). A Screen Failure/Enrollment Log will be maintained in the EDC system by the center to document select information about candidates who signed consent.

11.3 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.

11.4 Informed Consent

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

11.5 Baseline

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

11.6 Study Procedure

During the index procedure, the endoscopist or designated member of study staff will record: Clip information, and any activities completed or attempted during the procedure, regardless of original intent. Any ensuing adverse or device events will be recorded and reported.

11.7 30 Day (± 5 days) Telephone Interview Assessments

All enrolled subjects will be 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.

11.8 Study Completion

Subjects will be followed for 30 days (± 5 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.) and a Protocol Deviation form will be completed.

11.9 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.

12 Statistical Considerations

12.1 Endpoints

12.1.1 Primary Endpoints

12.1.1.1 Primary Effectiveness Endpoint:

Initial Cohort

Ability to complete the indication for the use of endoscopic clipping

Continued Enrollment Cohort

Clinical success defined as, where applicable,

- Absence of delayed bleeding
- Sustained closure of the targeted leasion

up to 30 days after the endoscopic clipping procedure

12.1.1.2 Primary Safety Endpoint:

Rate of serious adverse events (SAEs) related to the MANTIS™ clip or the endoscopic study portion of the procedure.

NOTE: If providing hemostasis to an active bleeding in Group A requires possible additional hemostasis after the index study procedure for management of bleeding SAEs within 7 days

of the index study procedure, then such bleeding SAEs are not counted for the Primary Safety Endpoint.

12.1.1.3 Hypotheses and Sample Size Justification

Initial cohort:

No hypotheses will be tested, only observational, summary statistics will be performed.

Continued enrollment cohort:

A systematic literature search was conducted on PubMed and Embase from January 1, 2016 to September 2022 to identify studies that evaluated the safety and effectiveness of an endoscopic clip device for closing various types of incisions, lesions, or defects in the gastrointestinal tract resulting from endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), polypectomy of polyps or adenomas, perforations, and fistulas. The primary objective of the search strategy was to identify studies that examined the closure of large mucosal defects by endoscopic clipping. Twenty studies were identified through a post-market literature review activity were included to the analysis with a total of 2257 patients.

We hypothesize that the **clinical success rate** of MANTIS™ clip will be greater than the performance goal of **89%** with expected clinical success rate of **94%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect:

- 20 publications representing 2257 patients: 93.9% (95% CI 88.6%-97.6%)

We hypothesize that the **serious adverse event (SAE) rate** related to MANTIS™ clip or the endoscopic clipping portion of the procedure will be lower than the performance goal of **19%** with expected related SAE rate of **10%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect:

- 9 publications representing 1019 patients: 9.8% (95% CI 3.7%-18.5%)

12.2 Using an exact test with an alpha level of 0.05, 217 subjects enrolled will provide at least 80% power for the performance and safety metrics. An additional 10% will be added for attrition, so total enrollment will be 240 subjects. These tests will only be performed for cases in the continued enrollment cohort General Statistical Methods

12.2.1 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 8.1 and Section 8.2 will be considered screen failures and excluded from the study.

Intent-to-Treat Cohort (ITT)

This cohort consists of enrolled subjects who are planned to have a MANTIS™ clip placed regardless if they met I/E criteria.

Treated Cohort

The treated cohort is a subset of the ITT subjects who have a MANTIS™ clip placed.

12.3 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).

12.3.1 Other Endpoints/Measurements

- Technical success at placement defined as ability to deploy the endoscopic clips in satisfactory position.
- Post procedural bleeding, defined as a severe bleeding event that required hospitalization, a blood transfusion (>5 units), or another invasive intervention (angiographic or surgery) within 30 days after the study clip placement.
- For active bleeding hemostasis cases only
    - Rate of patients requiring additional modalities of hemostasis.
    - Report of hemostasis of active bleeding 7 days after the index study procedure, defined as ability to stop the active bleed at the time of the study procedure and/or with additional clipping procedures to provide hemostasis of continued or recurrent bleeding within 7 days of the index study procedure

12.3.2 Baseline Data

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

12.3.3 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.

12.3.4 Post-Procedure Data

Post-procedure information will be collected as detailed in Table 11-1.1 Data Collection 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.

