Pre-operative Biliary SEMS RCT During Neoadjuvant Therapy

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Clinical Protocol

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Randomized Controlled Trial Comparing Covered and Uncovered Biliary Self Expanding Metal Stents (SEMS) for Pre-operative Drainage During Neoadjuvant Therapy in Patients with Pancreatic Cancer

Short Title
Pre-operative Biliary SEMS RCT During Neoadjuvant Therapy

CLINICAL PROTOCOL

E7034

Sponsored By

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Investigator's Signature Page

STUDY TITLE: Randomized Controlled Trial Comparing Covered and Uncovered Biliary Self Expanding Metal Stents (SEMS) for Pre-operative Drainage During Neoadjuvant Therapy in Patients with Pancreatic Cancer

STUDY CENTER: _____

(Print name of study center)

PROTOCOL VERSION: AE

We, the undersigned, have read and understand the protocol specified above and agree on its content. We agree to perform and conduct the study as described in the protocol. In addition, when applicable, we agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

_____ _____

Principal Investigator Date

Print name:

_____ _____

Co-Principal Investigator (if applicable) Date

Print name:

Protocol Synopsis

Full Title	Randomized Controlled Trial Comparing Covered and Uncovered Biliary Self Expanding Metal Stents (SEMS) for Pre-operative Drainage During Neoadjuvant Therapy in Patients with Pancreatic Cancer
Abbreviated Title	Pre-operative Biliary SEMS RCT During Neoadjuvant Therapy
Primary Objective	To demonstrate non-inferiority of Fully Covered biliary SEMS to Uncovered biliary SEMS in biliary drainage for the pre-operative management of biliary obstructive symptoms caused by pancreatic cancer in patients undergoing neoadjuvant therapy.
Devices	Stent Type: FC Arm: WallFlex Biliary RX Fully Covered Stent UC Arm: WallFlex Biliary RX Uncovered Stent Stent Diameter: 8mm or 10mm Stent Length: 40mm, 60mm, or 80mm The stent length will be selected to be such that the stent length should be long enough to cover the stricture completely but to leave sufficient length of normal bile duct for subsequent anastomosis.
Device Indication	The WallFlex Biliary RX Fully Covered Stent is indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms, relief of malignant biliary obstruction prior to surgery, and for treatment of benign biliary strictures. The WallFlex Biliary RX Uncovered Stent is indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms and relief of malignant biliary obstruction prior to surgery.
Study Design	Prospective, multi-center, randomized, post-market

Primary Endpoint	Successful pre-operative biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms. • For patients undergoing surgery: from stent placement until surgery • For patients transitioning to palliative management: from stent placement until transition to palliation
Secondary Endpoints	1. Occurrence and severity of adverse events related to the stent and/or stenting procedure 2. Occurrence and severity of surgical complications 3. Occurrence and severity of peri-surgical complications (up to 30 days after surgery) 4. Ability to deploy the stent in a satisfactory position across the stricture (Stent Placement Success) 5. Improvement of biliary obstructive symptoms during stent indwell at Week 1 and Monthly until surgery or transition to palliation as applicable, compared to Baseline 6. Improvement of Laboratory Liver Function Tests (LFTs) until surgery for patients undergoing surgery, and at Week 1 and Monthly until transition to palliation, and at 1 year after stent placement for patients not undergoing surgery. 7. Biliary Reintervention rate 8. Ability to complete neoadjuvant therapy as intended without stent related interruptions of neoadjuvant therapy 9. Stent migration rate 10. Assessment by surgeon of interference, if any, of SEMS on time to surgery and/or success of pancreaticoduodenectomy 11. For patients transitioning to palliative management: Successful biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms from stent placement to 1 year after stent placement
Hypothesis	Statistical testing will be performed to determine if the rate of success when using the Fully Covered SEMS is non-inferior to the rate of success when using the Uncovered SEMS. The following hypothesis will be tested: Ho: $\pi_{UC} - \pi_{FC} \geq \Delta$ (Inferior)

	Ha: $\pi_{UC} - \pi_{FC} < \Delta$ (Non-inferior) where π_{FC} and π_{UC} are the probabilities of having success in the WallFlex Fully Covered Stent and WallFlex Uncovered Stent arms respectively, and Δ is defined as the non-inferiority margin. The sample size was calculated for the test using an exact non-inferiority test. The assumed success rates for both study arms and the non-inferiority margin are guided by the following analysis of literature: The success rate estimate is extracted from a full literature search which yielded nine articles (377 patients) [2, 7, 21, 24, 25, 27, 29-31] on the use of metal stents for pre-operative biliary drainage. The nine articles yielded a success rate estimate of 84.6% with a 95% CI of (80.5% - 87.9%). Each arm is assumed to have a success rate of 80.5%. The non-inferiority margin (Δ) is set at 20%. Given these assumptions a sample size of 51 x 2 = 102 patients provide 80% power to reject the null hypothesis. If the p-value calculated for the test is below 0.05 it will be concluded that the test is significant, and that the WallFlex Fully Covered stent is non-inferior to the WallFlex Uncovered stent. An additional 20% of patients will be enrolled to compensate for possible loss of patients to follow-up, giving a total sample size of 122 patients.
Planned Number of Patients	122
Planned Number of Sites	6-12
Key Inclusion Criteria	1. Age 18 or older 2. Patient indicated for biliary metal stent placement for the treatment of jaundice and/or cholestasis 3. Willing and able to comply with the study procedures and provide written informed consent to participate in the study 4. Suspicion of pancreatic adenocarcinoma

