Prospective, Multi-center, Randomized Controlled Study Comparing Endoscopic Clearance of Non-Complex Biliary Stones Using Fluoroscopy/Radiation-Free Direct Solitary Cholangioscopy (DSC) to Standard of Care Endoscopic Retrograde Cholangiography (ERC)

Non-Complex Biliary Stones DSC vs ERC RCT
CLINICAL INVESTIGATION PLAN

E7131

Sponsored By

Boston Scientific Corporation
300 Boston Scientific Way
Marlborough, MA 01752-1234
USA

Boston Scientific International SA,
Le Val Saint-Quentin
2 Rue René Caudron
78960 Voisins le
Bretonneux, France

Boston Scientific India Private Ltd.
Building No. 5, Tower A 8th Floor
Cyber Terraces
DLF Cyber City-Phase 3
Gurgaon 12002, India

Contact Information

Role	Contact
Clinical Contact	**Pooja G. Goswamy** Clinical Project Manager Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752-1234 USA Phone: +1 (508) 683-4335 Email: Pooja.Goswamy@bsci.com **Raquel Mazariegos** Clinical Project Specialist Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752-1234 USA Phone: +1 (508) 683-4174 e-mail: Raquel.Mazariegos@bsci.com
Principal Investigator	**Subhas Banerjee, MD** Stanford University Medical Center 300 Pasteur Drive, H0262A MC: 5244 Stanford, CA 94305 USA

Original Release: November 15, 2017

Current Version: June 12, 2018

Protocol Synopsis

E7131 – Non-Complex Biliary Stones DSC vs ERC RCT	
Study Objective	To prospectively compare non-complex biliary stone clearance using fluoroscopy/radiation-free direct solitary cholangioscopy (DSC) utilizing the SpyGlass™ system with non-complex biliary stone clearance using standard endoscopic retrograde cholangiography (ERC).
Indication(s) for Use	• ***SpyGlass™ DS Digital Controller*** is intended to provide illumination and receive, process, and output images from the SpyScope™ DS Access and Delivery Catheter for diagnostic and therapeutic applications during endoscopic procedures in the pancreatico-biliary system including the hepatic ducts. • ***SpyScope™ DS Access and Delivery Catheter*** is intended to provide direct visualization and to guide both optical and accessory devices for diagnostic and therapeutic applications during endoscopic procedures in the pancreatico-biliary system including the hepatic ducts. • *The following devices will be available upon commercialization:* o ***SpyScope™ DS II Access and Delivery Catheter*** is intended to provide direct visualization and to guide both optical and accessory devices for diagnostic and therapeutic applications during endoscopic procedures in the pancreatico-biliary system including the hepatic ducts. o ***SpyGlass™ Retrieval Basket*** is indicated for the endoscopic removal of stones, stone fragments, or foreign bodies in the pancreaticobiliary system.
Device	SpyGlass™ Digital System
Study Design	• Prospective • Consecutive cases • Multi-center • Randomized 1:1 ratio: o Group A (ERC arm): Clearance of bile duct stones using standard-of-practice ERCP techniques o Group B (DSC arm): Clearance of bile duct stones using DSC techniques

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	○ Block-randomization by site • Non-inferiority hypothesis • Validation of stone clearance by ERC in DSC arm and by DSC in ERC arm.
Number of Subjects	• 250 subjects • An additional 5 Roll-in cases. Each participating endoscopist at each of the participating centers must perform 5 Roll-in cases. These roll-in cases will not count towards the enrollment ceiling of 250 cases. • Procedures to be conducted only by the Principal Investigator. Sub-Investigators will be authorized to do study procedures only on an exception basis. Such exception may be granted by the Sponsor in consultation with the Principal Investigator of the site and Lead Principal Investigator to the study.
Number of Sites	Up to 15 global sites
Primary Endpoint	Complete stone clearance by extraction of bile duct stones from the common bile duct (CBD) into duodenum as determined by fluoroscopy free cholangioscopy in the DSC arm and by cholangiography in the ERC arm.
Secondary Endpoints	1. Evaluation of all serious adverse events (SAEs) including all deaths (related and unrelated), severity, onset, time to resolution related to the DSC devices and/or procedure and/or the ERC procedure through 30 days post procedure. 2. Radiation exposure to the patient (total fluoroscopy time, total radiation dose, Dose Area Product (DAP), effective dose), from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm. 3. Duration of procedure defined as time from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm.
Follow-up Schedule	Telephone follow-up during the following post-procedure intervals: • 24 hours • 7 days • 30 days
Study duration	Approximately 2 years

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Inclusion Criteria	1. 18 years or older 2. Abdominal pain consistent with choledocholithiasis (procedure possible within 72 hours of onset of symptoms and imaging suggesting choledocholithiasis, contingent on persistent abdominal pain) 3. Abnormal LFTs 4. Non-complex biliary stone disease, defined as 5 or fewer stones in the common bile or common hepatic duct with largest stone no larger than 10 mm in size. If stones not seen on imaging (US, CT) the bile duct diameter should be ≤12 mm* * Given the poor sensitivity (approximately 20%) for biliary stones of CT and US, the diameter of the dilated CBD is used as a surrogate for largest stone diameter 5. Availability of non-invasive imaging to determine the diameter of the bile duct and number and size of bile duct stones if visible on imaging a. If probability of stones is high per investigator assessment based on ASGE criteria, any standard of practice imaging modality (eg. abdominal US) is acceptable. b. If the probability of stones is either intermediate or low per investigator assessment based on ASGE criteria, MRCP or EUS imaging is required to confirm presence of stones. 6. Willing and able to comply with the study procedures and provide written informed consent to participate in the study
Exclusion Criteria	1. Potentially vulnerable subjects, including but not limited to pregnant women and subjects in whom an endoscopic procedure is contraindicated 2. Location of the stones in intrahepatic ducts, cystic duct or proximal to strictures 3. Bile duct stricture noted distal to stone on MRCP, which would make extraction without lithotripsy impossible 4. Ongoing cholangitis at time of randomization, manifested by fever with tachycardia and hypotension or evidence of pus at the ampulla 5. Patients with prior biliary sphincterotomy

