RANDOMIZED, MUTI-CENTER, COMPARATIVE AND COST EFFECTIVENESS STUDY OF A LUMEN-APPOSING, COVERED, SELF-EXPANDING METAL STENT (AXIOS™) VERSUS MULTIPLE DOUBLE PIGTAIL STENTS IN THE MANAGEMENT OFF WALLED OF PANCREATIC NECROSIS

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Study Products: *A Lumen Apposing, covered, self-expanding metal stent (*AXIOS™*) [The* AXIOS™ *lumen-apposing stent (Xlumena Inc., Mountain View, California, USA)], and Double Pigtail Stents [Solus® Double Pigtail Stent with Introducer (Cook, Ireland Ltd.)]*

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List of Abbreviations

Study Summary

Title	*RANDOMIZED, MUTI-CENTER, COMPARATIVE AND COST EFFECTIVENESS STUDY OF A LUMEN-APPOSING, COVERED, SELF-EXPANDING METAL STENT (*AXIOS™*) VERSUS MULTIPLE DOUBLE PIGTAIL STENTS IN THE MANAGEMENT OFF WALLED OF PANCREATIC NECROSIS*
Short Title	*The* AXIOS™ *Stent Versus Solus® Double Pigtail Stents for WOPN*
Protocol Number	*TBD*
Phase	*Pilot – Phase NA*
Methodology	*Single Blind, Randomized, Active Control*
Study Duration	*2 year*
Study Center(s)	*Multi-center. Number of centers - 3*
Objectives	*Objective 1: Compare costs between the two management strategies* *Objective 2: To evaluate the efficacy of the* AXIOS™ *stent (Xlumena Inc., Mountain View, California, USA) versus multiple double pigtail stents [Solus® Double Pigtail Stent with Introducer (Cook, Ireland Ltd.)] in the management of walled off pancreatic necrosis*
Number of Subjects	*20 patients*
Diagnosis and Main Inclusion Criteria	*Walled off pancreatic necrosis (WOPN)*
Study Product, Dose, Route, Regimen	AXIOS™ *lumen-apposing stent (Xlumena Inc., Mountain View, California, USA)*
Duration of administration	*The* AXIOS™ *stent implantation should not exceed 60 days according to the manufacturer. The Double Pigtail Stents [Solus® Double Pigtail Stent with Introducer (Cook, Ireland Ltd.)] do not require removal*
Reference therapy	*Double Pigtail Stents [Solus® Double Pigtail Stent with Introducer (Cook, Ireland Ltd.)]*
Statistical Methodology	*Continuous data will be expressed as means with SDs or medians with interquartile ranges and compared using student's t-test. Catagoric data will be expressed as frequencies and percentages and be compared using Fisher's Exact test.*

1 Introduction

This document is a clinical research protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Acute pancreatitis (AP) is responsible for nearly a quarter million hospital admissions annually and will affect around 40 per 100,000 persons per year (1). The majority of patients experience a clinically mild course; however, as many as one in five patients develop a severe illness associated with a high mortality (2). In early phases of the disease, there is an acute inflammatory process that may involve necrosis of the pancreatic or peri-pancreatic tissues (3). There are also delayed complications that may develop locally, usually over a period of weeks, which include the formation of walled-off fluid collections. These are sometimes composed of simple fluid and termed pseudocysts, while in other cases they represent organization and encapsulation of sterile or infected necrosis and are termed walled-off pancreatic necrosis (WOPN) (4). The indication to drain or debride these collections usually depends upon on a number of factors, but principally on whether they are symptomatic, infected, or responsible for other local or systemic complications.

The contemporary management strategy for walled-off pancreatic fluid collections has shifted in recent years. Surgery, and even percutaneous catheter drainage, should no longer be considered the initial mainstay of therapy in place of endoscopic drainage for simple pseudocysts (5) (6). In addition there is good evidence to support an endoscopic approach for patients with *infected* necrosis (7). There are now numerous publications reporting the success of direct endoscopic transmural drainage or necrosectomy (ETD/N) for a variety of indications including infected and *sterile* walled-off collections (8).

The issue that now deserves attention is a matter of selecting the best *technique* to accomplish ETD/N. The current process involves first creating a cystenterotomy to gain access to the walled-off collection, dilating the tract, and then inserting a drainage device. However, there are a variety of available devices and methods in use for drainage, and to our knowledge, none to date have been directly compared in a randomized controlled trial.

The conventional approach involves inserting either a pair or more of plastic double pigtail stents or a self-expanding metal stent (SEMS) through a cystenterotomy: both approaches have limitations, and may require multiple endoscopic sessions before definitive resolution (9). One, the pigtail stents have a narrow lumen (7F-10F) and often migrate or become occluded (10). Two, the SEMS also have a tendency occlude, cause local trauma with bleeding and infection, and migrate, which has led some to also use double pigtails to help anchor the SEMS in place (11) (12).