12.3.5 Interim Analyses

12.3.6 There will be no formal interim analyses performed. irlSubgroup Analyses

Stratified analyses will include tabulating the primary and select secondary endpoints by gender, polyp location, polyp size, or use of periprocedural antithrombotic medications.

12.3.7 Justification of Pooling

The analyses will be performed using data pooled across institutions. An assessment of the poolability of patients across sites will be made by fitting generalized linear models with site as the factor of interest and the primary endpoints as the outcome variable.

12.3.8 Multivariable Analyses

Multivariable analyses may be performed to assess the effect of potential predictors on the primary endpoint.

12.3.9 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses.

13 Data Management

13.1 Data Collection, Processing, and Review

Subject data will be recorded in a 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 and will be issued to the site for appropriate response. Site staff will be responsible for resolving queries in the database.

Access to the clinical database will be changed to “Read only” after 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 the closeout activities are completed a request to IT is submitted to have the “Database Locked” or Decommissioned and database access revoked.

13.2 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.

13.3 Technical Source Forms

A Technical Source Form (TSF) may be developed by Boston Scientific or by the investigational site to capture protocol required data elements that are not duplicated in any other source documents. This form is to be used by the study sites as a source document. A Boston Scientific representative may complete the TSF at the request of the Principal Investigator. The TSF will be reviewed and signed for approval by the Principal Investigator or his/her designee at the end of each procedure.

14 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 using EDC. Sites may also be required to report deviations to the IRB/EC/REB, and the 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.

The sponsor will not approve protocol waivers.

15 Device Accountability

15.1 Investigationally-Labelled Devices

This section applies to items being distributed with investigational use indication on the device packaging.

For investigationally-labelled items, the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g. temperature, humidity, etc., as applicable)
- Maintain accurate and timely Device Accountability Records, providing copies to Sponsor upon request. Such records shall include the following content, at minimum:
    - Identification, quantity and expiry date (if applicable) of each item received. Include batch number, serial number or unique code, as applicable;
    - Date of receipt; open/use, and end disposition of each item and name of person(s) who performed those activities;
    - Subject identification / subject exposure to device and, if applicable, the date on which the item was returned/explanted from subject, if applicable;
    - Reason for repair, disposal or return to Sponsor (e.g. advisory/recall, sponsor request, other
- Return or dispose of items as directed by Sponsor
    - Complaint / deficiency related items should be returned whenever possible
    - Opened non-complaint / non-deficiency related items should be returned or disposed as directed by Sponsor
    - Unopened and reusable items should be returned to Sponsor or designee upon Sponsor request and in the condition in which they were provided, reasonable wear and tear excepted.

16 Compliance

16.1 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, Japan Medical Device 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.

16.2 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.
- In the event where commercial product is provided to sites for free, 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 for use or investigator brochure.
- 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/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 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.

16.2.1 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.

16.3 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. 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.

16.4 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.

16.4.1 Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include 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 during implant or follow-up, 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 instruction 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

16.5 Insurance

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

17 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.

18 Potential Risks and Benefits

18.1 Instructions for Use or Investigator Brochure

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

18.2 Risks associated with Participation in the Clinical Study

Risk associated with participation in the Clinical Study are similar to that of use of an endoscopic clipping device when used for hemostasis, closure, anchoring or marking.

18.3 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.

18.4 Anticipated Benefits

The safety and performance of the BSC endoscopic hemostatic clip devices have been established through studies reported in the literature and the market experience data. Medical science and future patients may benefit from this study.

18.5 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.

19 Safety Reporting

19.1 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 related to the Study Device and/or Study Procedure
- All Serious Adverse Events including those related to the Study Device and/or Study Procedure
- All events with a Fatal Outcome
- All 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, whether prior to, 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 19.2-1 for AE definitions).

Refer to Instructions for Use or Investigator Brochure for the known risks associated with the device(s).

19.2 Definitions and Classification

Adverse event definitions are provided in Table 19.2-1. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 19.2-1: 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 the 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.
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, users 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.