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	6. Patients with Primary Sclerosing Cholangitis (PSC) 7. Acute pancreatitis, defined as abdominal pain and serum concentration of pancreatic enzymes [lipase (required), amylase (optional)] three or more times the upper limit of normal 8. Surgically altered gastro-duodenal luminal anatomy other than prior Billroth I reconstruction, as these would be anticipated to lead to more complicated procedures 9. Coagulopathy or ongoing need for anti-coagulation
Statistics	• Preliminary DSC-guided stone clearance rate was established in a Pilot study[1] and found to be comparable to that of ERC-guided stone clearance. • Eight relevant peer-reviewed publications[2-9] reporting on ERC-guided biliary stone clearance rates, representing 2721 patients were analyzed. A meta-analysis was conducted of the biliary stone clearance rates, yielding a point estimate of 90% with a 95% CI of [85%, 94%] (see Forest plot below). • Based on the two observations provided above, we hypothesize that the DSC-guided stone clearance rate is non-inferior to that of the ERC-guided stone clearance rate. We assume a DSC-guided and ERC-guided stone clearance rate of 90% and use a 10% non-inferiority margin for the sample size calculation provided below. The 10% non-inferiority margin is based on the fact that in the references used for the meta-analysis[2-9] stone clearance rates above 80% eliminate the lowest performing publications. **Test Method:** An exact test will be used to test the one-sided hypothesis of non-inferiority of the DSC-guided vs ERC-guided stone clearance rates. **Sample Size:** To detect non-inferiority of the clearance rate in DSC arm compared to the ERC arm with 80% power and one-sided alpha=0.05, a sample of 250 total is needed.

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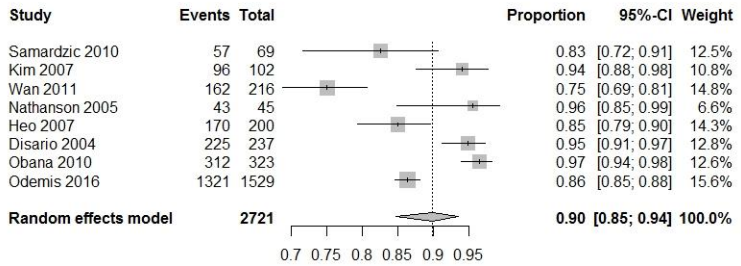

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1. Introduction

Prior to the advent of flexible endoscopy, imaging of the gastrointestinal lumen was performed predominantly using barium contrast studies. Over the last few decades, contrast studies for the upper and lower GI tract (barium swallow/barium meal) have largely been replaced by upper gastrointestinal endoscopy and colonoscopy. Similarly, balloon assisted enteroscopy and capsule endoscopy are replacing small bowel follow-through contrast studies for small bowel evaluation. This shift from radiological to endoscopic evaluation was driven by the many advantages of endoscopy, including the ability to provide more accurate real-time imaging with fewer false negative and false positive results, the ability to obtain biopsies to confirm visual impressions, and finally, the ability to deliver therapeutic interventions in the same procedure.

The bile and pancreatic ducts remain the "final frontiers" in the GI lumen where endoscopy is not yet the primary modality for diagnosis and therapy. Here, a hybrid endoscopic/radiological procedure, endoscopic retrograde cholangio-pancreatography (ERCP), remains the predominant diagnostic and therapeutic modality. Given the inevitable evolution of technology, it is possible in the future, that as with other GI luminal organs, direct endoscopic evaluation of the bile duct with cholangioscopy may replace cholangiography for the evaluation and management of at least some kinds of biliary disease. Non-complex biliary stone disease represents a potential such disease process, suitable for study. Development of a fluoroscopy-free cholangioscopy based approach to bile duct disease is desirable for several reasons that are discussed below.

From the viewpoint of endoscopy unit efficiency and safety, the requirement for fluoroscopy during ERCP creates several issues. A separate fluoroscopy room is necessary within the endoscopy unit to perform ERCP, which requires additional capital investment. The fluoroscopy room is typically busy and is often a bottleneck at high volume ERCP centers. A full schedule in the fluoroscopy room will result in delays for additional patients needing ERCP, even if other endoscopy rooms have availability, thereby impacting endoscopy unit efficiency and the timely delivery of patient care. Additionally, low volume ERCP centers often do not have a dedicated fluoroscopy room within the endoscopy unit and the endoscopist has to await availability of an open room within the Radiology Department.

If fluoroscopy-free cholangioscopy based clearance of uncomplicated common bile duct (CBD) stones becomes a safe and broadly accepted methodology, then one might envision that non-complex CBD stone removal might be performed in non-fluoroscopy endoscopy rooms. This would alleviate the scheduling delays inherent in requiring a specialized fluoroscopy room for the procedures. Additionally, in the future, one might envisage this procedure becoming possible in bedside settings in the Emergency Department, for patients presenting with symptomatic choledocholithiasis. A rapid procedure performed in the Emergency Department would accelerate the delivery of therapeutic care to the patient, while avoiding the need for admission, thereby resulting in cost savings. Similarly, bedside cholangioscopy based procedures performed in Intensive Care Unit settings would avoid the need for transfer of gravely ill patients to the endoscopy unit, thereby enhancing patient safety.

An additional concern with ERCP is that patients and endoscopy room personnel are exposed to ionizing radiation, which some consider to carry deleterious health consequences. The U.S per capita annual effective radiation dose from radiological procedures has increased six-fold over the last three decades and it is estimated that up to 2% of all cancers in the U.S. today may be attributable to medical radiation.[10] Therefore, in recent years, there has been growing interest in monitoring and minimizing radiation exposure to patients. The World Gastroenterology Organization, the American Society for Gastrointestinal Endoscopy, and the International Atomic Energy Agency together developed guidelines in 2009 for minimizing radiation exposure to patients and endoscopy room staff during endoscopy.[12] The U.S. Food and Drug Administration has published a White Paper entitled 'Initiative to Reduce Unnecessary Radiation Exposure From Medical Imaging'.[11] The European Society of Gastrointestinal Endoscopy has also published guidelines for radiation protection in digestive endoscopy.[13] Finally, the Stanford Endoscopy Research Group has done pioneering work in the field of minimizing patient radiation exposure during ERCP.[14,15,16] However, additional novel methods to further reduce or even eliminate radiation exposure are needed.

Radiation-free cholangioscopy based biliary procedures offer one such opportunity. Although previously predominantly utilized as a complementary technique to ERCP, digital cholangioscopy has now evolved sufficiently that it may finally offer a viable, robust, and purely endoscopic alternative to ERCP, allowing liberation from the fluoroscopy room and from associated radiation exposure. The platform is small and readily deployable in non-fluoroscopy rooms which are typically smaller.

In light of the current interests in minimizing patient radiation exposure during ERCP, eventually lowering healthcare costs and maximizing endoscopy room efficiency, we hypothesize that the Spyglass cholangioscopy system may be able to provide a radiation-free alternative to ERCP in patients with non-complex choledocholithiasis. We propose that in patients with non-complex choledocholithiasis who have undergone prior non-invasive imaging (US/MRCP/CT) that clearly defines the diameter of the bile duct and underlying pathology, the objectives of standard-of-care ERCP may be achievable with cholangioscopy alone, without the need for fluoroscopy.

