E7058

A Multi-Center, Prospective, Randomized Study Comparing Removable, Self-Expanding Metal Stents to Plastic Stents for the Treatment of Benign Biliary Strictures Secondary to Chronic Pancreatitis

WallFlex Biliary FC Chronic Pancreatitis RCT

NCT01543256

Clinical Protocol

February 15, 2013

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CLINICAL PROTOCOL

90913882 / E7058

Sponsored By

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Investigator's Signature Page

Study Title	A Multi-Center, Prospective, Randomized Study Comparing Removable, Self-Expanding Metal Stents to Plastic Stents for the Treatment of Benign Biliary Strictures Secondary to Chronic Pancreatitis
Protocol Version	90913882 Rev/Ver AA
Study Center	_____ (Print name of study center)

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the trial as described in the protocol and in accordance with applicable laws and regulations. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the trial as described in the protocol.

_____

Principal Investigator (Print Name)

_____ _____

Principal Investigator (Signature) Date

Protocol Synopsis

Full Title	A Multi-Center, Prospective, Randomized Study Comparing Removable, Self-Expanding Metal Stents to Plastic Stents for the Treatment of Benign Biliary Strictures Secondary to Chronic Pancreatitis
Short Title	WallFlex Biliary FC Chronic Pancreatitis RCT
Primary Objective	To compare the use of Self Expanding Metal Stents (SEMS) to plastic stents for the treatment of benign biliary strictures secondary to chronic pancreatitis as it pertains to stricture resolution rates, complication rates and number of ERCP procedures during 24 months.
Study Devices	**Group A: Metal Stents – MS Arm** WallFlex™ Biliary RX Fully Covered Stent System RMV **Group B. Plastic Stents – PS Arm** Per Investigator preference
Study Design	Prospective, multi-center, randomized
Planned Number of Subjects	164
Planned Number of Sites	Up to 15
Primary Endpoint	Stricture resolution at 24 months
Secondary Endpoints	1. Occurrence of adverse events related to the stent and/or the stent placement or removal procedures 2. Number of ERCP procedures through 24 months after initial stent placement 3. Ability to deploy the stent(s) in satisfactory position 4. Stent Removal: • Ability to remove the stent(s) without serious stent removal related adverse events at each procedure involving removal of stent(s) (technical success at removal) or • Complete distal migration without serious stent removal related adverse events 5. Liver Function Tests (LFT's): • Baseline LFTs compared to LFTs taken at time of original plastic stent placement for any subject with a prior plastic stent

	• LFT improvement at 1 month post-study treatment compared to baseline LFTs (and/or compared to LFTs taken at time of original plastic stent placement for any subject with a prior plastic stent) • LFTs at month 24 compared to LFTs at removal of last stent (applicable for subjects who had not been re-stented at time of month 24 visit) 6. Health Economic Endpoints: • Number of outpatient procedures • Number of hospitalizations • Duration of hospitalizations • Length of procedures • Number of devices
Randomization	Subjects will be randomized at the time of the procedure to a 1:1 ratio between Metal Stent Arm (Group A – MS) and Plastic Stent Arm (Group B – PS).
Follow-Up Schedule	• Baseline: Subject screening, enrollment, LFTs and symptoms. • Study Treatment Procedure: o Group A (MS): Stent Placement o Group B (PS): Stent Placement: Two or more 8.5 Fr. or 10 Fr. PS whenever possible • 1 Month Follow-up: o Group A (MS): LFTs and symptoms o Group B (PS): LFTs and symptoms • Stent Exchange Follow-up: o Group A (MS): None o Group B (PS): Month 4 and Month 8 • Stent Removal: o Group A (MS): Removal at Month 12, LFTs and symptoms o Group B (PS): Removal of last stents at Month 12, LFTs and symptoms • Post-Stent Removal Follow-Up o Group A (MS): Month 24 – LFTs and symptoms o Group B (PS): Month 24 – LFTs and symptoms • Additional ERCP visits as needed Note: Recurrent strictures will be treated with a metal stent in Group A (MS) and with plastic stents in Group B (PS) – no cross-over. Re-stenting after the per-protocol 12 month stenting period will be considered primary endpoint failures. Follow-up, however, will continue until Month 24 after initial stent placement for all subjects, in order to assess all secondary endpoints in a comparative fashion for the