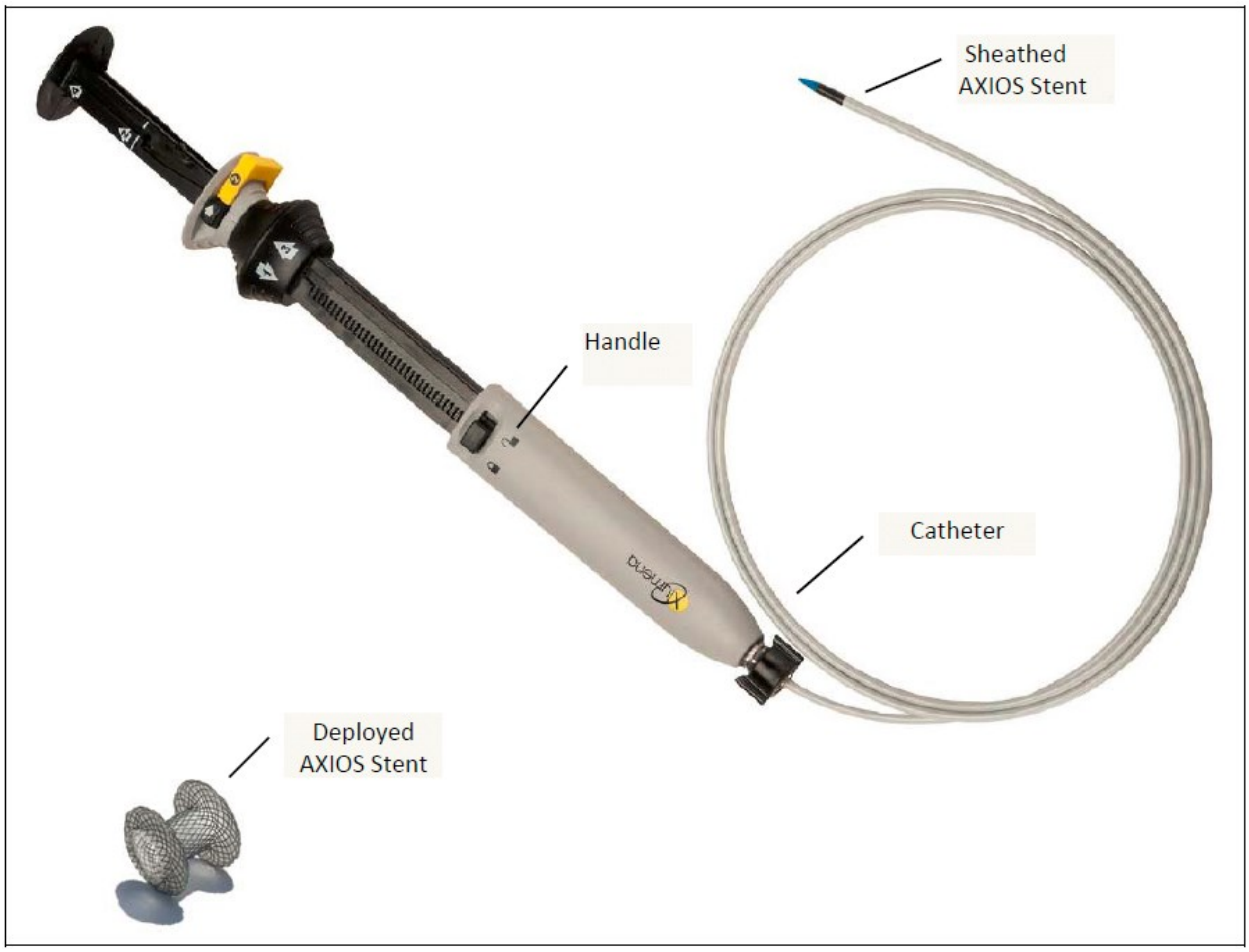
These challenges have led to the innovation of large caliber covered stents with flanges on either end to facilitate apposition of the cyst wall and enteral tissues, preventing migration, and allowing for necrosectomy through their wide lumen. To our knowledge there are at least two designs in production; the AXIOS™ stent and the Nagi stent (13) (14). There is now a fair amount of experience, particularly using the AXIOS™ stent (with or without a novel NAVIX access system) for both WOPN and pseudocysts, with the majority of reports showing it to be safe and effective (15) (16) (17) (18) (19) (20). The device has also been successfully used for novel indications including access and drainage of the gallbladder and an intrathoracic fluid collection (21) (22) (23). The AXIOS™ stent is FDA approved for the indication of draining walled off pancreatic necrosis.

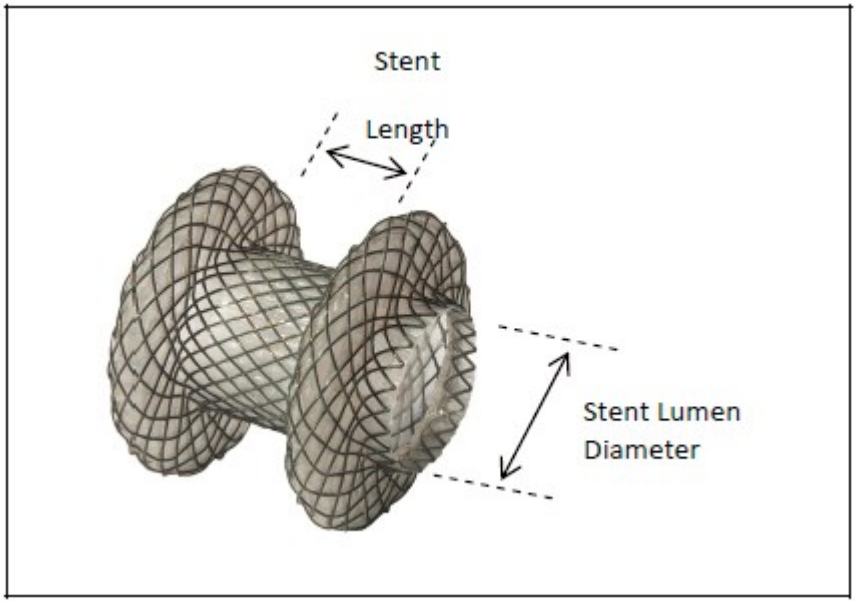
The present study aims to compare the clinical efficacy and cost effectiveness of the AXIOS™ stent versus the “conventional” approach using double pigtail plastic stents in the treatment of patients with walled-off pancreatic necrosis.

[For the remainder of this document, the AXIOS™ stent will be in reference the AXIOS™ Stent and Delivery System (*Xlumena Inc., Mountain View, California, USA),* and use of the terms “double pigtail stent(s)” will be in reference to the Solus® Double Pigtail Stent with Introducer *(Cook, Ireland Ltd.)*]

1.2 Investigational Agent

The AXIOS™ Stent is a flexible, fully-covered, self-expanding Nitinol stent, which is preloaded within the catheter-based delivery system. It is radiopaque and is fully covered with silicone. The AXIOS™ stent has been labeled as MR conditional. The stent permits passive drainage of material from within the accessed fluid collection to the gastrointestinal lumen, and serves as a conduit through which additional diagnostic or therapeutic endoscopic procedure can be performed. AXIOS™ is FDA-approved for treating WOPN.





AXIOS™ *Stent Sizes*

	AXS-10-10	*AXS-15-10*
Stent Lumen Diameter (mm)	*10*	*15*
Stent Length (mm)	*10*	*10*

1.3 Preclinical Data

Device information from the manufacturer discusses performance testing in animals to assess chronic performance of the device (long-term patency, removability, and migration), adverse events, and histopathology. Benchtop and animal testing in porcine models demonstrated ex-vivo durability, successful deployment across the stomach and gallbladder lumens of 4 animals, and stable positioning and patency. There was no hyperplastic tissue ingrowth or overgrowth, or tissue injury reported (20).

1.4 Clinical Data to Date

Use of the AXIOS™ stent for the treatment of walled off pancreatic fluid collections has been examined in a number of studies. A prospective study in 33 patients with either symptomatic pancreatic pseudocysts or walled off necrosis, reported successful placement in 91% of subjects, and resolution of the pancreatic fluid collection (PFC) in 93% of subjects. Complications were reported in n=5 (15.2%) of the subjects, and included access-site infection, stent migration/dislodgment, back pain, and abdominal pain requiring endoscopy (15). A study of 9 patients undergoing EUS-guided draining and AXIOS™ placement for a PFC (pancreatic pseudocysts and walled off necrosis included), reported a technical success rate of 88.8%. All patients were reported to have achieved complete cyst resolution in a mean follow up of 50 weeks. There was one fluid collection recurrence 4 weeks after stent removal, no migrations reported, and all stents were removed easily. There was one tension pneumothorax that developed immediately after transesophageal drainage of a fluid collection (16). A study of 33 patients reported successful placement of the AXIOS™ stent in 91% of subjects with pancreatic pseudocysts. Cyst resolution was achieved in 93% of the patients. Complications were observed in a total of 4 patients and included abdominal pain, spontaneous stent migration and back/shoulder pain, and access site infection and stent dislodgement (18). Technical success was reported in the case of one patient with more than one pancreatic fluid collection, one of which was drained using the AXIOS™ stent (19). A retrospective case series that included patients who received the AXIOS™ stent for drainage of

