SHARP Trial
SpHincterotomy for Acute Recurrent Pancreatitis Trial

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SPONSOR and Collaborator

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)

Investigator's Agreement

I have read the attached clinical protocol titled SHARP Trial and dated [05-May-2022] and agree to conduct the protocol as written in this document.

I agree to comply with the Code of Federal Regulations Title 45 part 46; ICH Good Clinical Practice Guidelines; and all other applicable guidelines.

I understand this document contains confidential information of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) and The Data Coordination Unit and cannot be disclosed to anyone other than members of my staff conducting this trial and members of my Institutional Review Board or Ethical Committee.

I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of this clinical trial without the prior written permission of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Medical University of South Carolina, and The Data Coordination Unit.

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Signature of Principal Investigator Date

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Printed name of Principal Investigator

1. SUMMARY

This is a sham-controlled, single blinded with a blinded outcome assessment, multi-center, randomized clinical trial of endoscopic retrograde cholangiopancreatography (ERCP) with minor papilla endoscopic sphincterotomy (miES) for the treatment of recurrent acute pancreatitis (RAP) with pancreas divisum. ERCP with miES is often offered in clinical practice to patients with RAP, pancreas divisum, and no other clear risk factors for their acute pancreatitis episodes. We hypothesize that obstruction at the level of the minor papilla is one cause of RAP in pancreas divisum; miES will relieve the obstruction, thereby reducing the risk of a recurrent attack(s) of acute pancreatitis. The trial requires a total sample size of approximately 234 subjects, and a planned enrollment period of approximately 3.5 years with total planned study duration of 5 years.

2. STUDY RELATED DEFINITIONS

LIST OF ABBREVIATIONS

CECT	contrast-enhanced computed tomography scan
CRF	case report form
DCU	Data Coordination Unit
DSMB	Data and Safety Monitoring Board
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
iRAP	idiopathic recurrent acute pancreatitis
miES	minor papilla endoscopic sphincterotomy
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MSM	Medical Safety Monitor
MUSC	Medical University of South Carolina
RAP	recurrent acute pancreatitis
SIRB	Single Institutional Review Board
TWEAK	Tolerance, Worried, Eye-opener, Amnesia, and K/Cut down

Acute pancreatitis. The definition of acute pancreatitis will be per consensus (Atlanta guidelines:)(Banks, Bollen et al. 2013) “The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on CECT and less commonly MRI or transabdominal ultrasonography.”

Post-ERCP pancreatitis. The definition of post-ERCP pancreatitis will be per consensus Cotton criteria (Cotton, Eisen et al. 2010): 1) New or increased abdominal pain that is clinically consistent with a syndrome of acute pancreatitis, and 2) amylase or lipase ≥ 3x the upper limit of normal at least 24 hours after the procedure, and, 3) hospitalization (or prolongation of existing hospitalization) for at least 2 days.

Recurrent acute pancreatitis (RAP). RAP will be defined as two or more discrete episodes of acute pancreatitis that occur >30 days apart with complete recovery from the first before commencement of the second episode.

Idiopathic RAP. A patient with RAP will be defined as idiopathic (iRAP) if no etiology is evident to the unblinded physician investigator after a thorough history, physical examination, routine laboratories (serum calcium, lipids (triglyceride level < 500mg/dL), liver chemistries), and cross-sectional imaging (transabdominal ultrasound and/or CECT). Patients with a history of current or previous smoking will be considered idiopathic if a second risk factor is absent.

Pancreas divisum. A patient will be considered to have pancreas divisum anatomy if the dorsal and ventral pancreatic ducts have incomplete (incomplete pancreas divisum) or nonexistent fusion (complete pancreas divisum).(Stern 1986)

Pancreas-related pain event. An episode of pancreatitis-type symptoms (most commonly pain) that requires emergency room or inpatient hospital evaluation.

Calcific chronic pancreatitis. Defined as parenchymal or ductal calcifications identified on computed tomography or magnetic resonance imaging scan.

Obstructive chronic pancreatitis. Defined as main pancreatic duct stone or main pancreatic duct stricture identified on computed tomography or magnetic resonance imaging scan, or endoscopic ultrasound.

3. SIGNIFICANCE, BACKGROUND AND RATIONALE

3.1 Patients with recurrent acute pancreatitis (RAP) are at high risk for additional episodes and progression to chronic pancreatitis.

Acute pancreatitis is among the most common gastrointestinal indications for hospitalization, and those suffering two or more episodes have a high risk of developing full-blown chronic pancreatitis.(Yadav and Lowenfels 2013, Peery, Crockett et al. 2015) There are ~150,000 incident cases of acute pancreatitis in the U.S. annually, and of these 40-50,000 will suffer recurrent bouts. Unlike most patients with chronic pancreatitis who present with irreversible fibrotic changes in the pancreas, patients with recurrent acute pancreatitis (RAP) are unique in that many do not have end organ morphological changes at the time of their clinical presentation. However, patients with RAP have a substantial (10-40%) risk of progressing to chronic pancreatitis and its sequelae: chronic pain, malabsorption, diabetes mellitus, poor quality of life, and progression to pancreatic cancer.(Bang, Benfield et al. 2014, Sankaran, Xiao et al. 2015) Many experts believe that “subclinical RAP” is the precursor for the majority of individuals who present with overt signs/symptoms of chronic pancreatitis.(Schneider and Whitcomb 2002, Aoun, Slivka et al. 2007, Aoun, Muddana et al. 2010) Therefore, treatments to attenuate RAP are needed.

3.2 Pancreatic duct obstruction causes acute pancreatitis.

Pancreas divisum occurs when the dorsal and ventral pancreatic ducts have incomplete or nonexistent fusion during early embryologic development. For patients with pancreas divisum, the duct of Santorini drains the majority of the pancreas through an orifice (minor papilla) that is notably smaller than the orifice of a normal sphincter of Oddi (major papilla). The duct of Santorini may have a narrow filamentous pathway to the duct of Wirsung or may drain a portion of the head independently. Hence the concept was promulgated in the 1970s that in pancreas divisum there is an anatomic impediment to the drainage of pancreatic exocrine secretions, resulting in an obstructive pancreatopathy (Cotton 1980). This is supported by RAP cohort studies where pancreas divisum is overrepresented compared to its expected baseline prevalence of 7-10%.(Coyle, Pineau et al. 2002, Gonoi, Akai et al. 2011)

Pancreatic duct obstruction and transient increases in intraductal pressure are believed to be potential triggers for acute pancreatitis, based on several concepts:

1. Gallstone pancreatitis is caused by transient occlusion of the sphincter of Oddi and consequential pancreatic ductal hypertension.(Lerch, Saluja et al. 1993) Early decompression of the duct attenuates progression to pancreatic necrosis (Lerch, Saluja et al. 1993, Runzi, Saluja et al. 1993).
2. In an animal model, sphincter of Oddi spasm induced by application of a topical cholinergic agonist increased intraductal pressure and acute pancreatitis (Chen, Thomas et al. 2000).
3. Use of a prophylactic pancreatic stent reduces the likelihood of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.(Sofuni, Maguchi et al. 2011)
4. The amount and force while infusing bile acids or other solutions into the pancreatic duct causes acute pancreatitis in animal models and correlates with disease severity (Arendt, Hansler et al. 1996, Haciahmetoglu, Ertekin et al. 2008).
5. Multiple pancreatic duct injections, contrast opacification extending to the pancreatic tail, and acinarization increase the risk of post-ERCP pancreatitis (Freeman, DiSario et al. 2001).
6. Pancreatic ductal adenocarcinoma and other tumors (e.g. intraductal papillary mucinous neoplams) cause acute pancreatitis by obstructing the pancreatic duct (Munigala, Kanwal et al. 2014).

Table 1. Utilization of endoscopic therapy in North American Pancreatitis Studies (2000-2014)

Endoscopic therapy N (%)	RAP with Pancreas divisum (n = 78)	CP (± RAP) with Pancreas divisum (n = 110)
Any endotherapy	48 (62)*	82 (75)*
Sphincterotomy (Biliary or pancreatic)	45 (58)*	73 (66)*
Pancreatic duct stent	38 (49)*	61 (56)*
Bile duct stent	6 (8)	9 (8)

*All comparisons (vs. no pancreas divisum): p<0.001. **RAP with no pancreas divisum (n=491):** any endotherapy (41%); sphincterotomy (32%); pancreatic duct stent (26%); **Chronic pancreatitis with no pancreas divisum (n=1085):** any endotherapy (48%); sphincterotomy (37%); pancreatic duct stent (29%).

3.3 Minor endoscopic sphincterotomy is widely performed for idiopathic RAP (iRAP).

ERCP is a moderately high-risk intervention that has unproven benefit for patients with iRAP. However, based on predominantly retrospective cohort studies and the notion that pancreas divisum anatomy predisposes some patients to acute pancreatitis, minor papilla endoscopic sphincterotomy (miES) is commonly performed in clinical practice. Although the technique of miES has been performed for >30 years, there has been only one pilot, open-label, randomized trial of 19 patients with iRAP published over 20 years ago.(Lans, Geenen et al. 1992) This study compared serial dilation of the minor papillary orifice via pancreatic stents – a surrogate for miES – vs. diagnostic ERCP. After mean follow-up of 29-32 months, 6/9 (67%) patients who underwent diagnostic only ERCP developed at least one bout of acute pancreatitis as compared to 1/10 (10%, p<0.05) that underwent serial pancreatic duct stent placement. Serial stent placement has been replaced by miES in clinical practice since serial stenting requires multiple ERCPs and increases the risk of stent-associated main duct strictures.