	MS and PS arms.
Key Inclusion Criteria	• Age 18 or older • Willing and able to comply with the study procedures and provide written informed consent to participate in the study • Chronic pancreatitis • Symptomatic bile duct stricture (defined by cholangitis or persistent jaundice for at least one month or cholestasis associated with at least 3 times normal alkaline phosphatase levels) documented at time of enrollment for naïve stricture or at the time of prior plastic stent placement in strictures that had one prior plastic stent inserted.[12] • Common bile duct stricture based on imaging assessment of dilatation of the common and/or intrahepatic bile ducts
Key Exclusion Criteria	• Biliary stricture of benign etiology other than chronic pancreatitis • Prior biliary metal stent or any plastic stenting other than one plastic stent of 10 Fr or less for 6 months or fewer • Developing obstructive biliary symptoms associated with an attack of acute pancreatitis • Biliary stricture of malignant etiology • Stricture within 2 cm of common bile duct bifurcation • Known bile duct fistula or leak • Subjects for whom endoscopic techniques are contraindicated • Known sensitivity to any components of the stent or delivery system • Symptomatic duodenal stenosis (with gastric stasis) • Participation in another investigational study within 90 days prior to consent • Investigator Discretion
Statistical Hypothesis	A literature search of metal and plastic stenting for treatment of benign biliary strictures secondary to chronic pancreatitis yielded 4 articles representing 70 subjects treated with metal stenting (MS) [1,9-11] and 3 articles representing 60 subjects treated with plastic stenting (PS) [3,4,8]. The following meta-analysis was conducted of the probability of stricture resolution: • Metal Stenting: A meta-analysis of the stricture resolution rate during the reported follow-up after initial stent placement yields a proportion

	of 0.762 [95% CI: 0.593 – 0.895] [1,9-11]. • Plastic Stenting: A meta-analysis of the stricture resolution rate during the reported follow-up after initial stent placement yields a proportion of 0.611 [95% CI: 0.311 – 0.870] [3,4,8]. Statistical testing will be performed to determine if the rate of stricture resolution for the metal stent is non-inferior to the plastic stent group. The null hypothesis is that the stricture resolution rate is non-inferior in the Metal Stent Arm versus the Plastic Stent Arm: $Ho: \pi_{test} - \pi_{control} \geq \Delta$ (Inferior) $Ha: \pi_{test} - \pi_{control} < \Delta$ (Non-inferior) where π_{test} and $\pi_{control}$ are the probabilities of having a stricture resolution in the metal stent arm and the plastic stent arm respectively, and Δ is defined as the non-inferiority margin. The sample size was calculated for a one-sided 0.050 Farrington-Manning test using SAS 9.2®. If the P value from the Farrington-Manning test is <0.05 then the metal stent group will be considered non-inferior to the plastic stent group. The expected probability of stricture resolution in the metal stent arm and plastic stent arm is 66.0%, which was taken from the 95% CIs from the meta-analysis above. The non-inferiority margin (Δ) is 20%. Given these assumptions and a one-sided 5% significance level, 2 x 74 = 148 subjects will provide 80% power to reject the null hypothesis, that the metal stent group is inferior to the plastic stent group. To compensate for possible loss of subjects after enrollment and complete assessment of inclusion/exclusion criteria, an additional 10% of subjects will be enrolled, for a total of 2 x 82 = 164.

Table of Contents

Table of Tables

1. Introduction

1.1. *Introduction*

Benign strictures of the common bile duct may occur in approximately 3%-45% of subject with chronic pancreatitis.[1-5] Previously, surgery was typically performed for subjects with chronic pancreatitis, but is associated with high morbidity and mortality.[3-5] Chronic pancreatitis subjects are also typically poor surgical candidates due to concomitant malnutrition, cirrhosis or portal hypertension.[1,3,4] Non-surgical candidates will usually undergo endoscopic treatment with one or more multiple plastic stents placed, resulting in adequate short-term resolution of pancreatitis but associated with high occlusion and migration rates and poor long-term results.[1,3]

Plastic stents, which are intended for temporary placement and are removable, have become standard of care for endoscopic treatment of benign strictures due to chronic pancreatitis.[2-8] More recently, physicians are using self-expandable metal stents (SEMS) for treatment of and removal from such strictures due to the long-term patency, lower occlusion and obstruction rates, of metal stents compared to single or multiple plastic stents. [1,9-11]

A summary of literature review below examines plastic stent placement and instances of metal stent placement for treatment of benign strictures in subjects with chronic pancreatitis.