Table 19.2-1: Safety Definitions

Term	Definition
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.
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 device under study.
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)

Table 19.2-1: Safety Definitions

Term	Definition
	• 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 another SAE criteria.
The following definitions will be used to determine the severity criteria for bleeding events.	
Bleeding Severity Criteria Ref: ASGE Guidelines (Adverse Events associated with ERCP 2017) Cotton et al[6]	**Mild Bleeding:** • Clinical (i.e. not just endoscopic) evidence of bleeding • Hemoglobin drop <3 g/dL and no need for transfusion **Moderate Bleeding:** • Transfusion (≤ 4 units) • No angiographic intervention or surgery **Severe Bleeding:** • Transfusion ≥ 5 units or intervention (angiographic or surgical)
The following definitions will be used to determine the severity criteria for perforation events	
Perforation Severity Criteria Ref: Odom, S. (2022, May). Overview of gastrointestinal tract perforation. *UpToDate.*	Perforation: A full thickness hole in the wall of the Gastrointestinal Tract. **Limited**: • Micro perforation, minor or no medical intervention **Moderate**: • Medical Intervention (Nothing by mouth, antibiotics, etc) **Severe:** • Surgical intervention
The following definitions will be used to describe the procedures performed in this study.	
Procedures:	**Endoscopic Procedure:** The procedure that will be done for hemostasis, closure, anchoring or marking in the gastrointestinal tract as a part of this study. **Study Procedure:** The portion of the endoscopic procedure where the study device is used for hemostasis, closure, anchoring or marking.

Table 19.2-1: Safety Definitions

Term	Definition
The following definitions will be used to describe the severity level of adverse events.	
Severity Level:	**Severe:** Significant illness or injury that results in permanent damage to a body structure or permanent impairment of a body function, or necessitates medical or surgical intervention to prevent permanent damage to a body structure or permanent impairment of a body function; immediate or substantial risk of death **Moderate:** Significant illness or injury that is temporary or reversible with moderate medical or surgical interventions **Mild:** No adverse health consequence nor clinically significant health consequence; the event is transient, minor illness or injury that is temporary or reversible with minor or no medical intervention

19.3 Relationship to Study Device(s) and/or Study Procedure

The Investigator must assess the relationship of the reportable AE to the study device(s), and/or study procedure. See criteria in Table 19.3 1:

Table 19.3 1: 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; - 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, 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 the 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.

19.4 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in below

Table 19.4 1: 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.	• Upon request of sponsor.

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)
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 after becoming aware of the event or as per local/regional regulations. • Reporting required through end of study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event as requested.	• 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. • Reporting required through the end of the study	• 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
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• 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	Complete Device Deficiency CRF 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.	• Upon request of sponsor	• Upon request of sponsor

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)
been less fortunate is considered a reportable event.			
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 • Upon request of sponsor	• 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.		

19.5 Device Deficiencies

Device deficiencies 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 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.

19.6 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/USADEs and SAEs as required by local/regional regulations.

20 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. NOTE: Hemostasis and closure can be needed in the setting of complications such as perforations or acute bleeding that are typically rare and sometimes emergent. In such circumstances consenting the patient before the procedure is not feasible and consent shall be obtained from the patient after the procedure but before any study data is collected.

The Principal Investigator may enroll a subject without obtaining the informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled.

- The prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation.
- There is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the device is used.
- Anticipated risks are outweighed by the potential benefits of applying the device.
- The legally authorized representative cannot be promptly reached and informed.

In either situation, arrangements shall be made to inform the subject or legally authorized representative as soon as possible about a) all aspects of the clinical study and b) the subject's inclusion in the clinical study.]

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.

21 Committees

21.1 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.

22 Suspension or Termination

22.1 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.

22.1.1 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.

22.2 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.

22.3 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 devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4 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 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.

23 Study Registration and Results

23.1 Study Registration

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

23.2 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.

23.3 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/).

24 Reimbursement and Compensation for Subjects

24.1 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.

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26 Abbreviations and Definitions

26.1 Abbreviations

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
CA	Competent Authority
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
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

26.2 Definitions

Definitions are shown in Table 26.2-1.

Table 26.2-1: Definitions

Term	Definition
Source data *Ref: ISO 14155*	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation Note 1 to entry: This includes source data initially recorded in an electronic format.
Source document *Ref: ISO 14155*	Original or certified copy of printed, optical or electronic document containing source data.
Vulnerable Subject *Ref: ISO 14155*	Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response