Several retrospective cohort studies also support the practice of miES for RAP in the setting of pancreas divisum, with >70% of patients in most studies reporting a significant improvement in their disease course (Gerke, Byrne et al. 2004, Attwell, Borak et al. 2006, Chacko, Chen et al. 2008, Borak, Romagnuolo et al. 2009, Crino, Bernardoni et al. 2017). While supporting the role of miES, these studies chose a subjective endpoint (self-perceived improvement) despite their open-label design and absence of a sham

comparison group. The controversy is a recurrent topic at national meetings, and opposite positions were nicely summarized after a debate at the 2006 meeting of the American Pancreatic Association (Fogel, Toth et al. 2007). Both sides acknowledged the need for randomized trials, yet there has been little progress in clarifying the benefit of miES on iRAP with pancreas divisum over the past decade.

In the North American Pancreatitis Studies (NAPS2), which prospectively ascertained patients from over 25 US centers from 2000-2014, pancreas divisum was identified by physicians as a risk factor in 14% (78/569) of RAP and 9% (110/1195) of chronic pancreatitis patients. Any endotherapy, biliary or pancreatic sphincterotomy, and pancreatic duct stenting was performed more often in patients with divisum (***Table 1,*** unpublished).

3.4 RAP significantly impacts quality of life.

Acute pancreatitis causes significant pain, loss of productivity, and has a small but measurable risk of permanent morbidity and mortality. The physical and mental burden on patients who have fully recovered from even one episode of acute pancreatitis is significant (Neoptolemos, Raraty et al. 1998, Soran, Chelluri et al. 2000, Halonen, Pettila et al. 2003, Hochman, Louie et al. 2006, Pezzilli, Morselli-Labate et al. 2009, Wright, Lochan et al. 2009). Patients with iRAP and pancreas divisum and no objective evidence of chronic pancreatitis who were enrolled in a recent prospective cohort (FRAMES, sponsored by the NIDDK and led by Joe Romagnuolo, MD at MUSC; Gregory Cote was a sub-I at Indiana University) reported a Physical Component Score 0.5 standard deviations below the national average (Romagnuolo 2013). Additionally, physical and mental quality of life in patients with RAP was intermediate between controls and chronic pancreatitis patients in the NAPS2 study, reinforcing the concept that RAP alone reduces quality of life. Perhaps the best illustration of the RAP disease burden is the emerging practice of performing total pancreatectomy for individuals with iRAP in the absence of morphologic features of chronic pancreatitis: in a series of 49 individuals with iRAP undergoing total pancreatectomy, >80% demonstrated histological changes of chronic pancreatitis and >90% had intractable pain between acute pancreatitis episodes.(Bellin, Kerdsirichairat et al. 2016)

3.5 Minor endoscopic sphincterotomy for iRAP is one of the highest risk indications for ERCP.

Post-ERCP pancreatitis is the most common complication of ERCP, occurring in 2-5% of all cases and at least 10% in high-risk patients (Dumonceau, Andriulli et al. 2014). The best way to prevent post-ERCP pancreatitis is not performing ERCP. With the exception of difficult biliary cannulation, the strongest procedure-related risk factors for post-ERCP pancreatitis include injection or manipulation of the pancreatic duct and pancreatic sphincterotomy; both of these maneuvers are required when performing ERCP with miES, and are strong (7-fold increased risk) independent risk factors for post-ERCP pancreatitis.(Moffatt, Cote et al. 2011) The highest risk indications for post-ERCP pancreatitis include the evaluation of iRAP and suspected sphincter of Oddi dysfunction, and are compounded by the ERCP-related risk of injection and duct manipulation.

3.5.1 Immediate impact of empirical evidence supporting or refuting the use of ERCP.

The absence of viable medical therapies, the plausibility that improving pancreatic flow may improve the disease course, the available (but weak)

data in support of miES, and patients' "desperation" have created the perfect storm for more than three decades of endoscopic intervention for iRAP. This controversial practice affects thousands of Americans each year, and those enduring the complications of ERCP (and their associated costs) are impacted the greatest. While these risks are acceptable if ERCP positively impacts the disease course, the only method to define the risk:benefit relationship is adequately powered, sham-controlled trials with long-term, standardized follow-up.

The EPISOD study irrefutably showed that ERCP should not be performed for patients with sphincter of Oddi dysfunction type III (abdominal pain alone) (Cotton, Durkalski et al. 2014). This leaves sphincter of Oddi dysfunction type II and iRAP as the most prevalent, highest risk indications for ERCP. Post-ERCP pancreatitis risk factors are multiplicative, so that performing an ERCP on a patient with iRAP + pancreas divisum requires pancreatic duct injection and manipulation, creating a "worst case scenario" from the standpoint of procedure risk. Prevention of post-ERCP pancreatitis begins with validating the indications for ERCP that confer the greatest risk: the proposed SHARP trial will clarify whether or not ERCP should be performed for iRAP with pancreas divisum.

3.6 Long-term risk of post-sphincterotomy stenosis of the minor papilla

A recognized risk of miES is the development of symptomatic post-sphincterotomy stenosis. While large-scale, prospective studies with discrete criteria are lacking, rates of post-sphincterotomy stenosis are estimated to be 20% or higher (Elton, Howell et al. 1998, Heyries, Barthet et al. 2002, Joo, Yoon et al. 2009, Clarke, Slivka et al. 2012). There are no objective definitions for post-sphincterotomy stenosis. However, symptomatic post-sphincterotomy stenosis is expected to result in either acute pancreatitis ***(aim #1)*** *or* pancreas-related pain event(s), defined as pancreatitis-type symptoms that prompt emergency room or inpatient hospital evaluation. Differences in these outcomes (pancreatitis and pancreas-related pain events) between subjects randomized to EUS+ERCP with miES and EUS+sham will clarify whether the risk of post-sphincterotomy stenosis is outweighed by its benefit. In this study, among subjects who undergo ERCP at randomization or follow-up, rates of post-sphincterotomy stenosis will be tracked as a secondary safety measure. At the time of repeat ERCP, post-sphincterotomy stenosis will be defined by the need to perform minor papillary orifice treatment (re-do minor papillotomy or minor papillary orifice balloon dilation).

3.7 Innovation

3.7.1 First sham-controlled clinical trial for patients with iRAP.

To date, there have been no sham-controlled intervention trials for patients with iRAP. For a disease with numerous patient-centered endpoints that include quality of life, pain, and disability, a sham-controlled study is of paramount importance. As compared to pharmacological interventions – none of which are on the immediate horizon and all of which would require indefinite administration – ERCP with miES is an attractive treatment modality for a sporadic disease such as RAP. Given the promising preliminary data supporting its practice, only a sham-controlled, randomized trial with long-term follow-up can address whether or not miES reduces the risk of having another bout(s) of acute pancreatitis over time. A sham-controlled study will also be an ideal platform for the careful

collection of natural history data among patients assigned to the sham group. The proposed rigorous experimental design will ensure robust and unbiased results.

Irrespective of the primary outcome, the results will directly impact patient care: a study favoring miES will expand the use of this intervention internationally, whereas a study that shows no impact of miES in reducing the risk of a subsequent bout of acute pancreatitis will refute the practice of ERCP with miES and raise further questions about the role of ERCP for iRAP in standard ductal anatomy.

3.7.2 Assessment of several important clinical endpoints for patients with iRAP.

Pancreas divisum is overrepresented in patients with iRAP (Fischer, Hassan et al. 2010, Gonoi, Akai et al. 2011) and pancreatitis susceptibility mutations such as in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (Bertin, Pelletier et al. 2012, Ballard, Flueckiger et al. 2015). Some have hypothesized that divisum protects against exocrine pancreas insufficiency during youth, and then later in life predisposes to RAP in patients with susceptibility mutations (Nicholson, Johnstone et al. 2012). The association between divisum and susceptibility mutations does not refute the potential benefit of miES in reducing the risk of future acute pancreatitis or other RAP sequelae. A sham controlled, randomized trial will be the ideal format for the careful collection of data on known and potential covariates. Other than pancreatitis susceptibility mutations, potential covariates that might impact the natural history of iRAP with pancreas divisum include smoking, age, number of previous attacks, main pancreatic duct diameter, and presence of definite chronic pancreatitis morphology. This study protocol will exclude patients with RAP who have obstructive chronic pancreatitis (e.g., main duct strictures or stones) since treatment of these entities would not address the overarching question of this study: does miES reduce the risk of acute pancreatitis in patients with iRAP?

3.7.3 Foundation for additional research on unproven, high-risk indications for ERCP

According to the American Society for Gastrointestinal Endoscopy, performing ERCP for an appropriate indication is strongly recommended.(Adler, Lieb et al. 2015) The society's Quality Indicators white paper states that "evaluation of pancreatitis of unknown etiology" remains an appropriate indication for ERCP; since MRI and EUS are widely accepted and less invasive diagnostic alternatives to ERCP, this recommendation assumes that miES confers benefit for patients with RAP and pancreas divisum as well as comparable benefits for patients with standard ductal anatomy. Among ERCP experts and the majority of the GI community, currently available data are sufficient to support the practice of ERCP with miES for iRAP with pancreas divisum. Clinical practice is very unlikely to change without executing a definitive trial measuring the effect of ERCP and miES on subsequent risk of having a recurrent bout of acute pancreatitis. Results from this study will also stimulate future research on the therapeutic role of ERCP for standard duct anatomy, which has been

challenged by a recent, single center, open-label, randomized trial (n=89) of biliary sphincterotomy vs. biliary + pancreatic sphincterotomy for patients with iRAP.(Cote, Imperiale et al. 2012)

4. OBJECTIVES

4.1 Primary outcome (Aim #1): Reduce the risk of subsequent acute pancreatitis episodes by 33%.

To test this aim, we will compare the incidence of acute pancreatitis > 30 days after treatment allocation as the primary outcome measure, using the next attack of acute pancreatitis as a time-to-event outcome.

4.2 Secondary outcome (Aim #2): To compare the incidence rate ratio of acute pancreatitis between treatment groups.

All randomized patients will be followed longitudinally until study completion, even if acute pancreatitis occurs during follow-up. A secondary benefit of miES may be a reduction in acute pancreatitis frequency, defined as the incidence rate (episodes/time pre- and post-randomization). Since baseline incidence rate is a probable predictor of post-randomization incidence rate, we will compare the incidence rate ratios between the two arms, keeping person-time equal between the pre/post periods.