1.2. *Plastic Stents in Chronic Pancreatitis Strictures*

A total of six studies (253 subjects) were analyzed for use of single or multiple plastic stents for benign biliary strictures; there were a total of 226 subjects with strictures due to chronic pancreatitis included in these studies.[2-6,8] The average number of ERCP's (Endoscopic Retrograde Cholangiopancreatography) with stent exchanges per subject was 4.3 (range 1-17).[3,5,8] Subjects with single plastic stents placed typically underwent stent exchange at 3-6 month intervals resulting in 1-4 exchanges per subject.[3,5,6] These subjects also had a stent indwell time ranging from 10-15 months.[3,4,6] Subjects with multiple plastic stents placed had stent indwell times ranging from 12-34 months.[3,8]

Overall clinical success ranged from 24%-46% for subjects treated with a single plastic stent[2-5], and 62%-92% for subjects treated with multiple plastic stents.[3,8] In the subset of data available for chronic pancreatitis subjects treated with single plastic stents, success rates ranged from 7.7%-46%[3-6] and one study specifying use of multiple plastic stents for chronic pancreatitis subjects had a reported success rate of 44%.[8]

Complications inclusive of all subjects in all studies of plastic stents included migration (10.2%-13%)[3,4], cholangitis (6.8%)[8], bleeding (5.1%)[4], occlusion (7.6%-46.5%)[4,5], pancreatitis (1.7%-3.4%)[5,8], liver abscess (1.7%)[5], dislocation (1.7%)[5], and clogging (92.3%).[6]

1.3. *Metal Stents in Chronic Pancreatitis Strictures*

A total of four studies (186 subjects) were analyzed for use of partially covered (n=99 subjects) or fully covered metal stents (n=87 subjects) for benign biliary strictures; there were a total of 71 subjects with strictures due to chronic pancreatitis included in these studies.[1,9-11] Types of stents used included the partially covered Wallstent (Boston Scientific), uncovered Wallstent (Boston Scientific), Viabil, fully covered metal stent with an anchoring flap (M.I. Tech) and a fully covered metal stent with both ends flared (Standard Sci Tech). Behm et al[1] noted a range of 1-3 procedures per subject. Stent indwell times ranged from 6 months to 28 months.[1,9,11] Success of metal stents in just chronic pancreatitis subjects ranged up to 95%.[1]

Complications inclusive of all subjects in all studies of metal stents included migration (5%-16.2%)[1,9,11], bleeding (1%-5%)[1,9,10], pain (2%-5%)[1,9,10], pancreatitis (5%-13.9%)[1,9,11], cholangitis (4.6%-35%)[11] and occlusion (9.3%)[11].

2. Device Description

The WallFlex Biliary RX Fully Covered Stent System RMV is indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms, and for treatment of benign biliary strictures, per CE Mark. This clinical study will be conducted only in countries where this indication for use is cleared or approved per local regulatory requirements. Enrolled subjects will have benign biliary strictures secondary to chronic pancreatitis.

Study devices are labeled on the box and inner pouch and include information not limited to name of legal manufacturer, device name and dimensions, lot number, expiration date and investigational use statement. Device labeling will be provided in local language(s) as per national regulations.

For a detailed description of the WallFlex Biliary RX Fully Covered Stent System RMV, please reference the Directions for Use (DFU) included in each device package.

The DFU indicates stent placement for the following use: the palliative treatment of biliary strictures produced by malignant neoplasms, and for treatment of benign biliary strictures. Investigators should use the WallFlex Biliary RX Fully Covered Stent System RMV in accordance with the DFU.

Description	Delivery System Working Length (cm)	Stent Diameter (mm)	Stent Length (mm)
WallFlex Biliary RX Fully Covered Stent System RMV	194	8	60
WallFlex Biliary RX Fully Covered Stent System RMV	194	8	80
WallFlex Biliary RX Fully Covered Stent System RMV	194	10	40
WallFlex Biliary RX Fully Covered Stent System RMV	194	10	60
WallFlex Biliary RX Fully Covered Stent System RMV	194	10	80

3. Primary Objectives

To compare the use of Self Expanding Metal Stents (SEMS) to plastic stents for the treatment of benign biliary strictures secondary to chronic pancreatitis as it pertains to stricture resolution rates, complication rates and number of ERCP procedures during 24 months.

4. Endpoints

4.1. *Primary Endpoint*

4.1.1. Primary Endpoint Definition

Stricture resolution at 24 months.

Stricture resolution at 24 months is defined by the following two criteria being met:

- Absence of re-stenting after the per-protocol stenting period through the 24 month visit
- Absence of cholestasis at the 24 month visit, defined as alkaline phosphatase level not exceeding 2 times the level at completion of the per-protocol stenting period

4.1.2. Primary Endpoint Failures

- Primary endpoint failures are 1) subjects who are re-stented during follow-up after the per-protocol stenting period and 2) subjects who have not been re-stented at month 24 but have alkaline phosphatase level exceeding 2 times the level at completion of the per-protocol stenting period.
- Subjects who experience early stent removal or complete distal stent migration without subsequent re-stenting will not be considered failures. If re-stenting occurs, but the

cumulative stenting period does not exceed 12 months, the subject remains eligible for primary endpoint assessment.