Radiation-free biliary procedures are already sometimes performed in pregnant women with choledocholithiasis or ICU patients who cannot travel, utilizing endoscopic ultrasound (EUS) to provide information regarding bile duct diameter and the number of stones present in the bile duct. A cholangioscopy based approach offers advantages over the EUS guided approach, including ensuring that the guidewire has been advanced into the bile duct and not into the cystic duct, allowing measurement of the distance from the ampulla to the bile duct bifurcation to guide subsequent balloon sweeps, and allowing direct visual confirmation of clearance of all stones from the bile duct. We wish to determine if Spyglass cholangioscopy can reliably facilitate radiation-free stone removal, thereby avoiding the costs of an additional EUS procedure preceding stone extraction.

Proof of concept was demonstrated in two single-arm, consecutive series reflecting experience in 31 patients at Stanford University Medical Center[1] and in 50 patients at King Chulalongkorn Memorial Hospital in Bangkok.[14] Fluoroscopy free CBD clearance of uncomplicated (CBD) stones <15mm in diameter was achieved in 93% and 90% of patients respectively in these two series. Post procedure complications reported in the 81 patients combined include pancreatitis in 4 patients, bleeding in 3 patients, and cholangitis in 1 patient. These series support the feasibility and safety for radiation-free cholangioscopic based management of uncomplicated CBD stones with success and complication rates comparable to those of standard ERCP. The present study aims to expand that concept to a multi-center, multi-national study, comparing fluoroscopy-free endoscopic and cholangioscopic stone clearance to ERCP-guided stone clearance in symptomatic patients with non-complex bile duct stones.

2. Device Description

This study will be conducted using commercially available devices. All devices will be used in accordance with the appropriate *Directions for Use* (DFU).

2.1. *SpyScope™ DS Access and Delivery Catheter*

The SpyScope™ DS Access and Delivery Catheter (SpyScope™ DS Catheter) is a sterile, single-use endoscope that enables access and delivery of accessories to targeted pancreatico-biliary anatomy and displays live video when connected to a SpyGlass DS Digital Controller.

2.2. *SpyGlass™ DS Digital Controller*

The SpyGlass™ DS Digital Controller is an electronic device that: receives video signals from a SpyScope DS Catheter, processes the video signals and outputs video images to a video monitor. The controller also generates and controls the light transmitted to the tip of the SpyScope DS Catheter to illuminate the area of interest within the anatomy. Buttons on the controller's front panel enable you 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 SpyScope DS Catheter to the controller. The controller provides direct visualization of the pancreatico-biliary duct anatomy and enables exploratory and endotherapy procedures.

The following devices will be available for use upon commercialization.

2.3. *SpyScope™ DS II Access and Delivery Catheter*

The SpyScope™ DS II Access and Delivery Catheter is intended to provide direct visualization and to guide both optical and accessory devices for diagnostic and therapeutic applications during endoscopic procedures in the pancreatico-biliary system including the hepatic ducts.

2.4. *SpyGlass™ Retrieval Basket*

The SpyGlass™ Retrieval Basket is indicated for the endoscopic removal of stones, stone fragments, or foreign bodies in the pancreaticobiliary system.

2.5. *Device Labeling*

A copy of the DFU for each product will be included in each device package. The study devices are labeled on the outer packaging of each device. The SpyScope™ Access and Delivery Catheter, SpyScope™ DS II Access and Delivery Catheter, SpyGlass™ Retrieval Basket, and SpyGlass™ DS Digital Controller labels contain the following information:

- Device name
- Device number
- SI units
- Graphical description
- Device diameter, length, channel inside diameter
- Lot number
- Expiration (use before) date or date of manufacture

3. Study Objectives

The objective of this study is to prospectively compare non-complex biliary stone clearance using fluoroscopy/radiation-free direct solitary cholangioscopy (DSC) utilizing the SpyGlass™ system with non-complex biliary stone clearance using standard endoscopic retrograde cholangioscopy (ERC).

4. Study Endpoints

4.1. *Primary Endpoint*

The primary endpoint is complete stone clearance by extraction of bile duct stones from the common bile duct (CBD) into duodenum by fluoroscopy free cholangioscopy in the DSC arm and by cholangiography in the ERC arm.

4.2. *Secondary Endpoint*

The following will be recorded as secondary outcomes during baseline and follow-up procedures:

1. Evaluation of all serious adverse events (SAEs) including all deaths (related and unrelated), severity, onset, time to resolution related to the DSC devices and/or procedure and/or the ERC procedure through 30 days post procedure.
2. Radiation exposure to the patient (total fluoroscopy time, total radiation dose, Dose Area Product (DAP), effective dose), from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm.

3. Duration of procedure defined as time from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm.

5. Study Design

This is a prospective, multi-center, randomized controlled study comparing endoscopic clearance of non-complex biliary stones using fluoroscopy/radiation free direct solitary cholangioscopy (DSC) versus standard of care endoscopic retrograde cholangiography (ERC) at up to 15 global sites.

5.1. *Scale and Duration*

A total of 250 patients will be randomized on a 1:1 ratio. Block randomization through an online database system will be used. Randomization will be stratified by study center. Prior to randomization each participating endoscopist at each of the participating centers must perform up to 5 Roll-in cases. These roll-in cases will not count towards the enrollment ceiling of 250 cases.

The study duration is anticipated to be approximately 2 years, namely 18 months for completion of enrollment of 250 randomized cases, 1 month follow-up per subject, and 3 months for data clean up and final data analysis.