4.3 Secondary outcome (Exploratory Aim #3): To compare changes in patient-centered outcomes between treatment groups.

The natural history of idiopathic RAP is primarily based on retrospective cohort studies with variable follow-up. We will measure relevant patient-centered outcomes, using validated instruments for each: pain, self-perceived quality of life, global impression of change, pain-related disability, and number and days of pain or pancreas-related hospitalizations.

4.4 Secondary outcome (Exploratory Aim #4): Progression to chronic pancreatitis and its sequelae.

Although the proportion of patients who may transition to chronic pancreatitis during the proposed time period of the study will be low, we will quantify the progression to chronic pancreatitis during clinical care as an exploratory analysis. To accomplish this, we will perform a secretin-enhanced magnetic resonance imaging (MRI) study with magnetic resonance cholangiopancreatogram (MRCP) at 18 months after enrollment (for those eligible based on enrollment month). Also, we will measure the rates of new-onset diabetes mellitus (using blood glucose and hemoglobin A1c) and exocrine insufficiency (using fecal elastase) at the same time.

4.5 Secondary exploratory aims (Exploratory Aim #5): Biological and Data repository

Post hoc genetic analysis of the effect of known pathogenic mutations on natural history will be performed. Biological samples, MRI scans and data will be stored for future exploratory analyses of genetic, laboratory and radiological associations with outcomes.

5. STUDY PLAN

5.1 Study Design

Following the informed consent process, patients diagnosed with iRAP and pancreas divisum will undergo an endoscopic ultrasound (EUS). During the EUS, the endoscopist will confirm the absence of exclusion criteria and reassess for the presence of pancreas divisum. If the patient meets all eligibility criteria, the patient will be randomized 1:1 to either EUS + sham or EUS + ERCP with miES.

Development of post-ERCP pancreatitis will be assessed at the 30-day follow-up visit, which will occur at the study site.

All patients will complete a follow-up study encounter on a semi-annual basis via a telephone visit until the end of the trial (a minimum of six months and maximum of 48 months depending on enrollment year). The month 18 visit will be in-person or virtually at the study site. Other visits may be conducted by a blinded "central caller" or a blinded site coordinator.

Blinded study personnel will complete the baseline clinical assessment, the Day 30 follow-up visit and the planned 18-month patient visit. This individual will also facilitate the process of randomization but remain masked to the assignment. Other planned semiannual study assessments will be completed by a blinded central coordinator. If a patient develops acute pancreatitis or a pancreas-related pain event (see definitions in ***Section 8.6***), a blinded local coordinator and physician will complete the applicable adverse event documentation. Subjects who experience acute pancreatitis or an acute pain event during the course of the study will be assessed for the need for treatment and will either be treated at the enrolling site or referred for treatment as appropriate. ***Please see the Manual of Procedures for clarification.***

Observational cohort

In addition to the 234 randomized patients, approximately 100 patients with iRAP and pancreas divisum who meet all other eligibility criteria but who refuse randomization, refuse ERCP, or those in whom ERCP is not recommended by the unblinded physician investigator will be invited to participate in an observational cohort study. Patients who provide consent will be followed for subsequent acute pancreatitis episodes (aim #1), systematic, semiannual assessments for patient-centered outcomes (aim #3), and clinical (observational) assessments for the interval development of chronic pancreatitis and exocrine or endocrine insufficiency (aim #4).

5.2 Study Population

All patients with iRAP as defined per protocol will be screened for study eligibility. The patient must have pancreas divisum (complete or incomplete) identified by radiographic imaging prior to randomization.

5.3 Study Sites

In order to achieve a targeted enrollment of approximately 234 randomized subjects during a 3.5-year period, we have identified sites who are regional referral centers for pancreatobiliary endoscopy. This would require approximately 67 patients/year at all sites, or 3-4 patients/year/site (assuming 16-20 enrolling sites). The choice of centers is deliberate to include those with high ERCP volumes and expertise in therapeutic endoscopy and pancreatitis care. The chosen centers include university-based and hospital-based practices; each site PI is a nationally or internationally recognized expert in ERCP, pancreatitis, or both.

5.4 Estimated Study Duration

In order to maximize follow-up data, we will follow all patients every 6 months until the end of Year 4.5 of the U01 funding period, when the database will be locked for analysis. We estimate starting enrollment within 6 months of the grant start date and completing enrollment over 3.5 years. Assuming consistent enrollment, this would provide us with a minimum follow-up of 6 months and maximum follow-up of 48 months.

6. ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

1) Patient must consent to be in the study and must have signed and dated an approved consent form.
2) ≥18 years
3) Two or more episodes of acute pancreatitis, with each episode meeting two of the following three criteria:
   - abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
   - serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal
   - characteristic findings of acute pancreatitis on CECT, MRI or transabdominal ultrasonography
4) At least one episode of acute pancreatitis within 24 months of enrollment
5) Pancreas divisum confirmed by prior MRCP that is reviewed by an abdominal radiologist at the recruiting site.
6) By physician assessment, there is no certain explanation for recurrent acute pancreatitis.
7) Subjects must be able to fully understand and participate in all aspects of the study, including completion of questionnaires and telephone interviews, in the opinion of the clinical investigator.

6.2 Exclusion Criteria

1) Prior minor papilla therapy (endoscopic or surgical)
2) Calcific chronic pancreatitis, defined as parenchymal or ductal calcifications identified on computed tomography or magnetic resonance imaging scan that is reviewed by an expert radiologist at the recruiting site.
3) Main pancreatic duct stricture*
4) Presence of a structural etiology for acute pancreatitis, such as anomalous pancreatobiliary union, periampullary mass, or pancreatic mass lesion on imaging*
5) Presence of a local complication from acute pancreatitis which requires pancreatogram
6) Regular use of opioid medication for abdominal pain for the past three months
7) Medication as the etiology for acute pancreatitis by physician assessment
8) TWEAK score ≥ 4
9) Hypertriglyceridemia, defined as a serum triglyceride level > 500mg/dL during a prior episode of acute pancreatitis
10) Hypercalcemia, defined as a corrected serum calcium level > 10.5mg/dL associated with a prior episode of acute pancreatitis
11) Clinical presentation consistent with type I or type II autoimmune pancreatitis
12) Pregnancy (urine test)
13) Low probability of follow-up on a regular basis to achieve study objectives
14) Life expectancy < 6 months based on the opinion of the physician investigator

15) Incarceration

*The possible presence of a pancreatic duct stricture or structural etiology for acute pancreatitis will be assessed for all subjects during review of the MRCP. If no evidence of either exclusion is identified during review of MRCP, and all other eligibility criteria are met, subjects who consent to randomization will be scheduled for the pre-randomization EUS. Absence of pancreatic duct stricture and structural etiology will be confirmed during EUS before a subject can be randomized.

6.3 Discussion regarding enrollment criteria

Exclusion criteria 2 and 3. Using these criteria, it is possible that some patients with early chronic pancreatitis will be included. We will capture this information and consider appropriate secondary per protocol analyses; however, the primary analysis will be intention to treat which will include all randomized subjects. Moreover, in the absence of calcifications, we will not exclude patients based on the number of EUS findings - rather, we will record the number and type of EUS criteria present, and during analysis determine if the number of EUS findings is a prognostic variable. We elected deliberately not to use the Cambridge classification system since "moderate" changes of chronic pancreatitis by this system include irregularity and dilation of the main pancreatic duct. For example, the presence of a Santorinicele (focal cystic dilation of the distal portion of the dorsal pancreatic duct, at the minor papilla) might be interpreted in this category. These individuals represent an important subgroup who may benefit from miES. Main pancreatic duct diameter – and the presence of a Santorinicele – will be measured in all subjects and is considered in the randomization scheme.

Inclusion criterion 4. Requiring at least one attack in the previous 24 months: In clinical practice, it is uncommon for a patient with RAP to present for ERCP in the absence of having an episode in the past 24 months. This criterion will assure that subjects randomized in SHARP have an adequate baseline incidence rate of acute pancreatitis episodes

Exclusion criterion 6. Patients will be queried about their use of pain medications in the preceding 3 months. This criterion is meant to minimize the risk of enrolling subjects with chronic pain, in whom minor papilla sphincterotomy is not expected to help and in whom future endoscopic or surgical interventions are more likely. Since these subsequent interventions would adversely impact the ascertainment of the primary outcome, these patients will be excluded.

Exclusion criterion 8. The threshold at which alcohol causes acute pancreatitis is poorly understood and patient-dependent. Therefore, we will rely on the TWEAK alcohol screening questionnaire, which defines harmful or at-risk alcohol use by a score of ≥ 3.(Russell, Martier et al. 1996, Bradley, Boyd-Wickizer et al. 1998) TWEAK is an acronym for the 5 questions used in the questionnaire: **T**olerance, **W**orry, **E**ye-opener, **A**mnesia, and "**K**"-ut down. Since patients may modify their alcohol consumption after suffering from pancreatitis, wording of the TWEAK questions and the reference period will be "in the months before getting pancreatitis". We will use a higher threshold of ≥ 4 (rather than ≥ 3) to allow evaluation of a modifying role of alcohol, while excluding patients with a high probability of having alcoholic pancreatitis. Alcohol use will also be quantified during the baseline assessment, and its role on the natural history considered in the *post hoc*

analysis.

7. PARTICIPANT RECRUITMENT

7.1 Methods

The methods used for recruitment of participants in the study will be devoid of any procedures that may be construed as coercive. The recruitment process will not involve any restrictions on sociodemographic factors including age, gender, or ethnic characteristics.