4.1.3. Re-stenting

- Re-stenting after the per-protocol 12 month stenting period should only be considered if subjects meet initial criteria for stenting:
    - Symptomatic bile duct stricture (defined by cholangitis or persistent jaundice for at least one month or cholestasis associated with at least 3 times normal alkaline phosphatase level) documented at time of enrollment for naïve stricture or at the time of prior plastic stent placement in strictures that had one prior plastic stent inserted.[12]
    - Common bile duct stricture based on imaging assessment of dilatation of the common and/or intrahepatic bile ducts
- To minimize the risk of recurrent obstructive symptoms due to sludge or stones in the post-stent removal period, every attempt should be made to clear the bile duct of sludge and/or stone (i.e., balloon sweep and/or flushing).

4.2. *Secondary Endpoints*

1. Occurrence of adverse events related to the stent and/or the stent placement or removal procedures
2. Number of ERCP procedures through 24 months after initial stent placement
3. Ability to deploy the stent(s) in satisfactory position
4. Stent Removal:
    - Ability to remove the stent(s) without serious stent removal related adverse events at each procedure involving removal of stent(s) (technical success at removal) or
    - Complete distal migration without serious stent removal related adverse events
5. Liver Function Tests (LFT's)
    - Baseline LFTs compared to LFTs taken at time of original plastic stent placement for any subject with a prior plastic stent
    - LFT improvement at 1 month post-study treatment compared to baseline LFTs (and/or compared to LFTs taken at time of original plastic stent placement for any subject with a prior plastic stent)
    - LFTs at month 24 compared to LFTs at removal of last stent (applicable for subjects who had not been re-stented at time of month 24 visit)
6. Health Economic Endpoints:
    - Number of outpatient procedures
    - Number of hospitalizations
    - Duration of hospitalizations

- Length of procedures
- Number of devices

5. Design

The study is designed as a post-market, multi-center, prospective, non-blinded, randomized study. At least 164 subjects (82 per arm) will be treated with 1:1 randomization between Group A and Group B and will be followed through 24 months post-initial stent(s) placement:

- Subjects in the MS arm will be treated with a single metal stent, which will be removed 12 months post-placement.
- Subjects in the PS arm will receive 2 plastic stents when possible. Subjects in this arm will undergo plastic stents exchange/bile duct calibration at 4 and 8 month post-initial stent placement. At each stent exchange, the goal should be to provide progressive stent therapy by increasing the number of plastic stents at 4 months and again at 8 months. Final plastic stent removal will occur 12 months post-initial stent placement.

5.1. *Inclusion Criteria:*

- Age 18 or older
- Willing and able to comply with the study procedures and provide written informed consent to participate in the study
- Chronic pancreatitis
- Symptomatic bile duct stricture (defined by cholangitis or persistent jaundice for at least one month or cholestasis associated with at least 3 times normal alkaline phosphatase levels) documented at time of enrollment for naïve stricture or at the time of prior plastic stent placement in strictures that had one prior plastic stent inserted.[12]
- Common bile duct stricture based on imaging assessment of dilatation of the common and/or intrahepatic bile ducts

5.2. *Exclusion Criteria:*

- Biliary stricture of benign etiology other than chronic pancreatitis
- Prior biliary metal stent or any plastic stenting other than one plastic stent of 10 Fr or less for 6 months or fewer
- Developing obstructive biliary symptoms associated with an attack of acute pancreatitis
- Biliary stricture of malignant etiology
- Stricture within 2 cm of common bile duct bifurcation
- Known bile duct fistula or leak
- Subjects for whom endoscopic techniques are contraindicated
- Known sensitivity to any components of the stent or delivery system
- Symptomatic duodenal stenosis (with gastric stasis)
- Participation in another investigational study within 90 days prior to consent

- Investigator Discretion

6. Subject Accountability

6.1. *Point of Enrollment*

A subject is considered enrolled after signing the Informed Consent Form (ICF). See Section 8.4 for further information on enrolled, intent-to-treat and per-protocol cohorts.

6.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported and recorded in the study database. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws consent. Withdrawn subjects will not be replaced. All open adverse events should be closed or documented as ongoing. Data collected up to the point of subject withdrawal may still be used.

7. Study Methods

7.1. *Data Collection*

The schedule of observations and assessments to take place during the study follows on the next page.