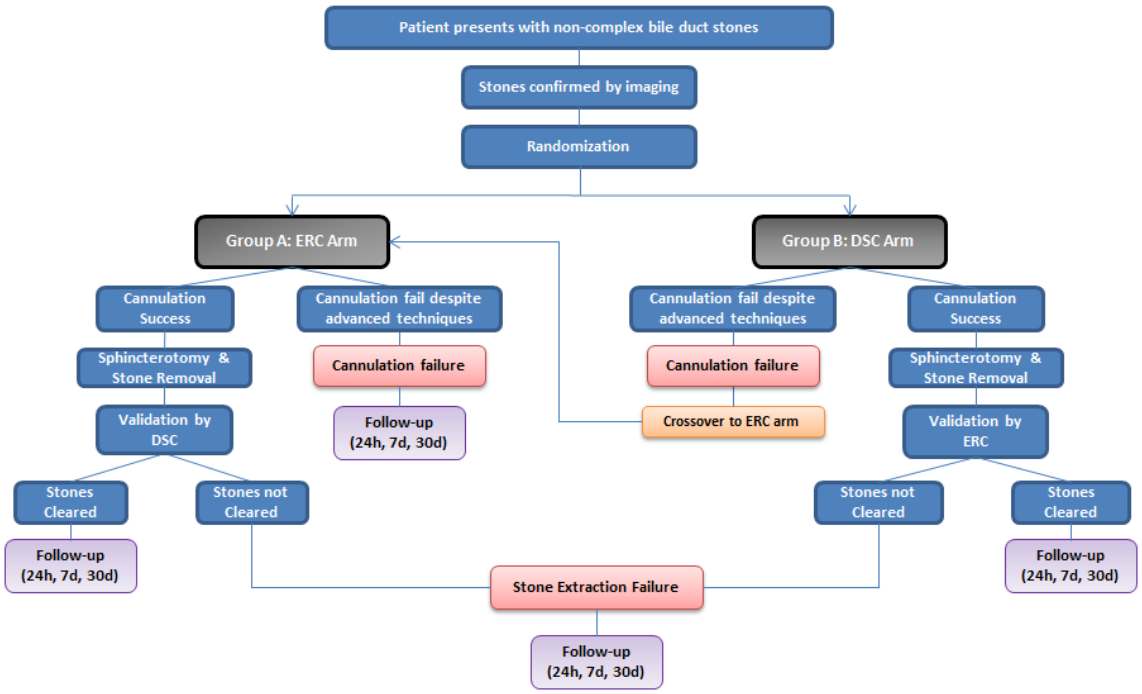

Figure 5.1-1: Non-Complex Biliary Stone DSC vs ERC RCT Study Design

5.2. *Treatment Assignment*

All consecutive patients seen at an investigational site during the enrollment period:

- Presenting with confirmed non-complex bile duct stones

Patients will be screened relative to the Inclusion and Exclusion Criteria provided below. Patients will sign the Informed Consent Form, and then undergo screening examinations. Once Inclusion and Exclusion criteria are met, and presence of non-complex bile duct stone(s) is confirmed by imaging, patients will be randomized to either DSC arm or the ERC arm.

5.3. *Justification for the Study Design*

- During ERCP, patients and staff are exposed to radiation associated with the fluoroscopy. This may increase their lifetime risk of developing cancer along with other harmful radiation effects.
- In 2010, the FDA and the Center for Devices and Radiological Health published an initiative to reduce unnecessary radiation exposure from medical imaging[10].

Cholangioscopy (direct visualization of the bile duct) using the SpyGlass™ DS System and the SpyGlass™ accessories can reduce the duration of radiation exposure and may even eliminate the need for radiation exposure by allowing radiation-free management of non-complex bile duct stones. This will cause a paradigm shift from a hybrid endoscopic-fluoroscopic procedure to a purely endoscopic procedure.

6. Subject Selection

6.1. *Study Population and Eligibility*

All consecutive patients who meet the selection criteria below will be invited for participation in the study. Patients who sign the informed consent form will be considered enrolled. All the patients will have documented biliary obstruction based on the labs and imaging performed as standard of care.

6.2. *Inclusion Criteria*

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 6.3) is met.

1. 18 years or older
2. Abdominal pain consistent with choledocholithiasis (possible procedure within 72 hours of onset of symptoms and imaging suggesting choledocholithiasis, contingent on persistent abdominal pain)
3. Abnormal LFTs

4. Non-complex biliary stone disease, defined as 5 or fewer stones in the common bile or common hepatic duct with largest stone no larger than 10 mm in size. If stones not seen on imaging (US, CT) the bile duct diameter should be ≤12 mm.*

   * Given the poor sensitivity (approximately 20%) for biliary stones of CT and US, the diameter of the dilated CBD is used as a surrogate for largest stone diameter

5. Availability of prior non-invasive imaging to determine the diameter of the bile duct and number and size of bile duct stones if visible on imaging.
   a. If probability of stones is high per investigator assessment based on ASGE criteria, any standard of practice imaging modality (eg. abdominal US) is acceptable. (see Figure 22.3-1, page 49).
   b. If the probability of stones is either intermediate or low per investigator assessment based on ASGE criteria, MRCP or EUS imaging is required to confirm presence of stones. (see Figure 22.3-1, page 49).
6. Willing and able to comply with the study procedures and provide written informed consent to participate in the study.

6.3. *Exclusion Criteria*

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

1. Potentially vulnerable subjects, including but not limited to pregnant women and subjects in whom an endoscopic procedure is contraindicated.
2. Location of the stones in intrahepatic ducts, cystic duct or proximal to strictures
3. Bile duct stricture noted distal to stone on MRCP, which would make extraction without lithotripsy impossible.
4. Ongoing cholangitis at time of randomization, manifested by fever with tachycardia and hypotension or evidence of pus at the ampulla
5. Patients with prior biliary sphincterotomy
6. Patients with Primary Sclerosing Cholangitis (PSC)
7. Acute pancreatitis, defined as abdominal pain and serum concentration of pancreatic enzymes (lipase (required), amylase (optional) three or more times the upper limit of normal.
8. Surgically altered gastro-duodenal luminal anatomy other than prior Billroth I reconstruction, as these would be anticipated to lead to more complicated procedures.
9. Coagulopathy or ongoing need for anti-coagulation

7. Subject Accountability

7.1. *Point of Enrollment*

Patients who are considered for participation into the study but do not provide informed consent or do not meet eligibility criteria are considered screen failures. Screen failures will be tallied at each study site.

In the case it is determined that the patient failed to meet the inclusion/exclusion criteria after the patient has agreed to participate in the study and has signed the informed consent, the study personnel will complete the Screening form as well as the End of Study form and indicate the specific inclusion/exclusion criterion that was not met.

7.2. *Withdrawal*

Subjects will participate in the study voluntarily and may withdraw at any time without prejudice to further treatment. If a subject withdraws from the clinical investigation, the primary reason shall be reported.

All applicable case report forms up to the point of subject withdrawal, including an End of Study form must be completed.

Subjects who are "lost-to-follow-up" should have three documented attempts to contact them prior to completion of the End of Study form. If withdrawal is due to investigator's discretion, the investigator will describe what follow-up activities the investigator is obligated to perform.

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.

8. Study Methods

8.1. *Data Collection*

Data collection will occur according to the Data Collection Schedule shown in Table 8.1-1.