The prevalence of RAP with pancreas divisum is balanced between men and women, although heavy alcohol use and smoking are more common among men. Therefore, per our enrollment criteria, we anticipate our cohort will have more women than men (since heavy alcohol use is considered an etiology for RAP, and thus not idiopathic). We anticipate our cohort will reflect national trends in this regard. We do not plan to actively pursue one sex, as we want our cohort to reflect the disease population. The clinical centers selected from the study represent a diverse geographic spectrum. Our clinical practice reflects our local regions in terms of minority populations, and we will recruit patients meeting eligibility criteria without discrimination.

Participants will be recruited through the sites' clinical practices and existing referral network. Patients referred to the clinical practices of participating sites will be screened for a diagnosis of acute or recurrent acute pancreatitis, pancreas divisum or both. Patients determined to be potentially eligible will be approached about study participation by their clinical care provider. It is expected that potentially eligible subjects will be approached regarding participation in the randomized trial well in advance of initiating randomization procedures to allow adequate time for the potential subject to consider the risks and benefits of participation.

In addition, regional referring physician practices will be notified by letter of the SHARP study in order to refer potential subjects. An informational video summarizing the purpose of the study and eligibility criteria will also be used as a recruitment tool and posted on widely used internet platforms, such as YouTube. It is expected that participating sites will approach all potentially eligible subjects regarding study participation.

8. PARTICIPANT ENROLLMENT

8.1 Presentation of Informed Consent

Consent will be obtained by either the Principal Investigator or by individuals delegated this responsibility by the Principal Investigator. Informed consent is to be obtained from the participant according to ***Section 16.1*** of this protocol. Informed consent must be obtained prior to the initiation of any screening procedures that are performed solely for the purpose of determining eligibility for the study that would not have been performed as part of standard patient care at the Clinical Center.

8.2 Eligibility Assessment

Any patient ≥ 18 years old who is believed to have iRAP and suspected pancreas divisum will be considered for inclusion in the study. Prior to approaching a potential subject regarding study participation, study staff may review the existing available medical

records for evidence of exclusion criteria. If no evidence of exclusion criteria is identified, the patient will be approached to discuss study participation.

As in all trials, the goal is to achieve a high level of compliance with protocol requirements by assuring, during the eligibility assessment, that the potential participant is fully informed and agrees to the protocol requirements. In addition, participants with a strong likelihood of non-adherence (e.g. for reasons such as difficulties in adhering to follow-up schedule) should not knowingly be enrolled. Adherence of the clinical center staff to careful assessment of the participant's understanding of the trial and a clinical center environment which supports the continued commitment of the participants are essential for the trial to be successfully completed.

Conditional Eligibility: Once a subject has agreed to study participation and informed consent has been obtained and documented, research personnel begin screening procedures required to determine conditional eligibility. Full eligibility for this trial cannot be assessed until EUS is performed immediately prior to randomization.

The following will be performed to assess conditional eligibility:

- The TWEAK alcohol screening test will be administered. A score of < 4 is required for study eligibility.
- Records of at least two previous attacks (including laboratory results and/or imaging studies) must be obtained and reviewed to determine if the attacks meet inclusion criteria.
- Films from a clinically indicated MRCP procedure must be reviewed with a radiologist at the recruiting site to confirm pancreas divisum, rule out definitive changes of calcific chronic pancreatitis, and to rule out other etiologies of acute pancreatitis. The MRCP procedure is performed as part of standard of care and will not be performed specifically for research purposes.
- Study personnel will interview the subject and review medical records to confirm remaining eligibility criteria.

Pre-Randomization Screening Procedures:
Additional procedures required to determine eligibility must be performed immediately prior to and during EUS at the Randomization/Treatment visit.

- Female subjects of child bearing potential must have a negative serum or urine pregnancy test within 2 days prior to EUS.
- During the EUS procedure, the investigator will confirm the absence of any previously unrecognized exclusion criteria. This is the final step required to determine final eligibility.

8.3 Central Randomization

Participants will be assigned to one of the treatment groups according to the randomization scheme described in ***Section 9***. Randomization is accomplished electronically within the WebDCU™ system. The Clinical Center will enter the eligibility criteria into the electronic case report forms. If all eligibility criteria are met and no exclusion criteria are identified, the WebDCU™ system will assign treatment according to the pre-specified randomization scheme.

9. STUDY PROCEDURE

9.1 Baseline Assessments

In addition to assessments related to eligibility, all patients will be administered the following questionnaires prior to the EUS:

- Demographics
- Previous pancreatitis episodes
- Smoking and alcohol use history
- Pancreatitis risk factors
- Pertinent medication utilization
- Quality of life (PROMIS29 and PROMIS Global)
- Pain assessment and related disability (PROMIS Nociceptive & Neuropathic Pain), and
- Opioid and other pain medication use

Information about the subject's medical history, including information about past pancreatitis episodes and pancreatitis risk factors will be collected from the subject's medical record.

If the subject has not already been diagnosed with diabetes mellitus, an assessment for diabetes mellitus will be performed at baseline (fasting or random blood glucose and hemoglobin A1c). If the subject has not been diagnosed with exocrine insufficiency, subjects will undergo fecal elastase testing during the baseline assessment. The diagnosis of diabetes mellitus will be established by use of antidiabetic medications or when a patient has abnormal values on two of the following tests or two abnormal values of the same test: a) fasting blood sugar ≥ 126 mg/dl; b) HbA1c ≥ 6.5%; c) random blood sugar ≥ 200 mg/dl.

The diagnosis of exocrine pancreatic insufficiency will be established by a clinical history suggestive of steatorrhea, quantitative fecal fat > 7g/day, or fecal elastase concentration <100mcg/g of stool. See Biospecimen SOPs for details of sample collection, shipping, storage and testing.

9.2 Treatment Procedures

Typically, randomization and study treatment procedures will be performed at a separate visit from the initial Screening/Baseline visit, during which consent is obtained. However, these procedures may be performed on the same day if all medical records necessary to confirm eligibility are available at the time of the visit.

Biospecimen collection

Please refer to the SHARP Biospecimen SOP and section 12.5 for additional details. Blood and urine specimens will be collected prior to the administration of anesthesia.

Endoscopy and randomization

During the EUS, an unblinded physician investigator will confirm the absence of exclusion criteria by reassessing for the presence of pancreas divisum and completing a standardized instrument documenting parenchymal and ductal changes in the pancreas. From the stomach and using a linear echoendoscope, the pancreatic duct diameter should be measured in the neck (at the location of the portosplenic confluence), body, and tail. The largest diameter will be entered as a stratification factor during randomization. Prior to randomization, the unblinded physician

investigator should document the amount and type of intravenous fluids to be administered during the periprocedural period (irrespective of treatment allocation) under the assumption that the subject will be randomized. This is done to preserve masking of subjects and blinded study staff.

Unless a definitive obstructive lesion or any other exclusion criterion is identified during EUS, the patient will be randomized 1:1 to either EUS + sham or EUS + ERCP with miES. Subjects excluded from study participation during EUS will be treated per standard of care.

Randomization procedure
If all eligibility criteria are met, the study personnel will complete the randomization procedure using the WebDCU™ system. Upon randomization, the WebDCU™ system will generate a numeric code that corresponds with a sealed envelope containing the subject's treatment assignment. Blinded study personnel may complete the randomization procedure in WebDCU™ and may retrieve the sealed envelope but will not open the envelope or be present when the envelope is opened. The sealed envelope will be provided to an unblinded individual responsible for informing the unblinded investigator of the subject's assignment.

Minor papilla cannulation and pancreatography (EUS + ERCP with miES group)
Subjects randomized to miES will undergo the procedure at the same time as EUS, under the same anesthetic. Indomethacin or diclofenac (100mg per rectum) will be administered for post-ERCP pancreatitis at the onset of the ERCP procedure in patients with no known allergy to indomethacin or diclofenac. Rectal indomethacin and diclofenac reduces the risk of post-ERCP pancreatitis and is routinely administered to patients at high risk of post-ERCP pancreatitis. Techniques for minor papilla cannulation will be left to the discretion of the treating endoscopist. In addition to standard techniques, other maneuvers to facilitate cannulation will be tracked using the ERCP case report form; these include the use of intravenous secretin and injection of methylene blue or other medium onto the surface of the duodenum to facilitate the identification of the minor papillary orifice. Deep cannulation of the minor papilla will be defined as: 1) guidewire access at or beyond the pancreatic genu, and 2) ability to insert an ERCP catheter or sphincterotome completely through the minor papillary complex. If both criteria are met, then deep cannulation will be defined as "successful." Superficial cannulation will be defined by the ability to achieve one of these two maneuvers or only the performance of pancreatography. Failed cannulation will be defined by the inability to perform a pancreatogram.

In some cases, the endoscopist may perform a precut sphincterotomy using a needle knife sphincterotome (performance of a partial minor papilla sphincterotomy using a needle knife sphincterotome before deep cannulation is achieved) or wire-assisted access sphincterotomy (performance of a partial minor papilla sphincterotomy using a needle knife sphincterotome after achieving deep cannulation using a guidewire, but before deep cannulation with an ERCP catheter or sphincterotome can be achieved). The performance of these maneuvers to facilitate cannulation will be left to the discretion of the treating endoscopist and tracked on the ERCP case report form.

There may be cases when deep minor papilla cannulation cannot be accomplished for technical reasons; the endoscopist should use their discretion in determining when additional efforts to achieve deep cannulation are considered futile. Reasons for futility

will be detailed in the case report form. Inability to achieve deep minor papilla cannulation will be defined as a technical failure. It is expected that the endoscopist performing the procedure has a track record of high (>90%) technical success rate with native papilla cannulation. To minimize the risk of technical failure, the treating physician may request the assistance of a colleague. Trainees will not have hands on involvement during the procedure to which the subject is randomized.

The extent of pancreatography (extent of injection) will also be left to the discretion of the treating endoscopist. The injection should be adequate to confirm the presence of pancreas divisum, characterize its subtype (incomplete vs. complete), and to provide a measurement of the pancreatic duct diameter at least in the pancreatic head and neck. The amount of contrast injected and the extent of pancreatic duct opacification will be recorded, as these are probable risk factors for post-ERCP pancreatitis.