Table 1. Study Event Schedule

Study Visit	Screening/ Baseline	Treatment	Mo. 1* (30 d)	Mo. 4 (120 d)	Mo. 8 (240 d)	Mo. 11-12 (330-360 d)	Mo 24* (720 d)	Additional ERCP
Window	≤ 5 days prior to treatment	N/A	±10 d	±30 d	±30 d	See range above	±30 d	NA
ICF	X							
Eligibility Assessment	X							
Demographics	X							
Medical History	X							
Liver Function Normal Ranges	X**						X	X****
Liver Function Tests	X		X	***	***	X	X	X
Assessment of Biliary Obstructive Symptoms	X		X			X	X	X****
Randomization		X						
Stent Placement/Exchange		X		PS Only	PS Only			X (if done)
Stent Removal						X		
Cholangiogram or other Common Bile Duct Imaging	X (prior to stent placement)					X (after stent removal)		X (if standard of practice)
AE/Device Malfunction Assessment	Report as occurs/needed per the Protocol Reporting Requirements – See Section 11.							
Protocol Deviations	Report as occurs/needed.							

*Visit may be conducted in the office or via telephone with liver function tests drawn and sent from local clinic/hospital.
**In addition to baseline LFTs, LFTs are also to be collected from time of original plastic stent placement for any subject with a prior plastic stent.
***If subject is not re-stented after Month 4 or 8 Plastic Stent Exchange, Liver Function Tests must be collected at that visit.
****Required for any visit that results in re-stenting

7.2. *Study Candidate Screening*

No study-specific testing will be conducted until after the subject has signed an ICF. A Screen Failure/Enrolled Log will be maintained in EDC by the center to document select information about candidates who signed consent.

7.3. *Informed Consent*

Written Informed Consent must be obtained for all subjects who are potential study candidates. Subjects will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed. The Informed Consent form is study-specific and must be approved by the study Institutional Review Board (IRB)/Ethics Committee (EC). Study personnel should explain that even if a subject agrees to participate in the study and signs the ICF, the ERCP procedure may demonstrate that the subject is not a suitable candidate for the study.

7.4. *Study Visits*

7.4.1. Screening/Baseline – Visits/Assessments must occur within 5 days prior to stent placement – *Office Visit*

- Informed Consent (See Section 7.3)
- Eligibility Criteria Assessment
- Demographics
- Medical History
- Collection of Liver Function Normal Ranges
- Liver Function Tests (at enrollment for naïve strictures or at the time of prior plastic stent placement in strictures that had one prior plastic stent inserted)
    - Alkaline phosphatase – mandatory
    - Total Bilirubin – mandatory
    - Gamma GT – optional
    - SGOT and SGPT (AST, ALT) – optional
- Assessment of Biliary Obstructive Symptoms
    - Right Upper Quadrant Pain
    - Fever/Chills
    - Jaundice
    - Itching
    - Dark urine
    - Pale stools
    - Nausea/Vomiting
- Cholangiogram or other Common Bile Duct Imaging
- Adverse Event/Device Malfunction Assessment

7.4.2. Randomization

Randomization is to occur only after verification of all inclusion/exclusion criteria. Once the subject has signed the Institutional Review Board (IRB)/Ethics Committee (EC)-approved study ICF and has met all general inclusion and none of the exclusion criteria, the subject will be eligible for randomization. Randomization schedules will be computer-generated in advance, using a pseudo-random number generator and loaded into the EDC system. Randomization assignments will be obtained from the EDC system at the time of procedure. 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.

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

7.4.3. Treatment – *Office Visit*

- Cholangiogram or other Common Bile Duct Imaging (prior to stent placement)
- Stent Placement Procedure
  NOTE: For subjects randomized to PS, at least two 8.5 or 10 Fr. PS should be placed whenever possible
- Adverse Event/Device Malfunction Assessment

7.4.4. Post-Stent Placement Follow-Up (Month 1) – *Office or Telephone Visit*

- Liver Function Tests
- Assessment of Biliary Obstructive Symptoms (See Section 7.4.1)
- Adverse Event/Device Malfunction Assessment

7.4.5. Plastic Stent Exchange (Month 4 and 8 – PS Only) – *Office Visit*

- Plastic Stent Exchange
- Adverse Event/Device Malfunction Assessment
- If subject is not re-stented after this visit, Liver Function Tests must be drawn.