Table 8.1-1: Data Collection Schedule

Procedure/Assessment	Screening	Baseline	Index Procedure	Follow-up Visits			Unscheduled Reintervention
				24 hours Telephone Follow-up	7 Days (± 2 Days) Telephone Follow-up	30 Days (± 10 Days) Telephone Follow-up	
Informed consent, Inclusion/Exclusion Criteria	X						
Demographics		X					

Procedure/Assessment	Screening	Baseline	Index Procedure	Follow-up Visits			Unscheduled Reintervention
				24 hours Telephone Follow-up	7 Days (± 2 Days) Telephone Follow-up	30 Days (± 10 Days) Telephone Follow-up	
Non-Invasive Imaging (Ultrasound, CT or MRCP)		X					
Medical history		X					
Lab Results		X					
Probability of bile duct stone based on ASGE criteria: high, intermediate or low		X					
Need for MRCP or EUS based on intermediate or low ASGE criteria		X					
Procedural details			X				
Post-procedure Follow up				X	X	X	
Biliary Re-interventions				X	X	X	X
Serious Adverse Events assessment			X	X	X	X	

8.2. *Study Candidate Screening*

Patients who present with abdominal symptoms of choledocholithiasis, or who have undergone imaging demonstrating choledocholithiasis as listed in Inclusion Criteria will be screened for trial enrollment. A Screen Failure/Enrollment Log will be maintained by the center to document select information about candidates who signed consent.

8.3. *Informed Consent*

Data collection or study procedure will not occur prior to the patient signing the ICF. Patients will be considered enrolled in the study once they sign the informed consent and affirm that they agree to participate in the study and adhere to the study schedule. Once a patient is considered enrolled in the study, baseline information may be obtained.

8.4. *Baseline*

The following baseline data will be collected for all subjects:

- Demographics
- Results of Non-Invasive Imaging (including Ultrasound, CT or MRCP)
- Medical History
- Lab Results (LFTs, Lipase, Hct, Platelet Count)
- Probability of bile duct stone based on ASGE criteria: high, intermediate or low
- Need for MRCP or EUS based on intermediate or low ASGE criteria

8.5. *Randomization*

Randomization is to occur only after verification of all inclusion/exclusion criteria. Once the patient has signed the IRB/EC-approved study ICF and has met all general inclusion and none of the exclusion criteria, the patient will be eligible for randomization.

Randomization will be stratified by clinical site. Within each site, eligible subjects will be randomized in a 1:1 ratio to receive each treatment method. This study is not blinded.

For back-up randomization, sites will be instructed to randomize patients via back-up envelopes only in cases of unsuccessful access to the online database system. Envelopes are sequentially numbered sealed opaque envelopes containing randomized treatments.

8.6. *Procedure*

The following procedural data will be collected for all subjects:

- Achievement of cannulation portion of procedure
- Biliary Sphincterotomy performed
- Additional sphincteroplasty performed

- Number and approximate size of stones extracted
- Time Stamps:
    - Duodenoscope in
    - Time cannulation commenced
    - Time biliary cannulation achieved (defined as free advancement of guidewire)
    - SpyGlass™ DS in (For DSC Procedure)
    - SpyGlass™ DS out (For DSC procedure)
    - Time stone clearance achieved
    - Duodenoscope out
- Total radiation exposure to patient (fluoroscopy time, total radiation dose, Dose Area Product (DAP), effective dose)
- Volume of injected saline during DSC procedure
- Total number of endoscopic devices used during the procedure.
- Procedure outcome: all stones successfully extracted during the procedure?
- Serious Adverse Events and Device Events and all cases of Cholangitis, Pancreatitis, Perforation and Bleeding.

The following steps are procedural guidelines:

In both arms:

1. Prior non-invasive imaging will be reviewed to determine the number and size of bile duct stones (if possible) and the diameter of the bile duct.
2. Once bile duct stones are deemed to be a high probability based on clinical presentation imaging and ASGE criteria, patients will be randomized to either the DSC arm or the ERC arm.
3. Patient will receive prophylactic antibiotics and rectal indomethacin.
4. The duodenoscope will be advanced to the duodenum and the major papilla will be identified.
5. Needle knife pre-cut sphincterotomy may be utilized for stones visibly impacted at the ampulla.
6. A sphincterotome with guidewire will be used to cannulate the bile duct following needle knife sphincterotomy AND for all other patients without visibly impacted stones.

In Group A (ERC arm):

1. Needle knife pre-cut sphincterotomy may be utilized for stones visibly impacted at the ampulla.

2. For all other patients, standard cannulation techniques with a sphincterotome to gain biliary access; contrast medium injected.
3. If initial cannulation has not been achieved within 15 minutes, a double wire technique and/or transpancreatic septotomy cannulation technique should be attempted.
4. If cannulation failure persists despite these advanced cannulation techniques for an additional 15 minutes, this will be considered a **cannulation failure**. Participating institutions may proceed with their standard of care interventions at this point.
5. Use of needle-knife other than for visibly impacted stones will be considered a **cannulation failure.** Patients will be followed through 30 days post index procedure as indicated in the follow-up schedule.
6. After cannulation succeeds, number and estimated size of biliary stones will be confirmed following contrast injection. Biliary sphincterotomy will be performed. Additional papillary large balloon dilation can be performed if the sphincterotomy is felt to be inadequate.
7. Stone removal using standard techniques. If unexpectedly large stones are encountered, papillary large balloon dilation or mechanical lithotripsy may be applied.
8. If stone clearance fails due to size/shape of the stone(s), **stone extraction failure** will have occurred. However, participating institutions may proceed with their standard of care interventions at this point, including cholangioscopy and EHL/LL or stent placement with repeat ERC on another day. Patients will be followed through 30 days post index procedure as indicated in the follow-up schedule.

Post ERC validation by DSC:

9. In patients in whom stone extraction is deemed to be complete, the SpyGlass™ cholangioscope will then be advanced to confirm complete clearance of the bile duct.
10. If residual stone(s) are noted, then additional balloon sweeps, and/or stone retrieval using a SpyGlass™ Retrieval Basket, of the bile duct will be performed with fluoroscopy assistance and supplemented by papillary large balloon dilation, mechanical lithotripsy and EHL/LL as needed.
11. The number of "missed stones" equal to or greater than 5 mm in size per endoscopist's estimate will be documented.

In Group B (DSC arm):

1. Needle knife pre-cut sphincterotomy may be utilized for stones visibly impacted at the ampulla.
2. Fluoroscopy-free cannulation technique to gain biliary access for all other patients.
    - Do not prime the sphincterotome with contrast.
    - Following deep cannulation, confirm free advancement of the guidewire into a ductal system.

- Aspiration of bile via the sphincterotome using a syringe to confirm bile duct cannulation.
- If clear fluid is aspirated, this may indicate that the pancreatic duct has been accessed. Re-attempt to access the bile duct. If no fluid is aspirated, or if there is remaining uncertainty over which duct was accessed, physicians if they wish, may use a brief tap on the fluoroscopy pedal to assess whether the guidewire appears to be in the bile duct. Alternatively, they may proceed to an early double wire and/or transpancreatic septotomy cannulation technique. They MUST proceed to double wire and/or transpancreatic septotomy cannulation techniques if fluoroscopy-free cannulation failure persists for 15 minutes. If brief fluoroscopy is used to confirm biliary cannulation, then the case is considered a primary endpoint failure, but the DSC technique for stone evaluation and clearance may be continued. Secondary endpoints will be assessed in these patients, including patient radiation exposure.
- If initial fluoroscopy-free cannulation failure persists for 15 minutes, a double wire and/or transpancreatic septotomy cannulation technique should be attempted.
- If cannulation failure persists despite these advanced cannulation techniques for an additional 15 minutes, this will be considered a **cannulation failure**. The patient will **crossover to the ERC arm** where these cannulation techniques will be continued with full fluoroscopy support. If cannulation in the ERC arm fails despite use of fluoroscopy and basic/advanced cannulation techniques for an additional 15 min then participating institutions may then proceed with their standard of care interventions at this point. Use of needle-knife other than for visibly impacted stones will be considered a cannulation failure for these crossover patients.
- Patients will be followed through 30 days post index procedure as indicated in the follow-up schedule.

3. After fluoroscopy-free cannulation succeeds, biliary sphincterotomy will be performed. Additional papillary large balloon dilation can be performed if the sphincterotomy is felt to be inadequate
4. The sphincterotome will be exchanged for the SpyGlass cholangioscope over the guidewire.
5. The cholangioscope will be advanced into the bile duct up to the bifurcation (hilum) and distance from ampulla to the bifurcation (hilum) will be noted. (Adhesive tapes placed on SpyGlass shaft where it exits the duodenoscope working channel when cholangioscope is at the bifurcation, and again when it just exits ampulla will allow measurement of this distance).
6. Injection of saline/water to be minimized to avoid driving stones more proximally (inject gently with a syringe rather than using the pump). Suction applied through the Spyglass cholangioscope and gentle ‘head-up’ tilt of the fluoroscopy table may be utilized.
7. Number and estimated size of biliary stones will be confirmed during cholangioscopy.

8. Visualized stones may then be extracted using a Balloon catheter and/or SpyGlass™ Retrieval Basket.

Retrieval using Balloon Catheter:

9. The cholangioscope will be exchanged for a stone extraction balloon catheter. This exchange should be performed over a **long 0.035" guidewire**; if a short guidewire or a 0.025" guidewire was used earlier in the procedure, it should ideally be changed prior to next steps. The balloon catheter should be of appropriate size to fill the bile duct lumen (based on known diameter from prior non-invasive imaging). The balloon catheter will have distance markings.
10. A stone extraction balloon catheter marked with the distance from ampulla to hilum will then be advanced over the guidewire long 0.035" guidewire.
11. For patients with multiple stones, the balloon will be sequentially advanced more proximally up the bile duct for balloon sweeps, and eventually advanced to the hilum guided by previously measured distance from ampulla to hilum. Where only a single stone is noted, a single sweep commencing at the hilum may be performed. Balloon sweeps will be performed and the number of extracted stones will be counted to confirm complete extraction.
12. Saline irrigation will be performed via the balloon catheter, with the catheter positioned at proximal to the bifurcation prior to the last 2 balloon sweeps, to ensure clearance of any residual sludge/stone fragments/debris. If possible a gentle head up tilt of the table may be performed prior to irrigation to encourage downward movement of stones.
13. The cholangioscope will then be re-inserted and advanced to the hilum to confirm complete clearance of the bile duct.
14. If residual stone/stones are noted, additional balloon sweeps will be performed followed by repeat cholangioscopy to confirm clearance. This cycle may be repeated as necessary until all stones are believed to have been successfully extracted.

Retrieval using SpyGlass™ Retrieval Basket:

15. Stones visualized at cholangioscopy may also be captured and retrieved sequentially using the SpyGlass™ Retrieval Basket, commencing distally and progressing proximally to the hilum as with balloon extraction. Extracted stones will be counted. If stone capture is difficult using the basket, the endoscopist may switch to balloon extraction at any point. Where retrieval is successful using purely SpyGlass™ Retrieval Basket alone (without need for balloon catheter), or if retrieval using SpyGlass™ Retrieval Basket is utilized for the final visualized stone, saline irrigation (Step 12) and cholangioscope re-insertion (Steps 13/14) will not be necessary.
16. EHL or LL may be performed for unexpectedly large/complex stones.
    - If stone clearance fails due to size/shape of the stone(s), electro-hydraulic lithotripsy (EHL) or laser lithotripsy (LL) can be performed.
    - If stone clearance still fails **stone extraction failure** will have occurred. However, participating institutions may proceed with their standard of care interventions at this point, including ERC with mechanical lithotripsy or stent

placement followed by repeat ERC on another day. Patients will be followed through 30 days post index procedure as indicated in the follow-up schedule.

Post DSC validation by ERC:

17. An occlusion cholangiogram will be performed using the stone extraction balloon catheter and presence or absence of filling defects will be documented.
18. If filling defects are noted, then balloon sweeps of the bile duct will be performed to determine if the filling defects are "missed" bile duct stones or simply air bubbles.

    The number of "missed stones" > 5 mm per endoscopist's estimate will be documented.

8.7. *24-Hour, 7-Day, and 30-Day Follow-up*

The following data will be collected for all subjects (including Roll-in cases) during these follow up periods:

- Phone call to patient
- Serious Adverse Events, all events of Cholangitis, Pancreatitis, Perforation, and Bleeding, and Device Events, including discharge summaries for any device-related hospitalizations.

8.8. *Study Completion*

Subjects will be followed for 30 days post-index procedure. 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 investigator will note the reason on the study completion form (e.g. subject withdrawn by investigator, subject withdrew consent, lost to follow-up, SAE, death, etc.).

9. Statistical Considerations

9.1. *Primary Endpoint*

Preliminary DSC-guided stone clearance rate was established in a pilot study[1] and found to be comparable to that of ERC-guided stone clearance. Eight relevant peer reviewed publications[2-9] reporting on ERC-guided biliary stone clearance rates representing 2721 patients were analyzed. A meta-analysis was conducted of the biliary stone clearance rates, yielding a point estimate of 90% with a 95% CI of [85%, 94%].

9.1.1. Hypotheses

We hypothesize that the DSC-guided stone clearance rate is non-inferior to that of the ERC-guided stone clearance rate. We assume a DSC-guided and ERC-guided stone clearance rate of 90% with a 10% non-inferiority margin. The following hypothesis will be tested:

$$H_0: P_{DSC} \text{ minus } P_{ERC} \leq -\Delta \text{ (Inferior)}$$

H_1: P_{DSC} minus $P_{ERC} > -\Delta$ (Non-inferior)

where P_{DSC} and P_{ERC} are the stone clearance rates for the DSC arm (test) and the ERC arm (control), respectively, and (Δdelta) is the non-inferiority absolute margin.

9.1.2. Sample Size

The sample size was estimated based on the following assumptions:

- Expected stone clearance rate of 90% in DSC-guided and ERC-guided group
- Non-inferiority margin: 10%
- Alpha (1-sided): 0.05
- Power: 80%

With the above assumptions, a sample of 250 patients (125 in each arm) is needed to detect the non-inferiority of the clearance rate in the DSC arm compared to the ERC arm. This sample size was calculated using StatXact 9®.

9.1.3. Statistical Methods

An exact test will be used to test the non-inferiority hypothesis of the DSC-guided vs. ERC-guided stone clearance rates.

9.2. *Analysis Populations*

9.2.1. Enrolled Cohort

A subject is considered enrolled after signing the study-specific Informed Consent Form (ICF). Patients who sign the ICF but subsequently do not meet one or more of the selection criteria will be considered screen failures and will be excluded from the study.

9.2.2. Intent-to-Treat Cohort (ITT)

This cohort consists of those enrolled patients who meet all inclusion/exclusion criteria and are subsequently randomized.

9.2.3. Per-Protocol Cohort (PP)

The per-protocol cohort is a subset of the ITT subjects who are treated per protocol post randomization with no major protocol deviations (ICH E9 definitions).

9.3. *Data Analyses*

9.3.1.Baseline

Baseline data will be summarized using but not limited to the following variables: subject demographics, medical history, and history of prior ERCP or sphincterotomy. Descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) will be reported for continuous variables and frequency tables for discrete variables.

9.3.2. Procedure Data

Procedure data, such as cannulation success, biliary sphincterotomy and stone removal will be collected and reported using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

9.3.3. Post-Procedure Data

Post-procedure data will be collected as described in Table 8.1-1 Data Collection Schedule and will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

9.3.4. Interim Analyses

No formal interim analyses are planned for this study.

9.3.5. Subgroup Analyses

Stratified analyses will include tabulating the primary and select secondary endpoints by gender.

9.3.6. 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 endpoint as the outcome variable.

9.3.7. Multivariable Analyses

Multivariable analyses may be performed to identify potential predictors and assess their effect on the primary endpoint.

9.3.8. Learning Curve Analysis

A generalized linear model will be fit to investigate the effect of time since first enrollment and sites/physicians (and potential interaction between time and sites/physicians) on the primary and select secondary endpoints.

9.3.9. 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.

10. Data Management

10.1. *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 Rave. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) 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 EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving applicable queries in the database.

10.2. *Data Retention*

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

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and 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.

11. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

12. Deviations

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

All deviations from the investigational plan, with the reason for the deviation must be documented and reported to the sponsor using the protocol deviation form in the EDC. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

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

13. Device/Equipment Accountability

The 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. 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 devices/ equipment from shipment of 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 devices/equipment.

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

- Date of receipt
- Identification of each device/piece of equipment (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification

- Date on which the device/piece of equipment was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning devices/equipment, if applicable.

Written procedures may be required by national regulations.

14. Compliance

14.1. *Statement of Compliance*

This study will be conducted in accordance with Good Clinical Practices as outlined in the ISO 14155:2011, ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155:2011, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, 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 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.
- Maintain the device accountability records and control of the device, ensuring that the device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC 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 investigational 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.

- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

14.2.1. Delegation of 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 and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

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

14.4. *Sponsor Responsibilities*

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

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

14.4.1. Role of 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.

- 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 worksheet
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- 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 without the approval and presence of the investigator
- 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

14.5. *Insurance*

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

15. 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 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.

16. Potential Risks and Benefits

16.1. *Anticipated Adverse Device Effects*

From the Anticipated Adverse Events listed above, the following anticipated adverse device effects (ADE) have been identified for SpyGlass DS™ System

The primary risks associated with the SpyScope™ DS Access and Delivery Catheter, and SpyGlass™ Retrieval Basket listed in the DFU include the following:

- Pancreatitis
- Perforation
- Hemorrhage
- Septicemia/Infection
- Cholangitis
- Allergic reaction

Additional primary risks associated with the SpyScope™ DS Access and Delivery Catheter listed in the DFU include:

- Mucous membrane damage
- Hematoma

The additional primary risks included in the DFU associated with the SpyGlass™ Retrieval Basket include:

- Basket impaction
- Cholecystitis

Any of these must be reported on the Adverse Event page of the eCRF if they are serious. If cholangitis, pancreatitis, perforation, or bleeding, all cases (AE and SAEs) should be

reported. If death occurs, it must be entered as an outcome to a specific SAE, rather than the SAE itself.

The rate of occurrence of potential risks and side effects associated with taking part in this study are listed in the table 16.2-1 and 16.2-2.

Table 16.1-1: Potential Risks Rates of Occurrence

SpyScope™ DS Access and Delivery Catheter

Risk Term	Rate of Occurrence	Sources
Pancreatitis	1.1% - 18.1%	15, 16, 17, 18
Abdominal pain	5.1% - 15.3%	19, 16
Sustained DSC-related bacteremia	13.9%	20
Cholangitis	1.4%-11%	21, 22, 23, 24, 15, 25, 26, 17
Mild pancreatitis	1.6% - 8.5%	22, 23, 24, 25, 28
Unexpected hospitalization	7.6%	16
Fever	5.8%	19
Self-limited pancreatitis	5.8%	19
Mild perforation	4.2%	24
Post-EST bleeding	0.8%-3.8%	21, 22, 28
Self-limited abdominal pain	3.5%	23
Asymptomatic amylasemia	3.5%	23
Bleeding	1%-2%	15, 25
Hemobilia	1.1%	23
Perforation	0.7%-1.1%	15, 16, 25
Aspiration pneumonia	0.8%	22
Infection	0.34%	

Table 16.1-2: Potential Risks Rates of Occurrence

SpyGlass™ Retrieval Basket

Risk Term	Rate of Occurrence
Post-ERCP Pancreatitis	3% - 6.6%, .13%
Cholangitis	6.6% - 7.5%
Bleeding	1.3%
Broken basket and impaction	6 case reports, .88%

16.2. *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.

16.3. *Anticipated Benefits*

There may be no benefit from participation this study. Medical science and future patients may benefit from this study; notably reducing radiation exposure, and wait times for procedure rooms.

16.4. *Risk to Benefit Rationale*

The SpyGlass™ DS is intended to provide direct visualization of the pancreaticobiliary system, including the hepatic ducts as stated in the DFU.

Benefits to the subject could potentially include reducing radiation exposure and wait times for procedure rooms, better diagnostic accuracy and therapeutic efficacy as compared to ERCP alone when SpyScope™ DS Access and Delivery Catheter is used with SpyGlass™ DS Digital Controller. Indeed, potential benefits may include for example, successful visualization and diagnosis of lesions, better identification of filling defects, and removal of large and and/or impacted bile duct stone(s).

The risks associated with the use of the SpyGlass DS are documented in the Directions for Use and clinical data for the system is currently reviewed by the Sponsor. The following conclusion was reported as it pertains to SpyGlass-related adverse events: Evaluation of bile duct disease and biliary stone therapy can be safely performed with a high success rate by using the single-operated cholangioscopy system.

17. Safety Reporting

17.1. *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 Serious Adverse Events
- All events of Cholangitis, Pancreatitis, Perforation, and Bleeding
- All Device Events, including Deficiencies
- New findings/updates in relation to already reported events
- All study Device related Adverse Events
- All Accessory Device related Adverse Events
- All study Procedure related Adverse Events
- All ERCP Procedure related Adverse 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 AE required by the protocol, 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 are not reported as AEs unless there is an increase in severity of 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 17.2-1 for AE definitions).

Unrelated AEs, except for any event of Cholangitis, Pancreatitis, Perforation and Bleeding, will not be collected in this study

Refer to Section 16 for the known risks associated with the study device(s).

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155:2011and MEDDEV 2.7/3 for clarification purposes.

Table 17.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational 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 investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational 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 investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or

Table 17.2-1: Safety Definitions

Term	Definition
	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) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **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: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

17.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device, including accessory devices and/ or procedure(s). See criteria in Table 17.3-1:

Table 17.3-1: Criteria for Assessing Relationship of Study Device, Including Accessory Device(s) and/or Procedure(s) to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying

Table 17.3-1: Criteria for Assessing Relationship of Study Device, Including Accessory Device(s) and/or Procedure(s) to Adverse Event

Classification	Description
	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 investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational 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 investigational 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.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in 17.4-1.

Table 17.44-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies**** (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event	Complete AE eCRF page with all available new and updated information.	a) Within 10 business days after becoming aware of the event or as per local/regional regulations. b) Reporting required through the 12-month Follow-up time point
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	c) When documentation is available
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	d) Within 10 business days after becoming aware of the event or as per local/regional regulations. e) Reporting required through the end of study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	f) When documentation is available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	g) Within 2 business days of first becoming aware of the event or as per local/regional regulations. h) Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	i) When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Event CRF with all available new and updated information.	j) Within 2 business days of first becoming aware of the event. Reporting required through the end of the study

Event Classification	**Communication Method**	**Communication Timeline post-market studies**** (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event	Complete AE eCRF page with all available new and updated information.	a) Within 10 business days after becoming aware of the event or as per local/regional regulations. b) Reporting required through the 12-month Follow-up time point
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	c) When documentation is available
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.	k) In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information l) Reporting required through end of study

Abbreviations: AE=adverse event; CRF=case report form;
**Please note that post-market studies are clinical studies where the medical devices used in the study bear the regulatory approval and are used for the same approved indications.

17.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction would be recorded as an adverse event on the appropriate eCRF.

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

17.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

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

18. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational 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 14155:2011, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC, 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. 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 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 body 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), 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. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

19. Suspension or Termination

19.1 Premature Termination of the Study

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

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- 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 of the device.

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

Any investigator, or IRB/ EC in the Non-Complex Biliary Stones DSC vs ERC RCT may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, 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 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 or EC terminates participation in the study, participating investigators, associated IRBs/ECs, 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 investigational 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 Corporation 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 6 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 and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed for 30 days after index procedure per the study protocol. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

20. 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 will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation 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.

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22. Abbreviations and Definitions

22.1. *Abbreviations*

Abbreviations are shown in Table 22.1-1.

Table 22.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
BD	Bile Duct
BSC	Boston Scientific Corporation
CBD	Common Bile Duct
CP	Chronic Pancreatitis
CRF	Case Report Form
CRO	Contract Resource Organization
CSEMS	Covered Self-Expanding Metal Stent
CT	Computed Tomography
DFU	Directions for Use
DSC	Direct Solitary Cholangioscopy
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
EHL	Electro-Hydraulic Lithotripsy
EPS	Endoscopic Pancreatic Sphincterotomy
ERC	Endoscopic Retrograde Cholangiography
ERCP	Endoscopic Retrograde Cholangiopancreatography
FDA	Food and Drug Administration
GCP	Good Clinical Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Table 22.1-1: Abbreviations

Abbreviation/Acronym	Term
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Standards Organization
ITT	Intent-to-Treat
LL	Laser Lithotripsy
LFT	Liver Function Test
MRCP	Magnetic Resonance Cholangiopancreatography
PD	Pancreatic Duct
PI	Principal Investigator
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

22.2. *Definitions*

Terms are defined in Table 22.2-1.

Table 22.2-1: Definitions

Term	Definition
Acute Pancreatitis	Abdominal pain and a serum concentration of pancreatic enzymes (lipase(required, amylase (optional)) three or more times the upper limit of normal, that required more than one night of hospitalization
Acute Cholecystitis	No suggestive clinical or radiographic signs of acute cholecystitis before the procedure and if emergency cholecystectomy is subsequently required
Perforation	Retroperitoneal or bowel-wall perforation documented by any radiographic technique or direc visual evidence.
Wound Infection	Requiring intervention otherwise considered as minor complication
Cholangitis	Elevation in termperature more than 38°C, thought to have a biliary cause, without concomitant evidence of acute cholecystitis, requiring intervention.
Hemorrhage	Bleeding after the index procedure requiring transfusion of ≥4 units of packed cells within a 24-hour period, or leading to relaparotomy/intervention

Table 22.2-1: Definitions

Term	Definition
(Emergency) (re)laparotomy	Any (other) reason following either preoperative biliary drainage or another surgical procedure
Pneumonia	Pulmonary infection with radiological confirmation and requiring antibiotic treatment
Mortality	In-hospital death, due to protocol complications or any cause, including progression of disease, within the study period.

Abbreviations are defined in Table 22.1-1.

Probability of stones based on ASGE criteria are defined in Table 22.3-1.

Table 22.23-2: Predictors of Choledocholithiasis

Predictors of choledocholithiasis Very strong CBD stone on transabdominal US Clinical ascending cholangitis Bilirubin >4 mg/dL Strong Dilated CBD on US (>6 mm with gallbladder in situ) Bilirubin level 1.8mg/dL – 4 mg/dL Moderate Abnormal liver biochemical test other than bilirubin Age older than 55 y Clinical gallstone pancreatitis
Assigning a likelihood of choledocholithiasis based on clinical predictors Presence of any very strong predictor — High

Presence of both strong predictors	High
No predictors present	Low
All other patients	Intermediate

Abbreviations are defined in Table 22.1-1.