Minor papilla sphincterotomy (EUS + ERCP with miES group)
The technique for miES will be left to the discretion of the study endoscopist. Techniques may include pull-type sphincterotomy, needle knife sphincterotomy over a pancreatic stent, dilation of the minor papilla orifice using a hydrostatic balloon catheter, or some combination of the above. If none of these techniques can be executed, this will be classified as a technical failure. The endoscopist may choose their preferred type of electrocautery (pure cut vs. blended cut current) as per their usual practice. The extent of sphincterotomy will be per the discretion of the treating endoscopist, with every effort made to execute a complete incision of the minor papilla by extending the incision to the top or apex of the minor papilla complex – as identified endoscopically. The study endoscopist will estimate the length of the incision (in mm); photo documentation of post-sphincterotomy minor papilla should not be performed in an effort to preserve blinding.

The endoscopist is expected to place an FDA-approved pancreatic duct stent for prophylaxis (no larger than 5Fr in diameter), in an effort to minimize the risk of post-ERCP pancreatitis. The stent's external characteristics (flange vs. pigtail), internal characteristics (with or without flanges), length, and diameter will be recorded.

This technical approach is intended to mimic real-life practice and maximize the study's external validity. These variables will be tracked in order to determine their impact on study outcomes.

Ultimately, the decision to abort the ERCP before deep minor papilla cannulation or completion of miES will be left to the discretion of the study endoscopist; conditions for this decision include futility and medical instability. In the event of technical failure, a second attempt will not be performed unless the subject meets one of the guidelines detailed in ***Section 9.6***.

Unless methylene blue (or similar chromoendoscopy agent such as indigo carmine) has already been used to facilitate minor papilla cannulation, a minimum of 3mL of diluted dye will be injected into the duodenum. If a prophylactic pancreatic duct stent cannot be deployed in the pancreatic duct, one should be deposited in the duodenal lumen (as done in the EUS + sham group) to minimize the risk of unblinding.

EUS + Sham

Subjects randomized to EUS + sham will already be sedated and have undergone the diagnostic EUS. The physician investigator will not make any attempts to achieve minor papilla cannulation, but photo document the minor papilla using a duodenoscope. A minimum of 3mL of diluted dye will be injected into the duodenum. A small caliber (3, 4, or 5Fr) prophylactic pancreatic duct stent will be deposited into the duodenal lumen. These maneuvers are performed to minimize the risk of unmasking.

Since sham endoscopy is expected to take less time than ERCP with miES, the subject should remain in the endoscopy procedure room for a minimum of 30 minutes (including the time required to complete the EUS with photo documentation of the minor papilla). Sedation will be stopped when the endoscopic procedure(s) is completed.

9.3 Observational cohort

In addition to randomized subjects, we plan to enroll approximately 100 patients with iRAP and pancreas divisum who refuse randomization, those who refuse ERCP, or those in whom ERCP is not recommended by the blinded physician investigator into an observational cohort. These subjects will be followed for subsequent acute pancreatitis episodes, systematic, semiannual assessments for patient-centered outcomes, and clinical (observational) assessments for the interval development of chronic pancreatitis and exocrine or endocrine insufficiency. Subjects in the observational cohort will undergo follow-up imaging and laboratory testing (including pregnancy testing) at the discretion of the treating physician(s).

Subjects enrolled into the observational cohort will follow the same follow-up schedule as patients who are randomized, with the following exceptions:

- No study-specific MRI/MRCP, and assessment of diabetes (endocrine) or exocrine insufficiency will be performed at 18 months. Therefore, these visits do not have to be in-person.

9.4 Follow-up Procedures

The goal of the study is to achieve complete and accurate follow-up until completion of the trial. Appropriate compliance strategies should be implemented at clinical centers to encourage and support participants in protocol adherence. The ultimate success of this trial will depend upon the timely submission of complete and accurate data on all follow-up forms.

The Day 30 and 18-month follow-up visits will be completed as in-person, by telephone, or by virtual visits at the enrollment site. Otherwise, planned semiannual study assessments will be completed by a blinded central coordinator with the assistance of blinded site coordinators on an as-needed basis. Central follow-up will be performed in a confidential manner, so that personal health identifiers required to complete remote follow-up visits will be stored separate from the SHARP database.

9.4.1 30-day follow-up

Blinded study personnel will direct the 30-day follow-up encounter, which will occur at the enrolling site, over the telephone or virtually. All randomized subjects will undergo an abdominal X-ray during this visit which is typically performed as part of clinical care to confirm spontaneous passage of a pancreatic stent. While subjects randomized to EUS + Sham

will not have a pancreatic stent placed into the pancreatic duct, subjects in both groups will undergo an abdominal x-ray in order to maintain the blind. If a patient reports abdominal pain and a CT scan is ordered as part of the standard of care, the results of the CT scan can be used to confirm a stent has not been retained.

If the stent is identified in the gastrointestinal tract but not in the pancreatic duct, the patient will not be notified; this reflects usual clinical care, since migrated stents in the small intestine or colon are not followed thereafter since their spontaneous passage is virtually assured. If the stent is identified in the pancreatic duct, removal will be performed as part of the subject's clinical care.

In addition, blinded study personnel will assess the subject for adverse events that may have occurred since randomization.

Development of post-ERCP pancreatitis will be an important assessment at the 30-day follow-up period. Post-ERCP pancreatitis will be defined per consensus guidelines(Cotton, Eisen et al. 2010):

1) New or increased abdominal pain that is clinically consistent with a syndrome of acute pancreatitis, and
2) Amylase or lipase ≥ 3x the upper limit of normal at least 24 hours after the procedure, and
3) Hospitalization (or prolongation of existing hospitalization) for at least 2 days.

The diagnosis of post-ERCP pancreatitis will be made based on review of medical records including clinical notes, results of lab tests and imaging studies.

Subjects who develop post-ERCP pancreatitis will be managed per standard clinical practice by the unblinded physician investigator. After recovery, subjects will continue to be followed per study protocol.

9.4.2 18 Month Follow-up

At approximately 18 months post-randomization, subjects will undergo an MRI with intravenous contrast (gadolinium) and MRCP protocol with secretin (a pancreatic secretagogue) enhancement if available to assess for interval morphological and/or functional changes of chronic pancreatitis. Gadolinium may be withheld if the glomerular filtration rate is < 30 mL/minute) or allergy. If there is a contraindication to MRI, a pancreas protocol contrast-enhanced computed tomography (CECT) scan will be performed. These images will be interpreted locally; de-identified images will be stored on a central radiology server at MUSC for future ancillary studies. Each site will have their own methods for removing personal health identifiers including metadata, before submitting the films to the Statistical and Data Coordinating Center for storage. If an MRI/MRCP had been performed within 6 months of these study time points, and is considered to be of adequate quality, then a repeat scan will be deferred. Images of MRI/MRCP scans, if performed at other intervals during the follow-up period, and available, will also be sent to a central radiology

server. If the subject is pregnant at the 18-month encounter, the MRI will not be performed until post-partum.

If the subject has not already been diagnosed with diabetes mellitus, assessment for diabetes mellitus will be performed at the 18-month follow-up encounter (fasting or random blood glucose and hemoglobin A1c). If the subject has not been diagnosed with exocrine insufficiency, subjects will undergo fecal elastase testing at the 18-month follow-up encounter.

9.4.3 Telephone follow-up (6 months, 12 months, 24 months, 30 months, 36 months, 42 months, 48 months)

In addition to in-person or virtual follow up visits completed at Day 30 and Month 18, subjects will complete a follow-up study visit by phone every 6 months until the end of the trial (a minimum of 1 year and maximum of 4 years depending on enrollment year). These telephone visits may be conducted by a blinded "central caller" or by a site coordinator. The central caller will collect the following information since last contact:

- New hospitalizations or ER visits
- New diagnoses of medical conditions
- New medications
- Smoking and alcohol consumption
- Patient reported outcomes (PROMIS Global Health, PROMIS29, PROMIS Neuropathic, PROMIS Nociceptive Pain assessment and pain and disability, Best Guess Subject Assessment)

Information collected by the central caller will be entered into the study database, where it can be reviewed by the enrolling site, which will be responsible for assessing and documenting reportable adverse events, events related to acute pancreatitis, and diagnoses of diabetes or exocrine insufficiency. Subjects will be given the option to complete the patient reported outcome assessments online by entering responses on a secure website. Subjects will access online assessments through a web link sent via email. If a subject is unable or unwilling to complete assessments online, the central caller will administer these assessments during the call.

9.4.4 First acute pancreatitis during follow-up

Subjects will be instructed to contact the enrolling site if they develop signs or symptoms suspicious for acute pancreatitis. Blinded study personnel at the enrolling site will direct the follow-up if an enrolled subject develops signs or symptoms suspicious for acute pancreatitis (first episode) >30 days after enrollment. The decision to proceed with a clinical evaluation (e.g., laboratory testing, radiology, or referral to a medical facility for evaluation) will be made by a blinded site investigator who did not perform the index procedure and is unaware of the subject's treatment allocation. Subjects will be given a standing order for laboratory testing and instructed to seek medical evaluation if symptoms reminiscent of their prior acute pancreatitis develop, and these symptoms are severe enough to interrupt their routine daily activities. If the subject received care for signs or symptoms suspicious for acute pancreatitis at another facility, medical

records will be requested for review. The blinded site investigator will determine if the subject's episode meets study criteria for acute pancreatitis.

Details of the acute pancreatitis event, such as need for and duration of hospitalization, presence of local and systemic complications of acute pancreatitis using the revised Atlanta criteria and treatment received will be assessed via history and review of medical records by the blinded coordinator and physician.