7.4.6. Primary Stent Removal Visit (Month 12) – *Office Visit*

- Stent Removal Procedure
- Cholangiogram or other Common Bile Duct Imaging (post-stent removal)
- Liver Function Tests
- Assessment of Biliary Obstructive Symptoms
- Adverse Event/Device Malfunction Assessment

7.4.7. Post-Stent Removal Follow-Up (Months 24) – *Office or Telephone Visit*

- Assessment of Biliary Obstructive Symptoms
- Collection of Liver Function Normal Ranges
- Liver Function Tests
- Adverse Event/Device Malfunction Assessment

7.4.8. Additional ERCP

- Liver Function Tests
- Collection of Liver Function Normal Ranges (required for any visit that results in re-stenting)
- Assessment of Biliary Obstructive Symptoms (required for any visit that results in re-stenting)
- Cholangiogram or other Common Bile Duct Imaging (only to be collected in database if standard of care per institution)
- Adverse Event/Device Malfunction Assessment

NOTE: Recurrent strictures must be treated with a metal stent in Group A (MS) and with plastic stents in Group B (PS) – no cross-over.

7.5. *Study Completion*

Each subject will be followed for 2 years post-initial stent placement. Recurrent strictures will be treated with a metal stent in Group A (MS) and with plastic stents in Group B (PS) – no cross-over. Follow-up will continue until Month 24 after initial stent placement for all subjects, in order to assess all secondary endpoints in a comparative fashion for the MS and PS arms.

Additional visits may be conducted at the Investigator's discretion in accordance with Adverse Event or Device Malfunction data collection. A subject will be considered lost to follow-up if the subject remains unresponsive to communication after three documented attempts by study staff.

7.6. *Source Documents*

The Investigator/institution guarantees direct access to original source documents, including cholangiogram and/or imaging documentation, by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

8. Statistical Considerations

8.1. *Objective*

Rate of Stricture Resolution in the Metal Stent group is non-inferior to the Plastic Stent group.

Statistical testing will be performed to determine if the rate of stricture resolution for the metal stent is non-inferior to the plastic stent group. The null hypothesis is that the rate of stricture resolution is non-inferior in the Metal Stent Arm versus the Plastic Stent Arm:
$Ho: \pi_{test} - \pi_{control} \geq \Delta$ (Inferior)

$Ha: \pi_{test} - \pi_{control} < \Delta$ (Non-inferior)

where π_{test} and $\pi_{control}$ are the probabilities of having a stricture resolution in the metal stent arm and the plastic stent arm respectively, and Δ is defined as the non-inferiority margin.

The sample size was calculated for a one-sided 0.050 Farrington-Manning test using SAS 9.2®. If the P value from the Farrington-Manning test is <0.05 then the metal stent group will be considered non-inferior to the plastic stent group. The expected probability of a stricture resolution in the metal stent arm and plastic stent arm is 66.0%, which was taken from the 95% CIs from the meta-analysis below. The non-inferiority margin (Δ) is 20%. Given these assumptions, and a one-sided 5% significance level, 2 x 74 = 148 subjects will provide 80% power to reject the null hypothesis, that the metal stent group is inferior to the plastic stent group. To compensate for possible loss of subjects between randomization and complete assessment of inclusion/exclusion criteria, an additional 10% of subjects will be enrolled for a total of 2 x 82 = 164.

8.2. *Justification for Study Design and Sample Size Calculations*

- A literature search of metal and or plastic stenting for treatment of benign biliary strictures secondary to chronic pancreatitis yielded 4 articles representing 70 subjects treated with metal stenting (MS) [2-7] and 3 articles representing 60 subjects treated with plastic stenting (PS) [8-13].
- The following meta-analysis was conducted of the probability of stricture resolution:
  - Metal Stenting: A meta-analysis of the stricture resolution rate during the reported follow-up after initial stent placement yields a proportion of 0.762 [95% CI: 0.593 – 0.895] [2-7].
  - Plastic Stenting: A meta-analysis of the stricture resolution rate during the reported follow-up after initial stent placement yields a proportion of 0.611 [95% CI: 0.311 – 0.870] [8-13].

We wish to demonstrate that the rate of stricture resolution using the metal stent approach is non-inferior compared to the plastic stent approach.

8.3. *Eligibility of Subjects, Exclusions, and Missing Data*

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure and will be analyzed per the SAP (Statistical Analysis Plan).

8.4. *Analysis Populations*

8.4.1. Enrolled Cohort

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

8.4.2. Intent-to-Treat Cohort

This cohort consists of those "enrolled" subjects who meet all inclusion/exclusion criteria and are subsequently randomized. Subjects in this cohort who do not receive a study stent(s) will be counted towards the enrollment ceiling. Any adverse events occurring or resulting from a treatment attempt will be collected. Protocol deviations will be collected as necessary.