symptomatic pancreatic pseudocysts (n=15) (or acute cholecystitis (n=5)), reported successfully placement and resolution of the pseudocysts in all patients. There were no pseudocyst recurrences during 11.4 months of follow up. All stents were later removed without procedure-related complications. Stent migration was reported in one case (21). A case report of transesophageal EUS-guided draining of a mediastinal pancreatic fluid collection reported technical success with placement and removal, and complete resolution of the collection at 6 weeks of follow up (23)

1.5 Dose Rationale and Risk/Benefits

Endoscopic transmural drainage and/or necrosectomy of either sterile of infected walled off pancreatic necrosis is an established management option. There are a variety of techniques currently used in practice; however, the optimal technique has not been established. The AXIOS™ stent and delivery system is one available method that has not been compared directly in any randomized trial to any other method. The duration of AXIOS™ stent insertion should not exceed 60 days based upon the manufactures recommendations. Patients selected for this study will be those who already have an indication for endoscopic drainage of their pancreatic necrosis. The general risks of not pursuing therapy in these cases include, but are not limited to, ongoing pain, gastrointestinal obstruction, infection, sepsis, and death. The typical risks of endoscopic cystogastrostomy/enterostomy and necrosectomy include uncontained visceral perforation, bleeding, infection, emergency surgery, and death. There is also the risk of needing repeat endoscopic procedures, and unintended reactions to sedation. There is a risk of stent migration with both the conventional double-pigtail stents and the AXIOS™ stent. The benefit of endoscopic cystogastrostomy/enterostomy and necrosectomy include resolution of the pancreatic fluid collection and its related complications (e.g., pain, infections, intestinal obstruction).

Specifically, the risks to subjects in the study are reasonable because subjects are not being exposed to risk beyond what they would ordinarily be exposed to for the treatment of their underlying condition. These are patients who have been referred for established therapy using devices that currently used in practice.

2 Study Objectives

Primary Objectives

1. To compare the **cost differences** of the AXIOS™ stent vs. multiple double pigtail stents in the management of walled-off pancreatic necrosis.

Secondary Objectives

1. To compare the relative efficacy in terms of **definitive resolution** of walled off pancreatic necrosis using the AXIOS™ stent vs. multiple double pigtail stents.
2. To compare the **number of endoscopic sessions** required to achieve definitive resolution of walled-off pancreatic fluid necrosis using the AXIOS™ stent vs. multiple double pigtail stents.
3. To compare the **number of additional procedures** (surgical, percutaneous, or nasocystic) required to achieve definitive resolution of walled-off pancreatic necrosis using the AXIOS™ stent vs. multiple double pigtail stents.
4. To compare the **frequency of stent migration** using the AXIOS™ stent vs. multiple double pigtail stents in the management of walled-off pancreatic necrosis.
5. To compare the **safety and tolerability** of the AXIOS™ stent vs. multiple double pigtail stents in the management of walled-off pancreatic necrosis.

3 Study Design

3.1 General Design

1. Multi-center, single blind, randomized controlled trial
2. Inclusion Criteria.
    a. Male or female between 18-80 years old (including patients aged 18 and 80)
    b. Subjects capable of giving informed consent
    c. Patients carrying the diagnosis or symptomatic sterile or infected walled-off pancreatic necrosis (WOPN) based upon Atlanta Classification (4) >4cm in largest diameter, deemed to require and amenable to endoscopic transmural drainage and/or necrosectomy by attending gastroenterologist
    d. Fluid collection size ≥ 4cm in largest diameter (based on CT, MRI, transabdominal or endoscopic ultrasound within 30days)
    e. Fluid collection that is adherent to the stomach/bowel wall allowing for fistula tract creation
    f. Fluid collection containing significant amount of necrotic material (defined as >30% of echogenic material by ultrasound/EUS, or necrotic debris by CT/MRI)

3. Exclusion Criteria:
    a. Inability to provide written informed consent
    b. Contraindications to endoscopic treatment as determined by the gastroenterologist attending
    c. Pregnant or nursing mothers
    d. Bleeding or coagulation disorder
    e. Previous surgical or endoscopic cystogastrostomy/enterostomy or necrosectomy
    f. Shock
    g. Cystic neoplasms or pancreatic malignancy
    h. Pseudocysts
    i. Subjects cannot be homeless or incarcerated
    j. Age younger than 18 or older than 80
    k. More than one pancreatic/peri-pancreatic fluid collection

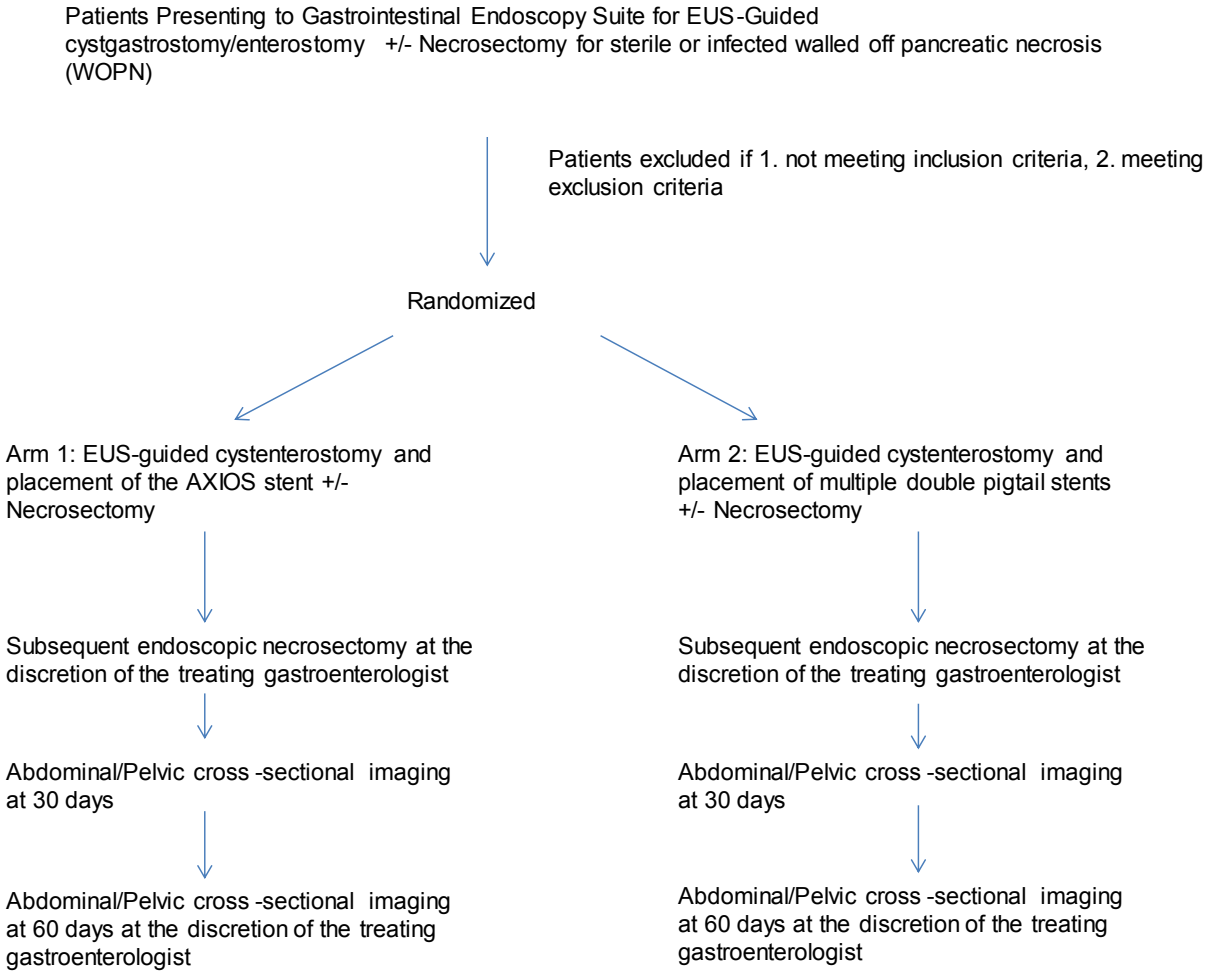
All eligible participants will be randomized to one of two arms:

1. Arm 1: EUS-guided cystogastrostomy/enterostomy and placement of the AXIOS™ stent
2. Arm 2: EUS-guided cystogastrostomy/enterostomy and placement of multiple double pigtail stents

The procedure will be performed under monitored or general anesthesia using a therapeutic linear array echoendoscop. Antibiotic will be administered at the start of the procedure (ciprofloxacin 500mg or acceptable alternative), and continued for 3 days. EUS will be performed to localize, confirm the size and features, and evaluate for bowel adherence of the target collection. Color Doppler will be performed to identify the presence of vascular structures within the planned drainage tract. The collection will be accessed by needle puncture. The fluid will be aspirated and sent for microscopic analysis and culture. A guidewire will then be threaded into the collection cavity and confirmed by fluoroscopy. The needle will then be withdrawn and the tract serially dilated using balloons passed over the guidewire through the tract, and expanded stepwise to 15-20mm at the discretion of the treating gastroenterologist.

1. Arm 1 will have an AXIOS™ stent 10-15mm (saddled diameter; choice at the discretion of the treating gastroenterologist) deployed though the tract into the cavity, and correct positioning of the inner flange confirmed by EUS prior to deploying within the stomach or duodenum.
2. Arm 2 will have multiple double pigtail (i.e. ≥2) stents placed through the tract into the collection cavity

Necrosectomy will be performed at the discretion of the treating gastroenterologist in all cases. The pancreatic fluid collections will be re-assessed at 30 days (all patients) and 60 days (at the discretion of the treating gastroenterologist) after the procedure by abdominal/pelvic CT or MRI – or sooner should the need arise. Repeat endoscopies for necrosectomy will be permitted in all patients at the discretion of the attending gastroenterologist. Patients who receive the AXIOS™ stent will routinely undergo a second endoscopy no later than 60 days after insertion of the stent for removal. Overall expected duration of study participation is 60 days.



3.2 Primary Study Endpoints

1. Cost of therapy using AXIOS™ stent versus double-pigtail stents; billing from individual center departments

3.3 Secondary Study Endpoints

1. Rate of recurrence of pancreatic fluid collection/definitive resolution
2. Complete or partial resolution of walled-off necrosis - (defined as >90% resolution on cross-sectional imaging)
3. Number of endoscopic sessions required to achieve complete or partial resolution of pancreatic necrosis
4. Requirement for surgical, percutaneous, or nasocystic intervention to facilitate resolution of walled-off pancreatic necrosis
5. Frequency of stent migration prior to resolution of walled-off pancreatic necrosis

3.4 Primary Safety Endpoints

1. Frequency of death, bleeding, infection, uncontained perforation, or need for urgent or emergent surgical or radiology guided procedure at any time during the study period

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Male or female between 18-80 years old (including ages 18 and 80)
2. Subjects capable of giving informed consent
3. Patients carrying the diagnosis or symptomatic sterile or infected walled-off pancreatic necrosis (WOPN) based upon Atlanta Classification (4) >4cm in largest diameter, deemed to require and amenable to endoscopic transmural drainage and/or necrosectomy by attending gastroenterologist
4. Fluid collection size ≥ 4cm in largest diameter (based on CT, MRI, transabdominal or endoscopic ultrasound within 30days)
5. Fluid collection that is adherent to the stomach/bowel wall allowing for fistula tract creation
6. Fluid collection containing significant amount of necrotic material (defined as >30% of echogenic material by ultrasound/EUS, or necrotic debris by CT/MRI)

4.2 Exclusion Criteria

1. Inability to provide written informed consent
2. Contraindications to endoscopic treatment as determined by the gastroenterologist attending
3. Pregnant or nursing mothers
4. Bleeding or coagulation disorder
5. Previous surgical or endoscopic cystogastrostomy/enterostomy or necrosectomy
6. Shock
7. Cystic neoplasms or pancreatic malignancy
8. Pseudocysts

9. Subjects cannot be homeless or incarcerated
10. Age younger than 18 or older than 80
11. More than one pancreatic/peri-pancreatic fluid collection

4.3 Subject Recruitment and Screening

Patients diagnosed with sterile or infected walled off pancreatic necrosis already referred for endoscopic treatment will be offered enrollment at the time they present to the endoscopy suite for their procedure. Patients will be informed that the techniques used for endoscopic transmural drainage and necrosectomy are operator and case dependent, and ordinarily may involve the use of multiple double pigtail stents or the AXIOS™ stent; however their relative efficacy and safety have not been directly compared and is the subject of investigation. Patient will be informed that should they consent to participating in the study, they will be randomly allocated to one of the two methodologies without knowing which technique they receive. Patients will need to have lab work within 14 days of the procedure that included a complete blood cell count, basic metabolic panel, liver function tests, and coagulation tests. Patients will be informed that they have the option to opt-out of the study, and will receive therapy at the discretion of the treating gastroenterologist.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients will have the option to withdraw at any time during the study period for any reason. Patients who fail to comply with follow up imaging will be reported as such in the final analysis.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Patients may prematurely withdraw from the study. Because survival and delayed complications are a subject of this study, efforts will be made to collect, at a minimum, survival data on all patients who elect to enroll. Before being considered truly lost to follow up, a minimum of three phone calls will be made to the patient and/or next of kin, and if contact is not established, a certified letter will be mailed. Contact information will be collected at enrollment.

5 Study Drug

5.1 Description

AXIOS™ Stent is a flexible, fully-covered, self-expanding Nitinol stent, which is preloaded within the catheter-based delivery system.

5.2 Treatment Regimen

1. Arm 1 will undergo EUS-guided cystogastrostomy/enterostomy and placement of the AXIOS™ stent 10-15mm (saddled diameter; choice at the discretion of the treating gastroenterologist) though the tract into the collection cavity, and correct positioning of the inner flange confirmed by EUS prior to deploying within the stomach or duodenum. Necrosecomy will be performed at the discretion of the attending gastroenterologist. Repeat endoscopy will be performed for stent removal at or before 60 days at the discretion of the attending gastroenterologist
2. Arm 2 will undergo EUS-guided cystogastrostomy/enterostomy and placement of multiple double pigtail stents (i.e. ≥2) through the tract into the collection cavity. Necrosectomy will be performed at the discretion of the attending gastroenterologist. Routine repeat

treating gastroenterologist for stent removal will not be necessary, but left to the discretion of the attending gastroenterologist.

5.3 Method for Assigning Subjects to Treatment Groups

Patients will be randomly assigned to either of the two treatment arms by a sequentially numbered card box that will be opened by the attending gastroenterologist in the procedure room

5.4 Preparation and Administration of Study Drug

The study devices are prepackaged by the manufacturer

5.5 Subject Compliance Monitoring

All participating centers will notify the study coordinator of any newly enrolled patient. All consent materials and the patient's chart will remain at the site of enrollment. A central and secure databank will be maintained by the study coordinator that includes the patient's basic information and a copy of the consent form. All patients enrolled will be provided a means of contacting the study coordinator during routine business hours for questions or concerns. They will be advised to go through the on-call system of their treating institution for off hour emergencies. All scheduled follow up imaging will ordered by the attending gastroenterologist overseeing the patients care, and arranged though the usual mechanisms unique to their institution. Scheduled imaging will be tracked by the study coordinator and updated weekly until completion of the study. Patients who do not show up for their scheduled imaging will be contacted (and/or next of kin) by phone with a minimum of 3 attempts, and if contact is not established, a certified letter will be mailed. Contact information will be collected at enrollment.

5.6 Prior and Concomitant Therapy

Patients will receive a short course of antibiotics around the time of their procedure, for a total of 3-5 days based on the discretion of the attending gastroenterologist per standard of care.

5.7 Packaging

All devices in use are pre-packaged by the manufacturer

5.8 Blinding of Study Drug

Patients will be blinded to which of the two devices they receive until the end of the follow up period

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

An inventory is routinely performed by the endoscopy suite for all supplies and devises being used in this study.

5.9.2 Storage

All devices are stored in the Endoscopy suite

5.9.3 Dispensing of Study Drug

Not applicable

5.9.4 Return or Destruction of Study Drug

Not applicable

6 Study Procedures

Visit 1: Endoscopy Suite: patients scheduled and presenting to the gastrointestinal endoscopy suite for EUS-Guided cystogastrostomy/enterostomy +/- Necrosectomy for sterile or infected walled off pancreatic necrosis (WOPN) will be offered the option to participate in the study. Patients interested will be screening for eligibility using the Case Report Form (See Attachment 1). Eligible patients will asked if they consent to 1. The endoscopic procedure and anesthesia plan as outlined by the treating gastroenterologist and participating anesthesiologist according to their routine pre-procedure consent practice, and 2. Participation in the research study as indicated, after review, by signature of a copy of the CPHS approved and stamped consent form (See Attachment 2). The Principal Investigator is responsible for ensuring all participants enrolling in this study have provided informed consent. The PI (Dr. Timothy Gardner) may authorize other appropriately trained individuals to obtain informed consent and sign as 'designee.' These designees include: Dr. Stuart Gordon, Dr. John Levenick, Dr. Jason Ferreira, Dr. Jeffrey Adler, Dr. David Rahni. Those consenting, will be brought into the procedure room, and assigned to either of the two treatment arms by a sequentially numbered card box that will be opened by the attending gastroenterologist in the procedure room. Following endoscopic intervention patients will recover in the endoscopy recovery area or PACU and will either be discharged home or admitted at the discretion of the treating gastroenterologist.

Visit 2: Subsequent endoscopic necrosectomy. This is variable and will be left to the discretion of the treating gastroenterologist (some patients will require additional routine endoscopic procedure(s) for necrosectomy after the initial intervention which will have to be decided on a case-by-case basis by the treating gastroenterologist)

Visit 3: All patients will be asked to return for abdominal/pelvic cross-sectional imaging (CT or MRI) at 30 days from the initial intervention; the modality will be left to the discretion of the treating gastroenterologist

Visit 4: Patients may be asked to undergo additional follow up imaging (up to 60 days after the initial procedure), which will be left to the discretion of the treating gastroenterologist.

Patients Presenting to Gastrointestinal Endoscopy Suite for EUS-Guided cystgastrostomy/enterostomy +/- Necrosectomy for sterile or infected walled off pancreatic necrosis (WOPN) →

Patients will be offered option to participate in the study →

Patients interested are screened for eligibility using Case Report Form (CRF) available for use by the gastroenterologist →

Eligible patients will be asked if they consent to: →
1. The endoscopic procedure and anesthesia plan as outlined by the treating gastroenterologist and participating anesthesiologist according to their routine pre-procedure consent practice
2. Participation in the research study as indicated, after review, by signature of a copy of the CPHS approved and stamped consent form (included in Attachments section)

Patients will be brought into the procedure room and assigned to either of the two treatment arms by a sequentially numbered card box that will be opened by the attending gastroenterologist in the procedure room →

Following endoscopic intervention patients will recover in the endoscopy recovery area or PACU and will either be discharged home or admitted at the discretion of the treating gastroenterologist →

Patients may require subsequent routine endoscopic procedures for necrosectomy, which will be determined on a case-by-base basis by the treating gastroenterologist →

All patients will be asked to return for abdominal/pelvic cross-sectional imaging (CT or MRI) at 30 days from the initial intervention; the modality will be left to the discretion of the treating gastroenterologist →

Patients may be asked to undergo additional follow up imaging (up to 60 days after the initial procedure), which will be left to the discretion of the treating gastroenterologist.

7 Statistical Plan

7.1 Sample Size Determination

As this represents a pilot study, we plan on enrolling only 10 patients in each study arm. This number is based on previous studies of endoscopic intervention – most notably the landmark PENGUIN trial from the Netherlands which compared endoscopic vs surgical treatment for WOPN (7). We feel confident that using 10 patients in each arm will allow us to complete the study, and likely see a difference in cost between the two procedures.

7.2 Statistical Methods

The statistical model will be very simple. For the primary outcome – cost – we will compare the overall mean costs (procedure, hospitalization, complication) for each type of stent using a student's t test. For secondary outcomes using continuous data, we will use the student's t-test and for categorical data we will use the Fisher's Exact test. Given the small number of subjects in each arm, regression models will not be built.

7.3 Subject Population(s) for Analysis

We will use an All-treated population: Any subject randomized into the study that received at least one dose of study drug.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported will include the period from the initiation of the study procedure to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 60 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality will be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will recorded in the source document, though will be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, will be reported to the study sponsor by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to: Timothy Gardner, phone 603-650-5206, fax 603-650-5225

Within the following 48 hours, the investigator will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This will include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 Investigator reporting: notifying the Dartmouth IRB

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth College IRB (CPHS) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Dartmouth IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths: more rapid reporting requirements
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Dartmouth IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Dartmouth IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Dartmouth IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.3.3 Investigator reporting: Notifying another IRB

Investigators who are not Dartmouth faculty or affiliated with a Dartmouth research site are responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

8.3.4 Sponsor reporting: Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

8.4 Unblinding Procedures

Study participants will be un-blinded in the event of a Serious Adverse Event (SAE) as outline in the preceding sections, and will be reported along with the report of the SAE. Patients will otherwise be un-blinded at the end of the study period. The investigator must inform the sponsor of all subjects whose treatment was un-blinded within 48 hours of un-blinding.

8.5 Stopping Rules

Complication rates associated with endoscopic necrosectomy approach 30%, and are mostly procedure related (89%). The mortality rate may be close to 5% (9). The study will be stopped early for complication and mortality rates that significantly exceed these rates and we will evaluate the outcomes after 10 patients have been enrolled for an interim analysis.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Independent Data and Safety Monitoring Board

Dr. Steven Bensen in the section of Gastroenterology and Hepatology at DHMC will serve as the internal DSMB. After 10 patients have been enrolled, he will be given access to all of the primary and secondary clinic outcomes in an unblinded fashion – including all adverse events. If there is a statistically significant difference in any of the appropriate outcomes or AEs, CPHS will be contacted and that their discretion the study will continue or be terminated.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 1 year after enrollment.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan by the CTO. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and Dartmouth compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment 2 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study will not require dedicated funding.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Dartmouth investigators will follow the Dartmouth conflict of interest policy.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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15 Attachments

#1 CPHS Protocol Plus
#2 Case Report Form (separate document)
#3 Consent to take part in research (separate document)