9.4.5 Subsequent acute pancreatitis follow-up

Subsequent episodes of acute pancreatitis will be managed in a similar manner to the first. To maintain consistency across centers, guidelines for recommending ERCP during the follow-up period are provided in ***Section 9.6.***

9.5 Maintenance of the blind

In order to ensure blinding of 1) subjects, 2) healthcare providers making clinical decisions that may directly impact the primary endpoint, and 3) study coordinators who will obtain outcomes data, the medical record documentation will NOT state whether an ERCP with miES was performed. Instead, the endoscopy report should include language indicating the subject's participation in a blinded research study in which he/she may or may not have undergone the ERCP with miES procedure. Sites who are unable to omit this information from medical record documentation must have a comparable method of preserving the blind via medical records in place. Alternative methods must be approved by the SHARP Executive Committee.

All sites will have a minimum of two physician investigators, of which one will serve as blinded investigator and one as unblinded investigator for each subject. The investigator in the "blinded" and "unblinded" role may be consistent for all subjects or may alternate based on subject.

For subjects randomized to EUS + ERCP with miES, the endoscopist should administer rectal indomethacin (all US sites) or diclofenac (non-US sites) for pancreatitis prophylaxis at the onset of ERCP. This will minimize the likelihood that the subject will pass a visible suppository in the recovery room. Since subjects randomized to EUS + ERCP with miES will undergo placement of a prophylactic pancreatic duct stent, all randomized subjects will require an abdominal X-ray at the Day 30 visit after ERCP to confirm spontaneous passage. To maintain the blind, all subjects will undergo this procedure. This will coincide with the first follow-up encounter to assess for adverse events. If the X-ray confirms retention of the stent in the pancreatic duct, it will be the responsibility of the unblinded physician investigator and his/her support staff to assure that the stent is removed endoscopically per clinical practice.

To prevent unblinding, in the EUS + sham group, 3 ml of dilute dye such as methylene blue in US sites, or similar due in non-US sites will be injected into the duodenum and a plastic stent will be left in the duodenum. In the EUS + ERCP with miES group, if dye was not used to assist in cannulation, 3 ml of dilute dye will be injected into the duodenum before the end of the procedure; in the EUS + ERCP with miES group, a stent will be left in the duodenum if one is not placed into the pancreatic duct.

Site study coordinators will be blinded to treatment allocation so that he/she may be involved in the follow-up assessments at Day 30, assist with data collection related to acute pancreatitis episodes and pancreas-related pain events, and during the 18-month follow-up visit.

If a subject develops symptoms suggestive of acute pancreatitis more than 30 days after the randomization procedure, on-site assessments will be directed by a physician who was blinded to the treatment allocation. Clinical decisions, including whether or not to obtain laboratory or radiographic testing for suspected acute pancreatitis, will not include the unblinded physician investigator. A diagnosis of acute pancreatitis during follow-up will be determined by a healthcare provider who is unaware of the patient's randomization group.

In order to maintain blinding of subjects, all facility and professional charges associated with the randomization procedure will be billed to the research study.

To test the effectiveness of blinding procedures, subjects and blinded study personnel will be asked at the 30-day follow-up assessment to which group they believe the subject has been assigned. This question will be repeated at the Month 18 visit

If the subject becomes aware of their treatment assignment at any point during study participation, this will be documented in the study database. The subject will remain in the study and be part of the analysis population.

9.6 Guidelines for performing ERCP during the follow-up period.

The following are guidelines to assist a blinded investigator who is evaluating subjects during the follow-up period. Since the primary aim is to determine the effect of ERCP with miES on the probability of developing another bout of acute pancreatitis, which is a time-dependent outcome measure, every effort should be made to avoid ERCPs during the follow-up period until this outcome has been reached.

Definitions:

- ***Acute pancreatitis*** The definition of acute pancreatitis will be per consensus (Atlanta guidelines):(Banks, Bollen et al. 2013) "The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on CECT and less commonly MRI or transabdominal ultrasonography."
- A ***pancreas-related pain event*** is defined as an episode of pancreatitis-type symptoms (most commonly pain) that requires emergency room or inpatient hospital evaluation.

<u>Guidelines for ERCP during the follow-up period:</u>

a) Two or more episodes of acute pancreatitis
b) One episode of acute pancreatitis with local complication as defined by Atlanta criteria, that warrants pancreatogram
c) One episode of acute pancreatitis *plus* at least one independent pancreas-related pain event.

d) Interval development of symptomatic pancreatic duct obstruction (main duct stricture or stone) on cross sectional imaging
e) Two or more pancreas-related pain events and minimum follow-up of 12 months

Ultimately the decision to recommend ERCP during the follow-up period is based on the best clinical judgement of a blinded physician investigator evaluating the subject.

10. DISCONTINUATION OF PARTICIPATION

10.1 Participant Withdrawal of Consent

The participant has the right to voluntarily withdraw consent from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. For the occasional participant who withdraws consent, the date and reason for consent withdrawal should be documented. Participant data will be included in the analysis up to the date of the consent withdrawal.

A distinction should be made between participants who fail to complete all forms on schedule or who miss some telephone visits and the withdrawal of consent. Missed or rescheduled visits will be documented, but the participant will continue to be followed in the future according to protocol requirements, and all follow-up data will be included in the analysis.

10.2 Participant Removal from Study Intervention/Procedures

If a participant withdraws consent for the protocol intervention and/or study related procedures, document whether the participant is willing to allow the submission of continued follow-up information. This documentation should include whether the subject will continue to be willing to be contacted during follow up to complete all questionnaires, or at a minimum will be willing to be contacted to provide information on the occurrence of an acute pancreatitis event (primary outcome).

11. RISKS TO SUBJECTS

Randomization: Subjects will be assigned to receive the EUS + ERCP with miES procedure or EUS + sham procedure by chance. One treatment group may prove to be less beneficial or have more risks than the other group.

Blinding: To keep the study free from bias, the protocol has been carefully developed to minimize the risk of unmasking subjects and investigators responsible for evaluating subjects during follow-up. If a subject develops a medical problem where it is important for treating providers to know whether or not an ERCP was performed, there will be a mechanism in place for urgent unmasking of treating providers through the Statistical and Data Coordination Center (SDCC).

Sham: Subjects in the sham group will not receive ERCP with sphincterotomy. While these subjects will not be exposed to the risks specific to ERCP, including post-ERCP pancreatitis, subjects will not receive the potential benefit which may occur from the ERCP procedure.

Endoscopic ultrasound (EUS): All subjects will undergo EUS to evaluate for etiologies of RAP. The risks of EUS are similar to a standard esophagogastroduodenoscopy and

include perforation (<0.1%) and sedation-related cardiopulmonary complications (0.1-0.5%). EUS is a routine diagnostic test performed in clinical practice for patients with iRAP.

(ERCP) with minor papilla endoscopic sphincterotomy (miES): If randomized to ERCP with miES (approximately 50% of subjects), the procedure will be performed immediately after EUS and under the same anesthetic. Subjects undergoing ERCP with miES will be at-risk for the ERCP-specific complications which include post-ERCP pancreatitis (10-20%), post-miES hemorrhage (1-2%), and post-sphincterotomy perforation (<1%). The use of duodenoscopes has a very small risk of bacterial transmission (fewer than 100 reported cases of resistant infections potentially or definitely transmitted from duodenoscopes over many years, with approximately 500,000 ERCPs performed each year in the U.S.). Echoendoscopes used to perform EUS (see above), have a similar elevator mechanism but the risk of bacterial transmission from echoendoscopes has not been defined. ERCP with miES is performed for many patients with pancreas divisum and participation in this study will not expose them to a higher risk of ERCP-related complications than if the procedure were performed during standard clinical practice.

Chromoendoscopy agents: The most common side effect of the proposed dye agents (Methylene Blue or Indigo Carmine) is abnormal urine color. Less common side effects include diarrhea, frequent urination, nausea and vomiting, stomach cramps and fever.

Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP). Subjects will undergo an MRI with MRCP at month 18 during the follow-up period (depending on their enrollment date). Subjects who have a contraindication to MRI (subjects who have heart pacemakers, metal implants, or metal chips or clips in or around the eyeballs, artificial heart valves, metallic ear implants, bullet fragments, and chemotherapy or insulin pumps) will not participate in this component of the study. There are no side effects of an MRI scan.

Contrast Agent (Gadolinium): The contrast material used for an MRI exam, called gadolinium, does not contain iodine and is less likely to cause side effects or an allergic reaction. There is a risk of an allergic reaction, so subjects will be queried about a prior history of allergy to gadolinium, fish, or shellfish (since a prior reaction to these foods increases the risk of an allergy to gadolinium). In addition, gadolinium is excreted by the kidneys, so a serum creatinine level will be checked immediately prior to the MRI scan (glomerular filtration rate < 30mL/minute). Gadolinium contrast agents may increase the risk of a rare, but serious, disease called nephrogenic systemic fibrosis in people with severe kidney failure. Nephrogenic systemic fibrosis triggers thickening of the skin, organs and other tissues. There is no effective treatment for this serious, debilitating disease.

Secretin (administered during MRI/MRCP): Side effects from secretin are uncommon, but include flushing, nausea, vomiting, abdominal pain, upset stomach, diarrhea, and a remote (less than 1 in 100) chance of acute pancreatitis. There is also a chance of an allergic reaction. Contrast-enhanced computed tomography scan (CECT). In subjects with a contraindication to MRI, a pancreas protocol CECT will be performed at month 18. The radiation exposure from one CECT (average dose = 10mSv) is roughly equivalent to the amount of radiation exposure one experiences from our natural surroundings in 3 years.

Indomethacin or diclofenac: Potential side effects of this medication include peptic ulcer disease, kidney failure, heart attack, stroke, worsening of congestive heart failure or high blood pressure. However, a single dose of this medication is extremely unlikely to result in these effects.

Stent Placement: It is possible for the stent to be placed within or migrate into the duct and cause pancreatitis, infection or perforation. Migrated stents may require an operation for removal. However, this is an extremely unlikely event.