8.4.3. Per-Protocol Cohort

The per-protocol cohort is a subset of the ITT subjects who receive a study stent(s) and no major protocol deviations (ICH E9 definitions).

8.5. *Analysis*

The following analyses are planned:

- Informal Interim Analysis (no hypothesis testing) once the first 50 subjects have reached 24 months post initial stent placement.
- Final Analysis after all subjects have reached 24 months post initial stent placement.

8.6. *Statistical Analysis*

All statistical analyses will be done using The SAS System software, version 8 or higher (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved). Subject demographics, clinical history, risk factors, pre- and post-procedure characteristics and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and frequency statistics (percent of conformers, number of conformers, number of observations) for discrete variables.

8.6.1. Baseline Comparability

The baseline characteristics of subjects among centers and between treatments will be assessed using standard statistical tests. Any significant differences will be identified and investigated per SAP.

8.6.2. Post-Procedure Endpoints

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical trial schedule and will be summarized using descriptive statistics for continuous variables and frequency statistics for discrete variables. Estimates of primary and secondary endpoints will be reported by treatment group, as well as differences between treatment groups and their 95% confidence intervals.

Impact of baseline variables on endpoints will be analyzed using logistic regression, ANOVA, stratified methods or Kaplan-Meier methods per section 8.6.1 and the SAP.

8.6.3. Pooling Across Institutions

The analyses will be presented using data pooled across institutions and poolability will be analyzed per the SAP.

9. Data Management

9.1. *Data Collection, Processing, and Review*

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

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by 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 all queries in the database.

9.2. *Data Retention*

The Investigator will maintain, at the investigative site, in original format 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 local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator 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.

10. Potential Risks and Benefits

10.1. *Anticipated Adverse Device Effects*

As per the commercial DFU included with the study devices, the potential complications associated with metal stent placement include, but are not limited to:

- Pain
- Bleeding
- Fever
- Nausea
- Vomiting
- Infection
- Inflammation
- Stent occlusion
- Tumor overgrowth around ends of stent
- Tumor ingrowth through the stent
- Mucosal hyperplasia
- Cholangitis
- Cholecystitis*
- Pancreatitis
- Ulceration of duodenum or bile duct
- Perforation of duodenum or bile duct
- Stent migration
- Death (other than that due to normal disease progression)
- Stent misplacement
- Perforation of the gallbladder due to the stent covering the cystic duct*
- Stent Fracture
- Hepatic abscess

  *Note: In a small clinical trial of this device, two out of four (50%) subjects who had a stent placed across the cystic duct developed cholecystitis. One of these subjects suffered a perforated gallbladder due to the stent covering the cystic duct, requiring a drain to be placed.

As per the commercial DFU included with the study devices, potential complications associated with stent removal include, but are not limited to:

- Pain
- Bleeding
- Fever
- Nausea
- Vomiting
- Infection
- Inflammation
- Recurrent obstructive jaundice
- Mucosal hyperplasia
- Cholangitis
- Cholecystitis
- Pancreatitis
- Ulceration of duodenum or bile duct
- Perforation of duodenum or bile duct

- Death (other than that due to normal disease progression)
- Impaction to the common bile duct wall

The following specific definitions will be used:

- Pancreatitis: Abdominal pain and a serum concentration of pancreatic enzymes (amylase or lipase) three or more times the upper limit of normal, that required more than one night of hospitalization
- Cholecystitis: No suggestive clinical or radiographic signs of cholecystitis before the procedure and if emergency cholecystectomy is subsequently required
- Perforation: Retroperitoneal or bowel-wall perforation documented by any radiographic technique or direct visual evidence
- Stent Occlusion: Recurring obstructive jaundice with necessary stent replacement
- Hepatic Abscess: Intra-hepatic fluid collection with positive cultures identified when possible by ultrasonography or computed tomography, associated with persistent fever and elevations of white blood cells
- Cholangitis: Elevation in temperature more than 38°C, thought to have a biliary cause, without concomitant evidence of acute cholecystitis, requiring intervention
- Bleeding: Bleeding requiring endoscopic hemostatic intervention and/or transfusion

10.2. *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.

10.3. *Anticipated Benefits*

Subjects may not receive any benefit from participating in this study. However, medical science and future subjects may benefit from this study.

10.4. *Risk to Benefit Rationale*

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

11. Safety Reporting

11.1. *Definitions and Classification*

Adverse event definitions are provided in Table 11.1-1.