	5. Likely indicated for neoadjuvant treatment 6. Distal biliary obstruction consistent with pancreatic cancer 7. Location of distal biliary obstruction such that it would allow the proximal end of a stent to be positioned at least 2 cm from the hilum 8. Endoscopic and surgical treatment to be provided at the same institution
Key Exclusion Criteria	1. Benign biliary strictures 2. Malignancy secondary to Intraductal Papillary Mucinous Neoplasm 3. Surgically altered anatomy where ERCP is not possible 4. Previous biliary drainage using a SEMS or multiple plastic stents 5. Contraindications for endoscopic techniques 6. Patients who are currently enrolled in another investigational trial that would directly interfere with the current study 7. Pregnancy
Visits	• Screening • Baseline • Stent Placement Procedure Visit • Pre-Operative Follow-Up Visit (Week 1 and Monthly until Surgery or Transition to Palliation) • Biliary Reintervention Visit (as needed) • Curative Intent Surgery • Transition to Palliative Management Visit (as needed) • Post-Operative Follow-Up Visit (30 day Post-Surgery visit) • Long Term Follow-Up Visit (1 year after initial treatment for patients that have transitioned to palliation or 1 year post-stent placement for patients that have not undergone surgery or transitioned to palliation (with or without Neoadjuvant Therapy))

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1. Introduction

In the United States, pancreatic cancer is the second most common digestive cancer[1] and the fourth leading cause of death with a 5-year survival rate of only 5%.[2] Globally, there are an estimated 216,000 new cases of pancreatic cancer annually.[3] Pancreatic cancer, which is the most prevalent peri-ampullary cancer, is located in the head of the pancreas in approximately two thirds of cases.[4] Patients with pancreatic cancer presenting with biliary obstruction can be stratified into patients with unresectable tumors, with borderline resectable or locally advanced tumors, or with resectable tumors. More than 70% of pancreatic cancer patients are poor candidates for surgery or are deemed unresectable[5]; the WallFlex Biliary SEMS are currently indicated for use in these patients.

Some patients may be candidates for PD with curative intent, however, 25%-41% do not undergo PD as planned due to disease progression, evolving comorbidities, or decline in performance status during the time between diagnosis and scheduled PD.[6-8] Pre-operative neoadjuvant chemo or chemoradiation therapy is increasingly considered in the treatment of patients with resectable or borderline resectable pancreatic cancer. The aim is to downsize tumors and improve the likelihood of a margin-free (R0) resection, to provide early treatment of micrometastases, and ultimately to optimize post-operative survival.[9-13] In a recent report, 32 of 84 (38%) patients with borderline resectable disease underwent a PD after neoadjuvant therapy, with R0 resection achieved in 94% of patients and resulting median survival of 40 months post PD.[13] In another report on 132 patients with resectable pancreatic cancer, it was found that combined neoadjuvant chemoradiation and PD yielded a median survival of 21 months from the time of tissue diagnosis, and at a median follow-up of 14 months 42 of 132 patients (32%) survived with no clinical or radiographic evidence of disease.[14] The duration of neoadjuvant chemoradiation typically ranges from 2 to 7 months[6,14] and tends to require a subsequent pre-operative resting and restaging period which can last up to several months.[7]

Periampullary cancer including cancer in the head of the pancreas is associated with biliary obstructive symptoms such as jaundice at initial patient presentation in approximately 50%-70% of patients.[7] Biliary obstruction requires biliary decompression.[6,15] Indeed, if left untreated, prolonged biliary obstruction leads to coagulopathy, malabsorption and consequent progressive malnutrition, pruritus, hepatic dysfunction, recurrent attacks of cholangitis and altered bile salt metabolism.[16,17] Pre-operative biliary drainage provides relief of biliary obstructive symptoms during neoadjuvant therapy[18,19] and improves post PD tissue healing in response to reduced bilirubin levels.[20] Without such pre-operative drainage patients may lose their resectable or potentially resectable status due to interruption of the neoadjuvant therapy and/or delayed scheduling of the intended PD. In addition, for patients receiving 3 to 4 months of neoadjuvant therapy, biliary drainage may be beneficial since some chemotherapeutic agents require adequate liver function and pre-operative immunosuppression can increase susceptibility to the risks of cholangitis if bile duct drainage is inadequate.[21] If severely jaundiced patients do undergo PD, they may be at risk of significant post-operative complications[36] such as renal failure and

sepsis.[22,23] It is therefore important that pre-operative biliary drainage be provided during neoadjuvant therapy and the subsequent restaging and resting period.

Pre-operative biliary drainage has traditionally been achieved with plastic stents. However, these stents have been associated with high complication rates and relatively low success rates in pre-operative management of biliary obstruction.[6,21,24-27] Plastic stents used for pre-operative drainage can occlude within a few weeks which in turn may necessitate additional pre-operative ERCPs[21]. The use of SEMS provides a viable alternative that has been shown to be superior to plastic stents for pre-operative biliary drainage due to lower rates of occlusion, fewer episodes of cholangitis/cholestasis, fewer additional ERCPs before surgery, and longer stent patency resulting in most patients completing uninterrupted neoadjuvant chemoradiation therapy and preventing delays of surgery.[1,24,27]

A literature review was conducted of clinical success of pre-operative biliary drainage using plastic or metal biliary stenting including all SEMS types used. Two associated meta-analyses were generated based on published reports of ratios of the number of patients experiencing clinical success in pre-operative biliary drainage without stent related complications over the total number of stented patients. A meta-analysis representing a total of 429 patients in six publications using plastic biliary stents yielded a biliary drainage success rate estimate of 45.9% [95% CI, 34.7% - 57.5%].[2,6, ,24-27] A meta-analysis representing a total of 377 patients in nine publications using SEMS yielded a biliary drainage success rate estimate of 84.6% [95% CI, 80.5% - 87.9%].[2, 7, 21, 24, 25, 27, 29-31] In patients who do ultimately undergo PD with curative intent, the SEMS is removed en-bloc inside the surgical specimen. Six of the 9 publications reporting on the use of pre-operative biliary drainage using SEMS state explicitly on the fact that SEMS do not interfere with successful PD and could be easily removed intra-operatively without complications. [7,21,24,25,27,31] Some studies have reported an increased risk of post-operative wound infection[13,33-35], but there were no other reported increases in intra-operative or post-operative complications related to the use of SEMS. In addition, SEMS could be easily removed intra-operatively without complications.[20, 27-30]

Pre-operative biliary drainage (PBD) prior to Pancreaticoduodenectomy (PD) continues to be routine in many centers despite retrospective data showing that PBD increases post-operative wound infection.[13,33-35] It was shown that these post-operative wound infections were classified on a grading scale of 1-5, with all reported occurrences rated as either 1 (oral medication and bedside intervention) or 2 (IV medication, TPN, enteral nutrition, or blood), and managed non-invasively.[33] Other studies have also reported an increase in post-operative wound infection in the PBD group, but have indicated that although there is an increase in length of hospitalization, the length of time under anesthesia, amount of blood loss, and transfusion requirements were unaffected.[32,34]

In line with the findings summarized above, SEMS have emerged as an alternative to using plastic stents for pre-operative biliary drainage. Several opinion-leading centers in this field have adopted SEMS drainage as their standard of practice in PD-bound patients undergoing

neoadjuvant therapy. Most recently leading cancer centers[7, 21, 32] have published that the use of pre-operative biliary SEMS, and not plastic stents, in patients with resectable or potentially resectable pancreatic or periampullary cancer receiving neoadjuvant therapy is effective and safe. Boston Scientific is proposing a multi-center, randomized, prospective, post-market trial on the use of SEMS for biliary drainage in patients with pancreatic cancer undergoing neoadjuvant therapy.

2. Objectives

The purpose of this clinical trial is to demonstrate non-inferiority of Fully Covered biliary SEMS to Uncovered biliary SEMS in biliary drainage for the pre-operative management of biliary obstructive symptoms caused by pancreatic cancer in patients undergoing neoadjuvant therapy.

3. Design

This is a post-market, prospective, multi-center, randomized study evaluating covered and uncovered SEMS for pre-operative management of patients with pancreatic cancer undergoing neoadjuvant therapy.

3.1. Scale and Duration

Patients that have gone to surgery will be followed for 30 days post-surgery. For patients that have transitioned to palliation, the Long Term Follow-Up Visit will occur one (1) year after initial treatment. Patients that have not gone to surgery and have not transitioned to palliation (with or without Neoadjuvant Therapy) will be followed up to 1 year post-stent placement. There will be 6-12 participating centers with anticipated enrollment of 122 patients.

At each investigational center, there will be one principal investigator (PI) who will be an endoscopist. Where possible at least one co-investigator should be a pancreaticobiliary surgeon.

3.2. Treatment Assignment

Patients will be randomized at Screening in equal proportions of 1:1 ratio between Arm 1 and Arm 2 as follows:

- Arm 1: WallFlex Biliary RX Fully Covered Stent
- Arm 2: WallFlex Biliary RX Uncovered Stent

Block randomization through an online database system will be used. Randomization will be stratified by study center.

4. Endpoints

4.1. Primary Endpoint

Successful pre-operative biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms.

- For patients undergoing surgery: from stent placement until surgery
- For patients transitioning to palliative management: from stent placement until transition to palliation

4.2. Secondary Endpoints

1. Occurrence and severity of adverse events related to the stent and/or stenting procedure
2. Occurrence and severity of surgical complications
3. Occurrence and severity of peri-surgical complications (up to 30 days after surgery)
4. Ability to deploy the stent in satisfactory position across the stricture (Stent Placement Success)
5. Improvement of biliary obstructive symptoms during stent indwell at Week 1 and Monthly until surgery or transition to palliation as applicable, compared to Baseline
6. Improvement of Laboratory Liver Function Tests (LFTs) until surgery for patients undergoing surgery, and at Week 1 and Monthly until transition to palliation, and at 1 year after stent placement for patients not undergoing surgery
7. Biliary Reintervention rate
8. Ability to complete neoadjuvant therapy as intended without stent related interruptions of neoadjuvant therapy
9. Stent migration rate
10. Assessment by surgeon of interference, if any, of SEMS on time to surgery and/or success of pancreaticoduodenectomy
11. For patients transitioning to palliative management: Successful biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms from stent placement to 1 year after stent placement

5. Patient Selection

5.1. Inclusion Criteria

Patients who meet all of the criteria listed below (see Table 1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Table 2) is met.

Table 1: Inclusion Criteria

Clinical Inclusion Criteria	1. Age 18 or older 2. Patient indicated for biliary metal stent placement for the treatment of jaundice and/or cholestasis 3. Willing and able to comply with the study procedures and provide written informed consent to participate in the study 4. Suspicion of pancreatic adenocarcinoma 5. Likely indicated for neoadjuvant treatment 6. Distal biliary obstruction consistent with pancreatic cancer 7. Location of distal biliary obstruction such that it would allow the proximal end of a stent to be positioned at least 2 cm from the hilum 8. Endoscopic and surgical treatment to be provided at the same institution

5.2. Exclusion Criteria

Patients who meet any one of the following criteria (See Table 2) will be excluded from this clinical study.

Table 2: Exclusion Criteria

Clinical Exclusion Criteria	1. Benign biliary strictures 2. Malignancy secondary to Intraductal Papillary Mucinous Neoplasm 3. Surgically altered anatomy where ERCP is not possible 4. Previous biliary drainage using a SEMS or multiple plastic stents 5. Contraindications for endoscopic techniques 6. Patients who are currently enrolled in another investigational trial that would directly interfere with the current study 7. Pregnancy

6. Study Devices

The WallFlex Biliary RX Fully Covered stent and the WallFlex Biliary RX Uncovered stent will be used for the treatment of patients.

The WallFlex Biliary RX Fully Covered and the WallFlex Biliary RX Uncovered Stent Systems are indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms and relief of malignant biliary obstruction prior to surgery; the WallFlex Biliary RX Fully Covered Stent System is also indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms and treatment of benign biliary strictures, per CE Mark. For a detailed description of the WallFlex Biliary Stent Systems, please reference the Directions for Use (DFU) included in each device package.

Investigators should use the WallFlex Biliary RX Fully Covered and Uncovered Stent Systems in accordance with the DFUs.

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

Study devices will be available in the following dimensions:

WallFlex Biliary RX Stent	Diameter	Length	Delivery System Diameter	Guidewire Diameter
Uncovered	8 mm 10 mm	40, 60, 80mm 40, 60, 80mm	8 Fr	.035”
Fully Covered	8 mm 10 mm	60, 80mm 40, 60, 80mm	8.5 Fr	.035”

Stent placement should be such that the proximal end of the stent is minimum 2 cm from the hilum. Performing a biliary or pancreatic sphincterotomy or enlarging a prior sphincterotomy will be done at the discretion of the endoscopist. Per literature, it is recommended that the shortest length of stent required to bridge the stricture[21] is used so as to leave enough of the normal bile duct above the stent available for subsequent anastomosis[7, 21,24,25,29]. It is hence anticipated that SEMS of 80 mm length will rarely or never be selected in this trial.

In case of a failed stent placement due to a device event, a new attempt to place a stent will be made. If a stent placement is not possible due to non-device related reasons (such as inability to cannulate the CBD or reach the papilla, extensive tumor growth at site of papilla, etc.), interventional radiologic (IR) access is allowed and, where possible, should be associated with placement of a study stent over a transhepatically inserted guide-wire in a "rendez-vous"

procedure. Percutaneous transhepatic cholangiography (PTC) and a subsequent internal drainage with a stent placement may be done at the same time (one-stage procedure), or PTC with external drainage may be performed 2-3 days before stent insertion (two-stage procedure) per standard of practice. If access to the biliary tree or endoscopic placement of the study stent through a "rendez-vous" procedure fails and patient requires percutaneous transhepatic biliary drainage (PTBD), then the patient will exit the study. In case of failure of SEMS functionality during the neoadjuvant therapy, a new investigational SEMS may be placed, covered or uncovered at the discretion of the investigator. In case of failure of SEMS functionality after transition to palliation, no new investigational SEMS will be provided and patient should be treated per standard of practice.

7. Study Visits

7.1. Visit Schedule

The schedule of observations and assessments to take place during the study is shown in Table 3 below.

Table 3. Study Event Schedule

Procedure/Assessment	Screening	Baseline	Stent Placement Procedure Visit	Pre-Operative Follow-Up Visits				Biliary Reintervention	Curative Intent Surgery	Transition to Palliative Management Visit	Post-Operative Follow-Up Visit - 30 days from surgery (±15 Days) Office Visit	*Long Term Follow-Up Visit (± 30 Days)
					Week 1 (± 2 Days) Office Visit/ Telephone Interview		Monthly (±15 Days) Office Visit/ Telephone Interview					
ICF	X											
Demographics		X										
Medical history		X										
Collection of Weight		X			X		X					
Assessment of Biliary Obstructive Symptoms		X			X		X		X	X	X	X (if applicable)
Laboratory Liver Function Test (LFTs)		X			X		X			X		X (if applicable)
Imaging[a]		X										
Tumor Diagnosis, Staging, and Characteristics		X										
Randomization	X											
Stent Details			X					X (if applicable)	X			
Procedure Details			X					X (if applicable)				
Operative Details									X			
Specimen Pathology									X			
Planned Neoadjuvant therapy		X										
Administered Neoadjuvant therapy (if applicable)					X		X		X			

Procedure/Assessment	Screening	Baseline	Stent Placement Procedure Visit	Pre-Operative Follow-Up Visits				Biliary Reintervention	Curative Intent Surgery	Transition to Palliative Management Visit	Post-Operative Follow-Up Visit - 30 days from surgery (±15 Days) Office Visit	*Long Term Follow-Up Visit (± 30 Days)
					Week 1 (± 2 Days) Office Visit/ Telephone Interview		Monthly (±15 Days) Office Visit/ Telephone Interview					
Surgical assessment of tumor invasion									X			
Patient's overall health status		X			X		X		X		X	X
Adverse events and reinterventions	X (as applicable)											
Device Events	X (as applicable)											
Protocol Deviation	X (as applicable)											

[a] ERCP, CT and/or MRI

*Long Term Follow-Up Visit: 1 year after initial treatment for patients that have transitioned to palliation or 1 year post-stent placement for patients that have not undergone surgery or transitioned to palliation (with or without Neoadjuvant Therapy)

7.2. **Screening –** *Office Visit*

- Informed Consent
- Eligibility Criteria Assessment
- Randomization

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

Written Informed Consent must be obtained for all patients who are potential study candidates. Patients 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). Study personnel should explain that even if a patient agrees to participate in the study and signs an Informed Consent Form, the inclusion/exclusion criteria may demonstrate that the patient is not a suitable candidate for the study. Screening and enrollment information will be collected in the database for all patients who sign a consent form.

7.3. ***Baseline Visit –*** *Office Visit*

- Demographics
- Medical history
- Collection of Weight
- Patient's overall health status
- Assessment of Biliary Obstructive Symptoms
    - Right Upper Quadrant Pain
    - Fever/Chills
    - Jaundice
    - Itching
    - Dark urine
    - Pale stools
    - Nausea/Vomiting
- Laboratory Liver Function Tests (LFTs)
    - Serum Albumin level
    - Total Bilirubin
    - Alkaline Phosphatase
    - SGPT (ALT)

- Imaging

7.4. ***Tumor Diagnosis, Staging, and Characteristics –*** *Office Visit*

- Tumor Diagnosis, Staging, and Characteristics can occur any time between the Screening Visit and the Stent Placement Procedure Visit

7.5. ***Planned Neoadjuvant Therapy***

- Planned Neoadjuvant Therapy can occur any time between the Screening Visit and the Stent Placement Procedure Visit

7.6. ***Stent Placement Procedure Visit –*** *Office Visit*

- Placement of WallFlex Biliary RX stent(s)
    - During WallFlex Biliary RX placement the stent should be adjusted with the proximal end of the stent no more than 1-2cm beyond the proximal end of the stricture. This favors both stability and homogeneous development of tissue hyperplasia at the proximal uncovered part.
- Procedure Details
- Stent Details
- Adverse Events (as applicable)
- Device Events (as applicable)

7.7. ***Pre-Operative Follow-Up Visit*** *– Phone and/or Office Visit*

- Week 1 and Monthly until surgery or transition to palliation as applicable
- Collection of Weight
- Patient's overall health status
- Assessment of Biliary Obstructive Symptoms
    - Right Upper Quadrant Pain
    - Fever/Chills
    - Jaundice
    - Itching
    - Dark urine
    - Pale stools
    - Nausea/Vomiting
- Laboratory Liver Function Tests (LFTs)
    - Serum Albumin level
    - Total Bilirubin
    - Alkaline Phosphatase
    - SGPT (ALT)

- Administered Neoadjuvant therapy
- Adverse events and reinterventions (as applicable)
- Device Events (as applicable)

7.8. ***Biliary Reintervention Visit (Arm 1 or 2)*** *– as needed*

- Timing
- Reason for Biliary Reintervention
- Type of Biliary Reintervention (including SEMS placement or removal)
- Adverse Events (as applicable)
- Device Events (as applicable)

7.9. ***Curative Intent Surgery –*** *Office Visit*

- Patient's overall health status
- Assessment of Biliary Obstructive Symptoms
    - Right Upper Quadrant Pain
    - Fever/Chills
    - Jaundice
    - Itching
    - Dark urine
    - Pale stools
    - Nausea/Vomiting
- Operative Details
- Stent Removal
- Surgical Complications including intraoperative blood loss
- Intra- and Post-Operative Transfusion
- Post-Operative Course
- Specimen Pathology
- Administered Neoadjuvant therapy
- Adverse events and reinterventions (as applicable)
- Device Events (as applicable)

7.10. ***Transition to Palliative Management Visit (as needed) –*** *Phone and/or Office Visit*

- Assessment of Biliary Obstructive Symptoms
    - Right Upper Quadrant Pain
    - Fever/Chills
    - Jaundice
    - Itching
    - Dark urine
    - Pale stools

  - Nausea/Vomiting
- Laboratory Liver Function Tests (LFTs)
  - Serum Albumin level
  - Total Bilirubin
  - Alkaline Phosphatase
  - SGPT (ALT)
- Adverse Events (as applicable)
- Device Events (as applicable)

7.11. ***Post-Operative Follow-Up Visit (30 days) –*** *Phone and/or Office Visit*

- Day 30 Post-Surgery Visit
- Patient's overall health status
- Assessment of Biliary Obstructive Symptoms
  - Right Upper Quadrant Pain
  - Fever/Chills
  - Jaundice
  - Itching
  - Dark urine
  - Pale stools
  - Nausea/Vomiting
- Adverse events and reinterventions (as applicable)
- Device Events (as applicable)

7.12. ***Long Term Follow-Up Visit (1 year after initial treatment for patients that have transitioned to palliation or 1 year post-stent placement for patients that have not undergone surgery or transitioned to palliation (with or without Neoadjuvant Therapy) –*** *Phone and/or Office Visit*

- For patients not undergoing surgery
- Patient's overall health status
- Assessment of Biliary Obstructive Symptoms
  - Right Upper Quadrant Pain
  - Fever/Chills
  - Jaundice
  - Itching
  - Dark urine
  - Pale stools
  - Nausea/Vomiting
- Laboratory Liver Function Tests (LFTs)
  - Serum Albumin level
  - Total Bilirubin
  - Alkaline Phosphatase

- SGPT (ALT)

- Adverse events and reinterventions (as applicable)
- Device Events (as applicable)

7.13. *Study Completion*

End of study will be reached at:

- Up to 30 days post-surgery for those patients undergoing potential curative intent surgery
- 1 year post stent placement for patients that have transitioned to palliation within 12 months after stent placement
- 1 year post stent placement for patients who do not undergo potential curative intent surgery and do not transition to palliation within 12 months after stent placement (with or without Neoadjuvant Therapy)

End of study will be reached at study completion, at patient withdrawal from study, or at death, whichever comes first.

8. Statistical Considerations

8.1 *Hypotheses*

Compared to the use of an Uncovered SEMS, use of a Fully Covered SEMS may present a higher risk of migration, but offers the ability to remove the stent were this deemed indicated by the treating endoscopist. Statistical testing will be performed to determine if the rate of success when using the Fully Covered SEMS is non-inferior to the rate of success when using the Uncovered SEMS. The following hypothesis will be tested:

$Ho: \pi_{UC} - \pi_{FC} \geq \Delta$ (Inferior)
$Ha: \pi_{UC} - \pi_{FC} < \Delta$ (Non-inferior)

where π_{FC} and π_{UC} are the probabilities of having success in the WallFlex Fully Covered Stent and WallFlex Uncovered Stent arms respectively, and Δ is defined as the non-inferiority margin.

8.2 *Sample Size*

The sample size was calculated for the test using an exact non-inferiority test in StatXact 9® software. The non-inferiority margin (Δ) is set at 20%. Each arm is assumed to have a success rate of 80.5%, which is the lower 95% CI boundary from the meta-analysis, which is

done below. Given these assumptions a sample size of 51 x 2 = 102 patients provides 80% power to reject the null hypothesis listed above. If the p-value calculated for the test is below 0.05 it will be concluded that the test is significant and that the WallFlex Fully Covered stent is non-inferior to the WallFlex Uncovered stent.

In order to compensate for possible loss of patients to follow-up or per Endoscopist's decision to select the Uncovered stent based on ductal anatomy, namely stricture involving the low cystic duct confluence, an additional 20% of patients will be enrolled giving a total sample size of 122 patients.

The success rate estimate is extracted from a full literature search which yielded nine articles (377 patients) [2, 7, 21, 24, 25, 27, 29-31] on the use metal stents for pre-operative biliary drainage. The nine articles yielded a success rate estimate of 84.6% with a 95% CI of (80.5%, 87.9%).

8.3 *Analysis Populations*

8.3.1 Enrolled Cohort

A patient is considered "enrolled" after signing the study-specific ICF. Patients who sign the ICF but subsequently do not meet one or more of the eligibility criteria provided in Section 5.1 and Section 5.2 will be considered screen failures and excluded from the study.

8.3.2. Intent-to-Treat Cohort

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

8.3.3. Per-Protocol Cohort

The per-protocol cohort is a subset of the ITT patients who are treated per protocol and have no major protocol deviations (per ICH E9 definitions).

8.4 *Data 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).

The distribution of prognostic factors between patients with and without data will be examined. Statistical models that account for censored data will be employed in appropriate circumstances, e.g. for time-to-event outcomes. Sensitivity analyses will be conducted to assess the impact of missing data on the interpretation of the results, e.g. a tipping point analysis.

8.4.1. Baseline Data

Patient demographics, clinical history, risk factors, obstructive symptoms, LFTs, tumor diagnosis, patient overall health, neoadjuvant therapy, and assessment of tumor invasion will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

8.4.2. Post Procedure Data

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study event schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables.

8.4.3. Interim Analyses

No formal interim analyses are planned for this study.

8.4.4. Subgroup Analyses

Stratified analyses will include tabulating the primary endpoint and select secondary endpoints by patients that undergo potentially curative surgery versus transition to palliation, by bilirubin level above or below 3 mg/dL, and gender.

8.4.5. 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.

8.4.6. Multivariable Analyses

Univariate and multivariate analyses may be performed to assess the effect of potential predictors on the primary endpoint using logistic regression or Cox Proportional Hazards regression.

Variables from the following categories will be considered as possible predictors: demographics, tumor diagnosis, baseline LFTs, neoadjuvant therapy protocol, obstructive symptoms, baseline health status, and medical history. Factors from the univariate model with $p \leq 0.20$ will also be modeled multivariately using a stepwise procedure in a generalized linear model or Cox Proportional Hazards regression model. The significance thresholds for entry and exit into the model will be set to $p \leq 0.10$.

8.4.7. Changes to Planned Analyses

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

9. Potential Risks and Benefits

9.1. *Anticipated Adverse Device Effects*

The following anticipated adverse device effects (ADE) should be reported only if they are related to the stent and/or stenting procedure. They have been identified for the WallFlex Biliary FC and UC Stent, as indicated in the commercial Directions for Use (DFU) and may include, but are not limited to:

- Pain
- Bleeding
- Fever
- Nausea
- Vomiting
- Infection
- Inflammation
- Recurrent obstructive jaundice
- 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

9.2. *Anticipated Surgical Adverse Events*

- Pancreaticojejunostomy leakage
- Hepaticojejunostomy leakage

- Gastro-duodenojejunostomy leakage
- Delayed gastric emptying
- Biliary leakage
- Intra-abdominal abscess formation
- Wound infection
- Portal Vein Thrombosis
- Cholangitis
- Hemorrhage
- (Emergency) (re)laparotomy
- Pneumonia
- Myocardial infarction
- Mortality

9.3. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized by performing procedures in the appropriate hospital environment, adhering to patient selection criteria, and close monitoring the patient's physiologic status during research procedures and/or follow-up visits. Promptly supplying BSC with all pertinent information required by this protocol may facilitate inter-center communications regarding serious AEs.

9.4. *Anticipated Benefits*

Patients may not receive any benefit from participating in this study but this study may provide a future benefit to medical science and other patients. To date there is no broadly accepted standard of practice pertaining to the use of SEMS for Pre-operative management of patients with pancreatic cancer undergoing neoadjuvant therapy.

9.5. *Risk to Benefit Rationale*

Based on prior BSC's 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 patients is required as outlined in the protocol.

10. Safety Reporting

10.1. *Definitions and Classification*

Adverse event definitions are provided in **Table 4**.

Table 4: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in patients, 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*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the patient, 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 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*	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

Table 4: Adverse Event Definitions

Term	Definition
	applicable, see MEDDEV 2.7/3 12/2010 for reporting timeline requirements.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **Note:** Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
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, misuse or 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 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 4** for AE definitions).

All device-related events and all surgery related events experienced by the study patient after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

10.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device as related or unrelated. Unrelated AEs will not be reported. Per protocol, only complications related to stent and/or stenting procedures will be reported. See criteria in **Table 5**.

Table 5: 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 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.

10.3. *Investigator Reporting Requirements*

Investigators will be required to report all SAEs and ADEs.

10.3.1. Serious Adverse Events

These events should be reported to the Sponsor **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 Safety Trial Manager, as applicable.

10.3.2. Adverse Events

Device-related events should be reported to the Sponsor **within 10 business days** of first becoming aware of the event. Unrelated AEs will not be collected.

10.3.3. Device Failures, Malfunctions, and Product Nonconformities

These events should be reported to the Sponsor **within 1 business day** of first becoming aware of the event. Events should be documented in the eCRF.

10.4. *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 patient'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.

10.5. *Reporting to Regulatory Authorities / IRBs / 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 and regulatory authorities of SAEs as required by local procedure.

11. Bibliography

1. Bonin E, Baron T. *Preoperative biliary stents in pancreatic cancer.* J Hepaticobiliary Pancreat Sci 2011;18:621-629
2. Adams M, Anderson M, Myles J, et al. *Self-expanding metal stents (SEMS) provide superior outcomes compared to plastic stents for pancreatic cancer patients undergoing neoadjuvant therapy.* J Gastrointest Oncol 2012;3(4):309-313.
3. The World Health Organization. "Global cancer rates could increase by 50% to 15 million by 2020". 3 Apr. 2003. http://www.who.int/mediacentre/news/releases/2003/pr27/en/
4. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. *Cancer statistics*, 2007. CA Cancer J Clin 2007;57:43-66.
5. Dumonceau J, Devière J. *Self-expandable metal stents*. Baillière's Clinical Gastroenterology. 1999; 1:109-130.
6. Boulay BR, Gardner TB, Gordon SR. *Occlusion rate and complications of plastic biliary stent placement in patients undergoing neoadjuvant chemoradiotherapy for pancreatic cancer with malignant biliary obstruction*. J Clin Gastroenterol 2010 Jul;44(6):452-5
7. Singal AK, Ross WA, Guturu P, et al. *Self-Expanding Metal Stents for Biliary Drainage in Patients with Resectable Pancreatic Cancer: Single-Center Experience with 79 Cases.* Dig Dis Sci 2011 Jul 13. [Epub ahead of print]
8. Katz MH, Want H, Fleming JB, et al. *Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma.* Ann Surg Oncol 2009 Apr;16(4):836-47.
9. Lowy AM. *Neoadjuvant therapy for pancreatic cancer.* J Gastrointest Surg. 2008;12:1600–1608.
10. Evans DB, Wolff RA, Crane CH. *Neoadjuvant strategies for pancreatic cancer*. Oncology (Williston Park). 2001;15:727–737.
11. Greer SE, Pipas JM, Sutton JE, et al. *Effect of neoadjuvant therapy on local recurrence after resection of pancreatic adenocarcinoma.* J Am Coll Surg. 2008;206:451–457.
12. NCCN, *Guideline: Pancreatic Adenocarcinoma*, 2012
13. Wolff R. *Neoadjuvant Therapy for Resectable and Borderline Resectable Adenocarcinoma of the Pancreas.* Curr Drug Targets. 2012 Jun;13(6):781-8

14. Breslin T, Hess K, Harbison D, et al. *Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration.* Ann Surg Oncol. 2001 Mar;8(2): 123-32

15. Hidalgo M. *Pancreatic cancer*. N Engl J Med. 2010;362:1605–1617.

16. Feig BW, Berger DH, Fuhrman GM. *The M.D. Anderson surgical oncology handbook*. Lippincott Williams & Wilkins, 2006

17. Das A, Sivak MV. *Endoscopic palliation for inoperable pancreatic cancer.* Cancer Control 2000 Sep/Oct; 7(5): 452-457

18. Garcea G, Chee W, Ong SL, et al. *Preoperative biliary drainage for distal obstruction the case against revisited*. Pancreas 2010;39:119–126.

19. Coates JM, Beal SH, Russo JE, et al. *Negligible effect of selective preoperative biliary drainage on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy*. Arch Surg 2009;144:841–847.

20. Jaganmohan S, Lee J. *Self-expandable metal stents in malignant biliary obstruction.* Expert Rev. Gastroenterol Hepatol 2012. 6(1), 105-114

21. Aadam AA, Evans DB, Khan A, et al. *Efficacy and safety of self-expandable metal stents for biliary decompression in patients receiving neoadjuvant therapy for pancreatic cancer: a prospective study,* Gastrointest Endosc 2012 Jul;76 (1) :67-75. Epub 2012 Apr 5.

22. Lacaine F, Fourtanier G, Fingerut A, et al. *Surgical mortality and morbidity in malignant obstructive jaundice: a review of 373 patients.* Eur J Surg 1995;161:729–734.

23. Armstrong CP, Dixon JM, Taylor V, et al. *Surgical experience of deeply jaundiced patients with bile duct obstruction*. Br J Surg 1984;71:234–238.

24. Wasan SM, Ross WA, Staerkel GA, Lee GH. *Use of Expandable Metallic Biliary Stents in Resectable Pancreatic Cancer.* Am J Gastroenterol. 2005;100:2056–2061

25. Mullen JT, Lee JH, Gomez HF, Ross WA, et al. *Pancreaticoduodenectomy After Placement of Endobiliary Metal Stents.* J Gastrointest Surg 2005;9:1094–1105

26. van der Gaag NA, Rauws EAJ, van Eijck CHJ, et al. *Preoperative Biliary Drainage for Cancer of the Head of the Pancreas.* N Engl J Med 2010;362:129-37

27. Decker C, Christein JD, Phadnis MA et al. *Biliary metal stents are superior to plastic stents for preoperative biliary decompression in pancreatic cancer.* Surg Endosc 2011 Jul;25(7):2364-7. Epub 2011 Mar 4

28. Sanders Mk, El Hajj II, Slivka A, et al. *Placement of Self Expanding Metal Biliary Stents (SEMS) in Patients with Resectable Pancreatic Cancer [Abstract]*. Gastrointest Endosc 2009; 69 (5)

29. Kahaleh M, Brock A, Conaway MR, et al. *Covered self−expandable metal stents in pancreatic malignancy regardless of resectability: a new concept validated by a decision analysis.* Endoscopy 2007 Apr;39(4):319-24

30. Pop GH, Richter JA, Sauer B, et al. *Bridge to surgery using partially covered self-expandable metal stents (PCMS) in malignant biliary stricture: an acceptable paradigm?* Surg Endosc 2011 Feb;25(2):613-8

31. Lawrence C, Howell DA, Conklin DE, et al. *Delayed pancreaticoduodenectomy for cancer patients with prior ERCP-placed, nonforeshortening, self-expanding metal stents: a positive outcome*, Gastrointest Endosc 2006 May;63 (6): 804-807

32. Cavell L, Allen P, Vinoya C, et al. *Biliary Self-Expandable Metal Stents Do Not Adversely Affect Pancreaticoduodenectomy*. Am J Gastroenterol 2013 April; doi: 10.1038/ajg.2013.93

33. Mezhir, J., et al. *A matched case-control study of preoperative biliary drainage in patients with pancreatic adenocarcinoma: routine drainage is not justified.* J Gastrointest Surg, 2009. 13(12):p. 2163-9

34. Heslin, M., et al. *A preoperative biliary stent is associated with increased complications after pancreaticoduodenectomy.* Arch Surg, 1998. 133(2): p. 149-54.

35. Povoski, S., et al. *Preoperative biliary drainage: impact on intraoperative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy.* J Gastrointest Surg, 1999. 3(5): p. 496-505.

36. Son, J., et al. *The optimal duration of preoperative biliary drainage for periampullary tumors that cause severe obstructive jaundice.* AM J Surg, 2013. 206, 40-46

APPENDIX B: SPONSOR REQUIRED PROTOCOL SECTIONS

B.1. Data Management

B.1.1. Data Collection, Processing, and Review

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

The clinical database will reside on a production server. 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 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.

B.1.2. 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 patients 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.

B.2. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the patient 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.

B.3. Device/Equipment Accountability

There are no investigational devices used in this study. The WallFlex Biliary Fully Covered and Uncovered Stent Systems are 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.

B.4. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a patient 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 patient 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 using the Protocol Deviation EDC CRF. 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 notification, center re-training, or discontinuation) will be put into place by the sponsor.

B.5. Compliance

B.5.1. Statement of Compliance

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

B.5.2. 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 patient.

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

- Prior to beginning the study, 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 patient 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, 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 patient during and after a patient's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the patient of the nature and possible cause of any adverse events experienced.
- As applicable, provide the patient with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the patient.
- Inform the patient of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the patient 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 patient is enrolled in this clinical study.
- Ensure that, if appropriate, patients 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 patient's approval or when required by national regulations, the patient's personal physician about the patient's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a patient's premature withdrawal from clinical investigation while fully respecting the patient'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.

B.5.3. Delegation of Responsibility

When specific tasks are delegated by an investigator, including 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.

B.6. 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 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 patients into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to patient recruitment or which will be provided to the patient.

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.

B.7. 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.

B.8. Insurance

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

B.9. Informed Consent

Patient participation in this clinical study is voluntary. Informed Consent is required from all patients 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 patient 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 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 patient's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of patients to participate,
- not waive or appear to waive patient's legal rights,
- use native language that is non-technical and understandable to the patient or his/her legal representative,
- provide ample time for the patient to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing patients throughout the clinical study.

The ICF shall always be signed and personally dated by the patient or legal representative and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the patient 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 patient 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 patient's future health and medical care, that information shall be provided to the affected patient(s) in written form via a revised ICF or, in some situations, enrolled patients 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 patient population to be re-consented.

B.10. 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.

B.11. Definitions of complication criteria (per van der Gaag article):

Specific PBD (ERCP, PTC) related:

- **Acute 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
- **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 direct visual evidence
- **Stent Occlusion:** Recurring obstructive jaundice with necessary stent replacement

Specific surgery related:

- **Pancreaticojejunostomy leakage:** Drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity, graded according to clinical course (ISGPS grade A, B, C), or direct visual evidence of defect at anastomosis
- **Delayed gastric emptying:** Gastric stasis requiring nasogastric intubation for 10 days or more, or the inability to tolerate a regular (solid) diet on or before the fourteenth

postoperative day, not due to sequelae of intra-abdominal complications (i.e. abscess, anastomotic leakage)

- **Biliary leakage:** Bilirubin in abdominal drain or dehiscence found at laparotomy
- **Gastro/-duodenojejunostomy leakage:** Conclusive radiographic or direct visual evidence of a defect of the anastomosis
- **Intra-abdominal abscess formation:** Intra-abdominal fluid collection with positive cultures identified by ultrasonography or computed tomography, associated with persistent fever and elevations of white blood cells
- **Wound infection:** Requiring intervention otherwise considered as minor complication
- **Portal Vein Thrombosis:** Conclusive radiologic evidence of thrombosis

Following either procedure:

- **Cholangitis:** Elevation in temperature 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
- **(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

B.12. Abbreviations and Definitions

B.12.1. Abbreviations

Abbreviations are shown in **Table 7.**

Table 7: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
BTS	Bridge to Surgery
CBD	Common Bile Duct
CI	Confidence Interval
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
DFU	Directions for Use
eCRF	Electronic Case Report Form

Table 7: Abbreviations

EDC	Electronic Data Capture
ERCP	Endoscopic retrograde cholangiopancreatography
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IDR	Independent Data Review Board
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVRS	Interactive Voice Response System
LFT	Liver Function Tests
MEDDEV	Medical Devices Directives
MRI	Magnetic Resonance Imaging
OUS	Outside of the United States
PAL	Palliative
PD	Pancreaticoduodenectomy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SEMS	Self-Expanding Metal Stent
SUB-I	Sub-Investigator
UADE	Unanticipated Adverse Device Effect
USA	United States of America