Abdominal X-ray: All randomized subjects will undergo an abdominal X-ray approximately 30 days after the randomization procedure. An abdominal X-ray (average dose = 0.7mSv) is an exceedingly low risk test that requires no specific patient preparation www.xrayrisk.com). The radiation exposure from one abdominal x-ray is roughly equivalent to the amount of radiation exposure one experiences from our natural surroundings in 100 days.

Blood Draw: The risks of blood drawing include temporary discomfort from the needle stick, bruising, infection or clot in the vein. Fainting could occur.

Genetic Testing: The research participant could feel some stress from donating their samples for future research. There is no intent to inform subjects, their family members or clinical care physicians of the results of future testing. The risks of not knowing what is found include not being aware if there is treatment for the problem being studied.

Loss of confidentiality: Protection of patient confidentiality is essential in human clinical trials. A HIPAA compliant de-identification process will be utilized which includes a unique computer-generated study id for each enrolled subject. Patient data maintained outside of the study site and within the WebDCU™ will be stored in a de-identified format with the key maintained with the local site PI. Furthermore, at each local site study binders will be maintained in locked physical facilities and only accessible to authorized study team members to protect patient privacy.

12. OUTCOMES DEFINITIONS

12.1 Aim #1 Subsequent acute pancreatitis. The primary endpoint will be development of the first episode of acute pancreatitis during follow-up (following the 30-day post-randomization visit). The definition of acute pancreatitis will be the same as for study enrollment and per consensus (Atlanta guidelines):(Banks, Bollen et al. 2013) “The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on CECT and less commonly MRI or transabdominal ultrasonography.” If the patient is evaluated at the participating institution where randomization occurred, a blinded physician will assess for and determine if each of the three criteria are present. The blinded physician will diagnose acute pancreatitis if two of these three criteria are met. If the patient is evaluated and treated at another facility (not the primary site of enrollment), a blinded site coordinator will collect medical records pertinent to the encounter(s). These records will be reviewed by a blinded site physician at the participating institution where the

randomization procedure occurred. After reviewing these records, the blinded physician will diagnose acute pancreatitis if two of these three criteria are met.

12.2 Aim #2. Incidence rate ratio. The first secondary endpoint will be the incidence rate ratio of acute pancreatitis episodes. The incidence rate ratio will be defined by the (number of acute pancreatitis episodes/time post-randomization) divided by the (number of acute pancreatitis episodes/time pre-randomization), keeping person-time equal between the pre/post periods.

12.3 Exploratory Aim #3. Patient-reported outcomes. Pain related outcomes will include presence and pattern of pain, type of pain (neuropathic or nociceptive) using short form PROMIS instruments, opiate use (average use, recent use based on 30-day recall), and pain-related disability). Quality of life will be measured using the PROMIS Global Health and PROMIS 29 instruments. Patient's Global Impression of Change will be measured using the PGIC scale. Number and days of pain or pancreas-related hospitalizations will be quantified.

12.4 Exploratory Aim #4. Progression to chronic pancreatitis.
Interval development of chronic pancreatitis will be defined as the development of morphological changes of chronic pancreatitis during follow-up; specifically, the interval development of parenchymal or ductal calcifications or main pancreatic duct stricture. These will be measured by radiographic interpretation of study MRI scans at month 18, or through other radiological imaging obtained during clinical care.

Interval development of new-onset diabetes mellitus will be confirmed when a patient has abnormal values on two of the following tests or two abnormal values of the same test: a) Fasting blood sugar ≥ 126 mg/dl; b) HbA1c ≥ 6.5%; c) Random blood sugar ≥ 200 mg/dl measured at month 18, or laboratory testing through routine clinical care, or are receiving antidiabetic medication(s) for treatment of diabetes mellitus.

Interval development of exocrine pancreatic insufficiency will be defined using the fecal elastase test measured at month 18 (or laboratory testing through routine clinical care), defined as one fecal elastase concentration <100mcg/g stool or two values between 100-200 mcg/g stool.

12.5 Exploratory Aim #5. Biorepository.
The goal of biospecimen procurement (exploratory specific aim #4) is to establish a biorepository for future translational studies. These studies would explore risk factors for recurrent acute pancreatitis, progression to chronic pancreatitis and its sequelae, and factors associated with response to miES. We will collect blood and urine from subjects in both the randomized and observational cohorts who consent to participation in the biorepository. All samples will be labeled with the SHARP study ID and no personal health identifiers. Samples collected at participating centers will be shipped to the University of Pittsburgh central biorepository and stored at this facility throughout the study period. Following the SHARP trial, remaining samples will be shipped to a designated NIDDK Biosample Repository.

All samples and data transferred to the Pittsburgh Repository will be under the custodianship of the SHARP PIs, although the study's Steering Committee will have proprietary control of and exclusive access to the samples and data for an agreed-upon period of time. Subsequently, samples and data will be available to the wider

scientific community in accordance with the NIH policy on Data Sharing as well as the NIDDK policy for data sharing in multi-center and large single-center clinical studies.

Biological samples from the biorepository will be used for targeted genotyping for the current study (in both randomized and non-randomized participants). The genes analyzed will be determined by the study Steering Committee at the time of statistical analysis. Refer to the SHARP Biospecimen SOPs document for additional information.

Genomic Data Sharing Plan

The SHARP trial is collecting biospecimens on all enrolled participants who provide written consent to allow biosamples to be used for future research by the SHARP investigators and the wider scientific community. All collected samples will be transferred for storage to a central repository at the University of Pittsburgh and only tracked by a unique study identifier. The SHARP investigators will have access to these samples for targeted genoyping during the grant funding period. No more than 12 months after completion of the primary study analysis, the anonymized genotype data will be submitted to the NIH controlled-access database of Genotypes and Phenotypes (dbGaP).

13. DATA MANAGEMENT

13.1 Site Monitoring

The Site Monitoring Plan will be guided by the FDA Guidance on Risk-Based Monitoring and will be a combination of remote and on-site monitoring. The Site Monitoring Plan will detail the monitoring plan and will be part of the MOP. Briefly, the designated monitor(s) will be able to check regulatory documents and certain CRFs remotely and the DCU will work with each site to develop the best plan (i.e., remote access to medical records). In addition to remote monitoring, the monitor(s) will visit the Clinical Centers at specified intervals for the purposes of comparing source documents (such as hospital/clinical charts) to electronic Case Report Forms (CRFs) and database verification. This review will also verify adherence to local regulations for conducting clinical research, protocol eligibility criteria and protocol schedule, and to ensure the consistency, accuracy, and completeness of the data. During both remote and on-site monitoring, the monitor will ensure that subject confidentiality is maintained and that PHI is protected. The investigator agrees that he/she will ensure that any issues, problems, or need for corrections that arise during the conduct of the study will be resolved in a timely manner.

13.2 Remote Monitoring of Informed Consent

In an effort to review informed consent forms in a timely manner, enrolling sites will upload a pdf of the signed informed consent form, into the password protected clinical trial management system, WebDCU™. The PDF file will be linked to the subject ID but will be stored on a secure server separate from the study's CRF data. The secure server on which these files are stored is not backed up to prevent copies of files containing Individually identifiable health information from being copied and stored on non-SDCC back up servers. The files on these servers can only be accessed by designated study personnel upon entry of a second password. SDCC staff will remotely monitor the informed consent forms and issues identified will be relayed to the clinical site for corrective and preventative action. After remote monitoring is complete, the PDF file containing the informed consent form will be permanently deleted from the secure server. If a subject must be re-consented, the process will repeat itself.

13.3 Data Management

Data management will be handled by the Data Coordination Unit (DCU) in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC). All study activities will be conducted in coordination with the study PIs, the clinical sites, and NIDDK, and will use an electronic data acquisition method where all study specific clinical data will be entered by the site personnel in real time. The latest version of each CRF will be available as a PDF file on the study website for use as worksheets and source documents by study personnel.

The study data will be managed (including data queries) by the DCU using the WebDCU™ system. This user-friendly web-based database system, developed by the DCU, will be used for regulatory document management, subject enrollment/randomization, data entry, data validation, project progress monitoring, subject tracking, site monitoring, user customizable report generation and secure data transfer. Upon entry of CRFs into the study database, quality control procedures will be applied at each stage of data handling in order to ensure compliance with GCP guidelines, integrity of the study data, and document processing system reliability. All sites will be monitored by the DCU and site monitors will conduct periodic site visits to review source documents and case report form information. A quality assurance record audit will be implemented. Audit findings will be used to identify and correct problems.

13.4 Data Security and Confidentiality

During the course of the trial, user access to the files with subject identifiers, and files with study outcomes will be restricted to core staff with any exceptions to be approved by the Executive Committee.

In addition to use of passwords and other security measures, all documents containing identifying information on individuals or physicians are considered confidential materials and will be safeguarded to the greatest possible extent. No information, which identifies a specific person, hospital, or physician, will be released to, or discussed with anyone other than study staff members.

Because the DCU uses a web-based system, source documents and CRFs will remain at the participating sites. The study database only identifies study subjects by unique study identification codes. All data will be stored in a manner that is HIPAA compliant, without the ability to track the information back to a specific subject except through a password protected system. All collected information about a subject will be stored by a unique identification code. All DCU personnel have completed human subject protection training and good clinical practice training.

13.5 Data Quality Assurance

Upon entry of CRFs into the study database, quality control procedures will be applied at each stage of data handling in order to ensure compliance with GCP guidelines, integrity of the study data and document processing system reliability. These procedures are outlined in the Data Management Plan study document.

14. ADVERSE EVENT REPORTING

14.1 Definition of Adverse Events and Serious Adverse Events

An Adverse Event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment, device, or procedure regardless of whether it is considered related to the medical treatment, device, or procedures (attribution of unrelated, unlikely, possible, probable, or definite). (For example, hyperventilation and dizziness during phlebotomy procedures) A Serious Adverse Event (SAE) is any adverse event that results in any of the following:

a) Death
b) In-patient hospitalization (for reasons other than observation) or prolongation of an existing hospitalization
c) A persistent or significant disability or incapacity
d) Congenital anomaly/birth defects

The attribution of an AE or SAE characterizes its causal relationship to the study-related intervention/procedure as follows:

a) Not Related
b) Unlikely
c) Reasonable Possibility
d) Definitely

The study will utilize the version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for Toxicity and Adverse Event reporting that is specified in the protocol. A copy of the CTCAE Criteria can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

14.2 Adverse Event Collection Period

All AEs, non-serious AND serious, must be reported by the clinical site investigator(s) from randomization through Day 30. Only SAEs must be reported through the end of the study period.

14.3 Reporting of Adverse Events

All AEs must be monitored and followed until they are adequately resolved or explained. The PI or the Study Coordinator at each Clinical Site is responsible for entering any and all reportable AEs into the database within the required timelines and updating the information (e.g., date of resolution, action taken) in a timely manner. All reportable events must be submitted to WebDCU via the AE CRF within 5 days of first knowledge of the event. Upon completion of the study protocol by the subject, premature withdrawal from the study by the subject, or the subject's death, all information regarding each reportable event must be completed, if not done so earlier. In the event of a subject death during study, that should be immediately reported and all possible efforts should be made by the site to obtain relevant records from the hospital or the subject's primary care provider to determine the cause of death.

14.4 Medical Safety Monitor

An Independent Medical Safety Monitor has been appointed to review all serious adverse events (SAEs) reported during the study. The MSM will adjudicate the relationship of the SAE to both the study intervention and the principles and intensity of overall care as described in the protocol as well as enter the expectedness of the reported SAE. In addition, the MSM will regularly review aggregated AE data (provided by the SDCC). The MSM will present any concerns regarding safety to the Study Executive Committee and the DSMB Liaison.

14.5 DSMB

The SHARP study will have an independent Data and Safety Monitoring Board (DSMB) appointed by the NIDDK to oversee study patient safety. The DSMB will receive reports on study progress and safety as well as data quality. The DSMB will meet in person or by teleconference on a minimum of a semi-annual basis to monitor cumulative safety data and data quality.

15. STATISTICAL CONSIDERATIONS

15.1 Sample Size and Power Estimation

Since the natural history of iRAP is poorly understood, risk estimates are based on previous small clinical trials and epidemiological studies. Based on a previous small trial of ERCP for RAP in pancreas divisum with limited (1-year) follow-up for the majority of patients, the probability of developing a third episode of AP is 70%.(Lans, Geenen et al. 1992) Natural history studies specific to divisum are lacking, but retrospective cohort studies and one surgical series suggest the recurrence rate following minor papilla stenting, miES, or surgical sphincteroplasty are 15-50%(Attwell, Borak et al. 2006, Chacko, Chen et al. 2008, Borak, Romagnuolo et al. 2009, Crino, Bernardoni et al. 2017). Given the short-term risk of post-ERCP pancreatitis (~10%), costs of ERCP, and potential for post-sphincterotomy re-stenosis, we believe a minimum effect size of 33% (relative risk reduction) is of clinical relevance. This effect size was agreed upon by the site principal investigators as the least clinically significant benefit for ERCP, considering the risks of ERCP and available data on this topic. Since AP recurrence is variable and time sensitive, we propose a reduction in risk of subsequent acute pancreatitis during follow-up as the primary outcome, defined by the median time to acute pancreatitis recurrence (a time-to-event measure). We assume the risk of recurrence within 12 months of randomization is 60% in EUS + sham and 40% in EUS + ERCP with miES groups, with the median time to recurrence being 9.1 and 16.3 months for EUS + sham and EUS + ERCP with miES groups, respectively. Assuming an exponential hazard, a 2-sided alpha error of 5%, power 85%, and non-adherence of 20% (this includes technical crossovers when sphincterotomy cannot be performed and competing events/risks), the trial requires a total sample size of approximately 234 (n=117 per group).

We recognize that sample size estimation is based on assumptions and if the event rate is lower than assumed, we may begin to see a decrease in power. To reduce the likelihood of an underpowered study due to incorrect assumptions, a sample size re-estimation will be conducted during the enrollment period. Details of this plan as well as all statistical considerations are outlined in the SHARP Statistical Analysis Plan.

15.2 Treatment Allocation

Enrolled patients will be assigned to either EUS + sham or EUS + ERCP with miES (1:1 randomization). A dynamic stratification system will be implemented to ensure well-balanced subgroups for the specified variables. Site, duct diameter (1, 2, 3, 4, 5, 6 or ≥ 7) and a dichotomized variable for number of attacks (1-2 vs ≥3) in the two years prior to randomization will be included in the randomization algorithm to ensure baseline balance between treatment arms. The superior balancing characteristics of dynamic randomization over blocked randomization have been well established. The randomization algorithm, which will be programmed into the data capture system, will employ biased-coin minimization and the variance method with stratification weights.

When a new patient is enrolled, the site will enter the stratification factor values into the eCRF (electronic case report form) on WebDCU™. The details of the randomization algorithm are located in the Randomization Plan study document.

15.3 Statistical Analyses

The primary analysis of the trial will be done in accordance with the "intent-to-treat" (ITT) principle, *i.e.,* all randomized participants will be included in the analysis. This means that once a participant is randomized to an intervention group, the participant's data will be included in the primary analysis regardless of compliance with the protocol-specified intervention or follow-up requirements.

A cox-proportional hazards model will be used to assess time to first occurrence of acute pancreatitis (primary outcome). Subjects without an outcome event will be censored at the last known status or at the end of study time point. We will adjust for duct diameter and number of attacks in the past 24 months in the primary analysis. Additional analyses will explore the impact of the other potential prognostic variables. This study is designed to test the primary hypothesis. However, it also offers the opportunity to conduct analyses to evaluate important additional patient outcomes. Details of the full analysis plan are in the Statistical Analysis Plan document.

15.4 Observational Cohort

The observational cohort will aid in the interpretation of the findings of the randomized study. We are most interested in comparing the two cohorts, randomized and observational, in terms of baseline characteristics that may cause bias. These comparisons will be primarily descriptive. Two-sided 95% confidence intervals will be constructed and hypothesis tests will be conducted at an alpha level of 0.05.

Based on data from other endoscopic and surgical studies with sham arms, and correspondence with some of the authors(Larson, Blute et al. 1998, Moseley, O'Malley et al. 2002, Salem, Rotevatn et al. 2004, Cotton, Durkalski et al. 2014), we anticipate that anywhere between 25-50% of eligible subjects will decline to participate in the randomized study. A sample size of 100 for the observational cohort was chosen based on enrollment projections for the randomized trial.

16. REGULATORY AND ETHICAL OBLIGATIONS

16.1 Informed Consent

It is the investigator’s responsibility to ensure that informed consent is obtained from the participant before participating in an investigational study, after an adequate explanation of the purpose, methods, risks, potential benefits and participant responsibilities of the study. Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research.

Each participant must be given a copy of the informed consent. The original signed consent must be retained in the institution’s records and is subject to review by the

sponsor, DCU, representatives from regulatory agencies, and the IRB responsible for the conduct of the institution.

Informed consent will be obtained by either the Principal Investigator or by individuals approved by the Clinical Center's Principal Investigator and whose names have been submitted to DCU. Informed consent will be obtained from the participant after the details of the protocol have been reviewed. The individual responsible for obtaining consent will assure, prior to signing of the informed consent, that the participant has had all questions regarding therapy and the protocol answered.

16.2 Single Institutional Review Board (SIRB)

In accordance with US federal regulations and ICH Good Clinical Practice Consolidated Guideline) all research involving human subjects and changes to the research plan must be reviewed and approved by an IRB.

Per NIH policy (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html), the Medical University of South Carolina Institutional Review Board will serve as the Single Institutional Review Board for all participating U.S. sites. The **Single Institutional Review Board (SIRB)** for multicenter protocols is the single IRB of record.

The Medical University of South Carolina IRB will initiate reliance agreements with each relying institution. The relying institution will be responsible for performing a local context review of the study to ensure that the protocol is appropriate and reasonable for their respective study populations.

Each relying site must undergo SIRB review and obtain SIRB approval before initiating any study activities at the site. SIRB approved study materials (such as informed consent documents, patient-facing materials, etc.) will not be provided to a site until that site has received SIRB approval.

Study wide amendments and/or modifications to the study will not be initiated without prior written approval of the SIRB except when necessary to eliminate immediate hazards to patients.

17. ADMINISTRATIVE AND LEGAL OBLIGATIONS

17.1 Study Termination

The study will be complete when all subjects have had their final study assessments. The Sponsor or Executive Committee reserves the right to terminate the study if new information becomes available on the safety or efficacy of the study product or if such action is justified.

If the study is terminated, the investigator will provide any outstanding data or documentation related to the study at the time.

The Clinical Center reserves the right to terminate the study according to the contract. The SHARP PIs are responsible for notifying the SIRB in writing of the trial's completion or early termination. A copy of the notification must be uploaded into the regulatory database as part of the study regulatory documents.

17.2 Study Documentation and Storage

Source documents are the original or valid records of participant information from which case report form data are obtained. These include, but are not limited to, reports of test results, hospital charts and medical records, and correspondence. Case report form entries may be considered source data if the case report form is the site of original notation, such as the patient questionnaires or quality of life instrument.

In June 2005, a new Federal law was implemented that extends the statute of limitations to six (6) years to bring forward an allegation of research misconduct. In response to this extension, research records must be retained for a sufficient period to investigate an allegation of research misconduct - **a minimum period of six (6) years.** An agreement must be in place between the Site Investigator and the Principal Investigator regarding records that may be destroyed.

17.3 Publication Policy

Investigators will be offered the opportunity to publish as a group or with recognition of individual authors. This decision will be made before analyses are conducted. Refer to the study Publication Policy for more details.

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