Table 11.1-1: Adverse Event Definitions

Term	Definition

Table 11.1-1: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011*	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal lab findings) in subjects, users or other persons, whether or not related to the investigational medical device. This includes events related to: • The investigational medical device or comparator • The procedures involved (study-required) For users/other persons, this definition is restricted to events related to the investigational device
Adverse Device Effect (ADE) *Ref: ISO 14155-2011*	Adverse event related to the use of an investigational medical device: • This includes adverse events resulting from insufficient or inadequate instructions for the use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device. • This includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011*	An adverse event that: • Led to death • Led to a serious deterioration in the health of the subject that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolonged hospitalization (of an existing hospitalization), or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **Note**: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event. **Note**: For SAE reporting requirements see the information below for SADE.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011*	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. **Note**: All SAEs that could have led to a SADE if suitable action had not been taken or if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the protocol. If applicable, see MEDDEV 2.7/3 12/2010 for reporting timeline requirements.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note**: Device deficiencies include malfunctions, use errors, and inadequate labeling. **Note**: All device deficiencies that could have led to a SADE if suitable action had not been taken or if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the

Table 11.1-1: Adverse Event Definitions

Term	Definition
	protocol. If applicable, see MEDDEV 2.7/3 12/2010 for reporting timeline requirements.

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

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 11.1-1 for AE definitions).
Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

Refer to Section 10.1 for the known risks associated with the study device(s).

11.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 11.2-1.

Table 11.2-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product. • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely. • There is no other reasonable medical explanation for the event.

11.3. *Investigator Reporting Requirements*

11.3.1. Serious Adverse Events

These events should be reported to the Global Safety Office and/or Project Manager **within 2 business days** of first becoming aware of the event. Events should be documented in the eCRF and all relevant source documentation for the event should be provided to the Global Safety Office, as applicable.

11.3.2. Adverse Events

Device and procedure-related events should be reported to the Global Safety Office and/or Project Manager **within 10 business days** of first becoming aware of the event. Unrelated AEs will not be collected.

11.3.3. Device Failures, Malfunctions, and Product Nonconformities

These events should be reported to Project Manager and/or Global Safety Office **within 1 business days** of first becoming aware of the event. Events should be documented in the eCRF.

11.4. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies, failures, malfunctions, and product nonconformities are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

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

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

The Principal Investigator is responsible for informing the IRB/EC and regulatory authorities of SAEs as required by local procedure.

12. 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/CA) of the revised protocol must be obtained prior to implementation.

13. 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 and the date of occurrence, must be documented and reported to the sponsor via the EDC CRF page in the database. Site 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 notification, center re-training, or discontinuation) will be put into place by the sponsor.

14. Device/Equipment Accountability

There are no investigational devices used in this study. The WallFlex Biliary RX Fully Covered Stent System is available for commercial use in the geographic areas in which this clinical study is taking place; therefore, there is no requirement for device accountability for the purposes of this study. Device lot information must be maintained in the subject's medical record and recorded on the appropriate case report form.

Any individual country/region requirements that depart from the aforementioned will be implemented on a case-by-case basis.

15. Compliance

15.1. *Statement of Compliance*

This study will be conducted in accordance with relevant sections of the International Standard (ISO) 14155: Clinical Investigation of Medical devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study will not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

15.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155, 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 study start, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center 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 and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, per local requirements, ensuring that the investigational 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 monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with 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.

15.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the 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.

15.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center 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.

15.4. *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 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' 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.

15.5. *Insurance*

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

16. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the 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 Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The 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 Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

17. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their 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, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center'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 center's IRB/EC. Any modification requires approval 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 center 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 be conducted as follows:

- 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 and by the investigator 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 center 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. 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 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. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

18. Suspension or Termination

23.1 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.

23.1.1 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.

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

Any investigator, or IRB/ EC 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.

23.3 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 centers 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 an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility, detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 2 months after center initiation or if the center has multiple or severe protocol violations/non-compliance without justification and/or fails to follow remedial actions. In the event of termination of investigator participation, the EC, as applicable, should be notified.

19. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, 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. In accordance with the Corporate Policy for the Conduct of Human Subject Research, 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.

20. Bibliography

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21. Abbreviations and Definitions

Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BSC	Boston Scientific Corporation
CRF	Case Report Form
CT	Computed Tomography
DFU	Directions for Use
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
ERCP	Endoscopic Retrograde Cholangiopancreatography
FDA	Food and Drug Administration
Gamma GT	Gamma-Glutamyl Transpeptidase
GCP	Good Clinical Practices
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ISO	International Standards Organization
LFT	Liver Function Test
MS	Metal Stent
PI	Principal Investigator
Plastic Stent	Plastic Stent
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SEMS	Self-Expanding Metal Stent
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase