# ***P***ancreatic ***E***ndotherapy for ***R***efractory ***C***hronic ***P***ancrea***T***itis (PERCePT)

**STUDY CHAIR**

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## 1.0 Objectives / Specific Aims

The overarching hypothesis is that endoscopic treatment of main pancreatic duct obstruction due to chronic pancreatitis reduces pain and improves quality of life. There is a critical need to test this hypothesis, since ERCP is often performed in clinical practice despite limited data and potential negative short- and long-term consequences on the natural history of chronic pancreatitis.

### 1.1. Aim #1. To determine the feasibility of a sham-controlled pancreatic endotherapy trial.

The ***PERCePT*** study is a pilot, sham-controlled, randomized clinical trial to evaluate the feasibility of recruitment, retention, and blinding procedures, as well as to refine the enrollment criteria for a subsequent definitive clinical trial. Patients with painful chronic pancreatitis and main pancreatic duct obstruction will be randomized to endoscopic ultrasound (EUS) + sham versus EUS + ERCP with pancreatic endotherapy, the latter being defined by the use of extracorporeal or intraductal lithotripsy, stone extraction, stricture dilation, stent placement, or some combination. Pancreatic duct obstruction will be defined by the presence of a main pancreatic duct stone, stricture, or both, with consequential upstream dilation of the main pancreatic duct ≥ 6mm. After completion of the initial endoscopic intervention, patients will be assessed by individuals blinded to treatment allocation for 90 days. At this time, subjects will complete a comprehensive assessment including measures of pain, quality of life, sleep, mood, functioning, and medication use. All subjects will continue to be followed for 12 months after the randomization procedure to assess longer term outcomes.

### 1.2. Aim #2. To define the optimal outcomes for a definitive clinical trial.

The goals of pancreatic endotherapy are to reduce pain, improve pancreatic function, and thus improve quality of life and other patient-centered outcomes. The optimal outcome measures for a definitive clinical trial will be defined. Pain, pain-related disability, patient expectation of response, and quality of life will be measured at baseline, 90 days, 6 months, and 12 months following the randomization procedure. Changes in pain and disability and the relationship to quality of life and patient expectation (the nocebo effect)[1] will be evaluated. An essential component to defining outcomes related to pain is to identify what is important to the patient. The baseline case report forms and follow-up assessments will include querying subjects to prioritize outcomes of pancreatic endotherapy.

## 2.0 Background

### 2.1 The fibrotic pancreas, pain, opioid dependence, and quality of life

Pancreatic duct obstruction causing pancreatic duct hypertension is one of several mechanisms of pain, the most debilitating symptom for patients with chronic pancreatitis.[2, 3] Smoking and alcohol are the principal etiologic factors for chronic pancreatitis, a fibroinflammatory disease that is overrepresented in men, soldiers, and veterans given the high prevalence of smoking and alcohol.[4, 5] Due to the paucity of effective interventions for painful chronic pancreatitis, many patients require the use of opioids for long-term management; this often leads to opioid dependence, reductions in quality of life, and pain-related disability.[6] Endoscopic retrograde cholangiopancreatography (ERCP) with treatment of main pancreatic duct obstruction is often used in the management of painful chronic pancreatitis, despite a paucity of clinical trials and no sham-controlled data to support its use.

The ***PERCePT*** study is a pilot, sham-controlled, randomized clinical trial evaluating the feasibility of pursing a definitive trial to examine the efficacy of a procedure (ERCP) and endoscopic devices used to treat pancreatic duct obstruction.

### 2.2 Pancreatic duct hypertension is one mechanism for chronic pancreatitis-related pain

By causing intraductal hypertension, pancreatic duct obstruction from stones (a.k.a., calcifications), stricture, or both is one of several pathophysiologic bases for pain due to chronic pancreatitis. This has been elucidated in animal models [7] and is the foundation for endoscopic and surgical interventions for painful chronic pancreatitis. Duct obstruction is typically defined by the presence of a main pancreatic duct stricture, stone, or both in association with upstream pancreatic duct dilation. Furthermore, pancreatic duct dilation is considered a phenotypic manifestation of increased pancreatic duct pressure, which is hypothesized to represent one mechanism for pain in chronic pancreatitis.[8, 9] However, small studies suggest poor correlation between findings at ERCP, pain scores, and intraductal pressure.[3, 10]

It is widely recognized that the etiology of pain is multifactorial, with pancreatic duct obstruction representing one of several mechanisms that include pancreatic ischemia, intrapancreatic nerve damage (manifested by inflammation, enlargement, fibrosis, or some combination), and impaired central nervous system modulation. Given the complex pathogenesis of chronic pancreatitis pain and variability in pain phenotypes [11], treatment of pancreatic duct obstruction (and thus, pancreatic duct hypertension) is logical but not unequivocally beneficial – three randomized trials comparing endoscopy with surgery or extracorporeal shock wave lithotripsy reported favorable outcomes in < 50% of the endoscopy population.[12-14] Therefore, a sham-controlled trial of pancreatic endotherapy is needed.

### 2.3 Sham-controlled studies of endoscopy for painful chronic pancreatitis are lacking

The usual response to sham procedures in blinded interventional studies is closer to 35%.[15-17] Society guidelines [18] acknowledge that pain relief is achieved in 32-68% of patients, suggesting the possibility of a profound placebo effect and other mechanisms for pain relief in this population. Despite variability in patient response and potential for a marked placebo effect, there have been no sham-controlled studies evaluating pancreatic endotherapy for the relief of painful chronic pancreatitis. Sham trials in interventional endoscopy are few and far between. The importance of the sham design is best illustrated by the Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction (EPISOD) trial, a sham controlled, randomized clinical trial of ERCP with endoscopic sphincterotomy for patients with abdominal pain attributed to sphincter of Oddi dysfunction.[15] At enrollment, all subjects had high levels of pain-related disability, as defined by the Recurrent Abdominal Pain Intensity and Disability (RAPID) instrument. Among 73 subjects randomized to sham, 47% reported > 50% reduction in pain (as defined by RAPID) after 12 months. When asked about their satisfaction at long-term follow-up (median 4.8 years) using the Patient Global Impression of Change (PGIC) instrument, 73% (of 22 followed long-term) of subjects randomized to sham reported much, or very much improvement; only 37% who had undergone intervention (endoscopic sphincterotomy) met this definition.

The intricacies of the healing process are often minimized in favor of technical interventions.[19] This is exemplified by the Western approach to treating painful chronic pancreatitis: when the pancreatic duct appears obstructed, patients are often offered pancreatic endotherapy to relieve their pain. Since pain relief and other patient-centered outcomes such as pain-related disability and quality of life are influenced by numerous factors, it is possible that reported improvement to pancreatic endotherapy is not solely due to the technical management of main pancreatic duct obstruction.

**2.4 Endotherapy requires repeated interventions, possibly having a negative long-term impact**

Pancreatic endotherapy includes a spectrum of maneuvers performed during ERCP: pancreatic endoscopic sphincterotomy, lithotripsy and extraction of main pancreatic duct stones, and dilation with stenting of main pancreatic duct strictures. All of these maneuvers are completed using devices approved for use by the FDA, and are employed in clinical practice today. The short-term risk (up to 40%) of adverse events from pancreatic endotherapy include exacerbation of pain, post-procedure infection, pancreatitis, bleeding, and perforation.[18] The effect of prior pancreatic endotherapy on subsequent surgical therapy is unknown but may be deleterious.[20] Long-term adverse events include the development of symptomatic strictures secondary to pancreatic stents and post-sphincterotomy re-stenosis.[21] The risks of pancreatic endotherapy and the need for repeated endoscopic interventions to treat pancreatic duct obstruction illustrate the need to prove whether or not pancreatic endotherapy is effective.

**2.5 Depression, opioid misuse, quality of life, and catastrophizing are important covariates in the treatment of pain associated with chronic pancreatitis**

Pain is a complex experience that has sensory-discriminatory, motivational-affective, and cognitive-evaluative dimensions. [22] Numerous psychosocial factors may influence, and are influenced by, pain experience including depression, sleep, anxiety, pain catastrophizing, quality of life, activity level, alcohol, and opioid use/misuse. In a pilot, quasi-experimental study, clinical variables potentially associated with risk for opioid misuse were assessed in individuals with chronic pancreatitis at the Medical University of South Carolina (MUSC) [6]. The study included 307 individuals with non-alcoholic chronic pancreatitis engaged in chronic opioid therapy for pain. Participants completed the Chronic Opioid Misuse Measure (COMM), Brief Pain Inventory (BPI), Short Form Health Survey (SF-12), Center for Epidemiological Studies 10-item Depression Scale (CESD), and a single item asking about current alcohol use. Mean scores on the CESD, COMM, BPI pain-on-average item, and the SF-12 physical and psychological quality of life factors (t-scores) were: 11.2±6.7, 8.5±7.3, 4.8±2.8, 39.7±7.0, and 45±9.0, respectively. Descriptive analyses revealed that 55% met criteria for depression and 39% for opioid misuse. Regression analyses identified several factors associated with higher opioid misuse measure scores, including increased depressive symptoms (ß=.38, $p<0.0001$), increased pain at the time of the office visit (ß=.16, $p=0.03$), impairment of psychological quality of life (ß=-.27, $p=0.001$) and endorsement of alcohol use (ß=.16, $p=0.03$). These factors accounted for 37% of the variance in current opioid misuse scores. Thus, depression, quality of life, pain intensity, and alcohol use may be good candidate variables for prospective studies to determine clinical risk factors for opioid misuse among patients with acute recurrent pancreatitis and chronic pancreatitis. Additionally, another MUSC study confirmed that interprofessional care combining behavioral approaches to pain management, behavioral contingency management for opioid delivery, psychological, and psychotropic treatments for depression, anxiety, and addiction are associated with lower resource utilization.[23] Finally, an MUSC study identified a correlation between opioid misuse and improvement in quality of life following total pancreatectomy for refractory chronic pancreatitis.[24]

A second cross-sectional study was performed to determine if depressive symptoms were associated with variability in pain perception and quality of life (QOL) among patients (n=692) with nonalcohol-related chronic pancreatitis [25]. The mean age of the sample was 52.6 (SD = 14.7); 41% of the sample was male. Participants completed the SF-12, CESD, and a numeric rating scale measure of "pain on average" from the Brief Pain Inventory. Depressive symptoms were significantly related to participants' reports of increased pain and

decreased QOL. The mean CESD score was 10.6±6.5 and 52% scored above the cutoff for significant depressive symptomology. Patients scoring above the clinical cutoff on the depression screening measure rated their pain as significantly higher than those below the cutoff ($P < 0.0001$) and had significantly lower physical and mental QOL ($P < 0.0001$ for each). These findings suggest that among patients with nonalcoholic chronic pancreatitis, depressive symptoms are a common and important covariate in research assessing pain and QOL.

Pain catastrophizing (i.e., cognitive characterizations of pain as awful, horrible and unbearable) is increasingly being recognized as an important factor in the experience of pain and pain exacerbation. Catastrophizing appears to augment pain by enhancing attention to painful stimuli and heightening limbic circuitry responses.[26] Catastrophizing has been associated with depression as well as activity in areas of the brain associated with central sensitization which is often seen in patients with chronic pancreatitis. [27] This phenomenon affects both the cognitive (dorsolateral prefrontal cortex; DLPFC) and limbic aspects of pain processing, and can affect activity in cingulate cortex (ACC) and medial frontal cortex.[26] Therefore, pain catastrophizing is an important covariate when examining the effectiveness of clinical interventions for pain.

### 2.6 Quality of life is significantly reduced among patients with chronic pancreatitis, primarily due to pain

Patients with chronic pancreatitis have lower quality of life, as quantified by significantly lower physical and mental component scores compared to healthy controls and even patients with acute recurrent pancreatitis.[28, 29] The presence of constant abdominal pain and disability due to chronic pancreatitis-related symptoms are two of the most important factors associated with lower quality of life. Reductions in opioid utilization following total pancreatectomy are closely associated with improvements in physical and mental components of quality of life.[30] Since interventions to improve pain would be expected to improve quality of life and disability, the primary outcome for this pilot study will focus on pain. Recognizing the complex interaction between pain, depression, quality of life, catastrophizing, and opioid misuse, among others, a secondary aim of this pilot study is to examine several potential outcome measures in anticipation of a definitive clinical trial to follow.

## 3.0 Intervention to be studied

The intervention being tested in this pilot, sham controlled, clinical trial is a composite of maneuvers classified as pancreatic endoscopic therapy (i.e., "pancreatic endotherapy"). This term represents a combination of complementary maneuvers offered in clinical practice for the treatment of pancreatic duct obstruction. The components of pancreatic endoscopic therapy are detailed below:

**Figure 1. Examples of pancreatic stents**

### 3.1 Main pancreatic duct drainage.

The majority of patients with main pancreatic duct stones, strictures, or both require the endoscopic placement of one or more pancreatic duct stents across the area of obstruction (if two or more are placed, they are deployed side-by-side so that the overall diameter is larger than one stent alone) ***(figure 1)***. These stents are FDA-approved for drainage of the pancreatic duct and widely used in clinical practice, so an Investigational Device Exemption is not required for this study.[31] Pancreatic duct stents are comprised of

polyethylene (Cook Zimmon® and Cook Geenen®, Cook Medical, Winston-Salem, NC, USA), polyethylene and polyurethane blend (Cook Geenan Sof-Flex® and Cook Johlin Wedge®, Cook Medical, Winston-Salem, NC, USA), or proprietary polymers (Boston Scientific Advanix™ Pancreatic Stent, Boston Scientific Corp., Marlborough, MA, USA and Freeman Pancreatic Flexi-Stent, Hobbs Medical, Inc, Stafford Springs, CT, USA). Since there are no data to suggest the superiority of one brand versus another, the choice of stent type and manufacturer is typically based on physician preference and facility purchasing agreements. For these reasons, a specific type of stent will not be required; however, stent characteristics (manufacturer, external and internal characteristics, length, and diameter) will be measured during the randomization and follow-up ERCP procedures, as applicable.

### 3.2 Main pancreatic duct stone lithotripsy and extraction

For some patients with painful obstructive chronic pancreatitis, the etiology of pancreatic duct obstruction is in part due to the presence of a main pancreatic duct stone (a.k.a., calcification). Pancreatic stones often begin to form within pancreatic duct side branches but may evolve to occlude the main pancreatic duct. The majority of stones may be removed from the main pancreatic duct via direct stone extraction, intraductal lithotripsy, extracorporeal shock wave lithotripsy (ESWL), or some combination. The requisite technique(s) depend on several variables including physician expertise, location of stone (pancreatic head, genu, or body), and size of unaffected pancreatic duct. In order to maximize technical success in this pilot clinical trial, physicians will be allowed to perform any combination of these maneuvers to successfully remove main pancreatic duct stones during the index (randomization) ERCP. The performance of each maneuver will be measured through case report forms. This will minimize the likelihood that failure to meet one or more of the study outcome measures is due to technical failure of pancreatic endotherapy.

### 3.3 Main pancreatic duct stricture dilation

Pancreatic duct obstruction may also occur in the setting of a fibrotic stricture in the main pancreatic duct. A main pancreatic duct stricture is defined by the presence of upstream main pancreatic duct dilation ≥ 6mm, and technical success in treating this process is defined by the ability to insert at least one pancreatic stent across the area of narrowing.[18] Dilation of the stricture using a bougie or hydrostatic balloon catheter is often performed prior to stent placement, but treatment via dilation alone is not performed due to poor outcomes.[18]

## 4.0 Study Endpoints

### 4.1 Pilot primary outcome

The primary efficacy outcome for this pilot study will be average daily pain from the electronic diaries during the 14-day period preceding the 90-day assessment, compared to the average daily pain reported during the 14-day run-in. Clinical improvement will be defined by the change in the average pain score between these two intervals, and without the need for increased opioids or additional interventions/procedures. A standardized 11-point Numeric Rating Scale (NRS) will be used to capture average daily pain with the empirically-supported anchors of 0=No Pain and 10=Worst Pain Imaginable.[32]

### 4.2 Pilot secondary outcomes

At 90-days, change from baseline in functional impairment due to pain (BPI), quality of life, opioid misuse, pain catastrophizing, depression, and central sensitization will be examined.

## 5.0 Inclusion and Exclusion Criteria/ Study Population

Patients referred to Oregon Health and Science University (OHSU) and Medical University of South Carolina (MUSC) for endoscopic treatment of pain related to chronic calcific pancreatitis will be considered for enrollment in the PERCePT trial.

### 5.1 Inclusion Criteria

- Age ≥ 18 years
- Main pancreatic duct obstruction, defined by the presence of one or both of the following features:
    - Main pancreatic duct calcification with upstream main duct dilation ≥ 6mm.
    - Main pancreatic duct stricture, defined by the presence of main pancreatic duct narrowing with upstream main duct dilation ≥ 6mm.
- Baseline average abdominal pain score ≥ 4 during the run-in period, based on Ecological Momentary Assessment 11-point Numeric Rating Scale
- Ability to provide written, informed consent

### 5.2 Exclusion Criteria

- Symptoms attributable to a pancreatic pseudocyst or walled off necrosis
- Clinical suspicion of pancreatobiliary malignancy*
- Low probability of follow-up to complete study objectives
- Pregnancy or incarceration
- Medical comorbidities that contraindicate the performance of ERCP
- Previous pancreatic endotherapy

* Pancreatobiliary malignancy will be ruled out immediately prior to randomization, during endoscopic ultrasound

## 6.0 Number of Subjects

This study will randomize 30 subjects into a dual center, pilot, sham-controlled clinical trial of ERCP with pancreatic endotherapy for pain secondary to chronic pancreatitis with main pancreatic duct obstruction. We plan to enroll approximately 10 subjects at OHSU and 20 subjects at MUSC.

## 7.0 Setting

Participant enrollment, screening, intervention, and follow up procedures will take place at the Medical University of South Carolina as well as Oregon Health and Science University, which are both high volume ERCP centers with expertise in therapeutic endoscopy and pancreatitis care. Some follow up visits may be completed by phone.

## 8.0 Recruitment Methods

Patients will be recruited through the Medical University of South Carolina and Oregon State Health and Science University's clinical practices and existing referral network. Potential subjects will be identified in the GI medicine and surgery clinics where they will be screened for eligibility. 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 chronic pancreatitis is higher in men (approximately 60:40), since heavy alcohol use and smoking are more common among men. Therefore, per our enrollment criteria, we anticipate our cohort will reflect the epidemiology of chronic pancreatitis and have more men than women. We do not plan to actively pursue one sex, as we want our cohort to reflect the disease population. Both the Medical University of South Carolina and Oregon Health and Science University treat patients across a diverse geographic and socioeconomic spectrum. The clinical practices reflects the local regions in terms of minority populations, and we will recruit patients meeting eligibility criteria without discrimination. Race, ethnicity, and gender will be tracked and monitored in the study database and in the study screening log, both of which are part of the online data and trial management system, to ensure that the distribution among enrolled subjects is not skewed from the distribution among eligible patients. This allows us to monitor for disparities which can then be investigated to determine if any intervention is necessary to prevent disproportionate enrollment. Pregnant women are excluded from this protocol because of potential risk to the fetus. Patients who do not have access to a mobile phone will also not be included in the study.

## 9.0 Consent Process

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. The informed consent to participate in the research study will be obtained at the time of a planned clinical encounter. This will occur in the ambulatory clinics (GI surgery and Gastroenterology) at the Medical University of South Carolina and Oregon Health and Science University where the discussion regarding the study protocol is held in private between the investigator and subject with or without family members present (standard of care).

Designated study investigator(s) will discuss the study, its purpose and study protocol with potential patients in detail. Potential subjects who are interested to take part in the study will be asked to sign the informed consent. Potential subjects will have adequate opportunity to review the informed consent and to ask any questions they may have about the research, risks, and benefits. No study procedures will be performed prior to obtaining a signed and dated informed consent from the patients. Recruitment and informed consent will be completed by physician investigators with the support of one or more research coordinators.

## 10.0 Study Design / Methods

### 10.1 Study procedures

#### 10.1.1 Run-in period

A schedule of study procedures is detailed in **Table 1.** To summarize, potential subjects will be identified in GI medicine and surgery clinics where they will be screened for eligibility. If eligible and the subject completes the informed consent process, a 14-day run-in period

will commence. During this time, the subject will complete a daily diary using an Ecological Momentary Assessment tool developed for this pilot study. The diary will include the 11-point Numeric Rating Scale for pain, number of hours of sleep the night prior, activity level (11-point scale), and details on opioid medication use in the past 24 hours. In addition, the subject will undergo Quantitative Sensory Testing (QST).

**Baseline Assessment**. Once consent is obtained, eligible subjects will be enrolled and complete a baseline assessment, which will include several validated instruments measuring pain, pain quality, quality of life, psychological factors and comorbidities, sleep, opioid use, alcohol use, and pain-related disability **(Table 2)**. Additionally, patients will undergo QST to assess thermal pain thresholds, tolerance and central sensitization via wind-up and conditioned pain modulation tasks. The baseline assessment is estimated to include an approximately 1-hour visit to complete the baseline measures and a separate 1-hour visit for the QST in the Behavioral Medicine laboratory.

**Quantitative Sensory Testing (QST**). QST provides indices of baseline perception and changes in specific peripheral and central nociceptive and proprioceptive processing. Using QST we will assess: (1) mechanical pain threshold using the IITC Life Sciences Digital Aesthesiometer applied to the distal phalange of the digiti minimi of the left hand (increased at rate of 10grams/sec; pressure recorded in grams); (2) thermal pain tolerance using 5 trials of cutaneous heat stimuli via the ATS thermode of the Medoc TSA-II Neurosensory Analyzer; (3) thermal wind-up pain (3 trials) with the ATS thermode delivering 20 brief (0.75s) suprathreshold thermal pulses at the rate of 1 pulse per 1.5 secs thereby selectively stimulating C-fibers (during the 3 trials of 30sec of repeated heat stimulation, subjects will indicate their level of pain severity using a dynamic visual analogue scale); and (4) conditioned pain modulation (3 trials) using mechanical pain thresholds assessed via the IITC Life Sciences Digital Aesthesiometer applied to the right trapezus (increased at rate of 10grams/sec; pressure recorded in grams) with and without simultaneous stimulation via the ATS thermode (tonic 30sec heat stimulus to the left volar forearm using participants' individualized thermal pain threshold temperature).

**Ecological Momentary Assessment (EMA).** Given the variability in pain patterns and potential for recall bias, all eligible patients will complete a 14-day run-in period where pain, psychological status, and use of analgesics will be measured prospectively. Ecological Momentary Assessment (EMA) will be employed via Electronic Daily Diaries administered by phone, SMS or using survey links sent to the patient's cellphone or e-mail address. If a subject does not have access to a smartphone, they may be provided with a smartphone for the duration of the study (up through the 90-day follow-up assessment). We will assess daily (via standard 11-point numeric rating scales (0-10); NRS) average pain, pain at its worst, pain unpleasantness, mood, anxiety, activity level, opioid cravings, and will assess amount of prescription opioid and other substance use. We have developed a SMS/MMS encrypted gateway which enables ecological momentary assessment of these variables. This communication system was selected due to its widespread availability on all major cell phone types and their carriers. Measures will be collected at random times during waking hours each day to minimize response bias associated with event related reporting.

Medical management during the run-in period will include dose adjusting analgesic medication, if necessary. During the run-in period and prior to randomization, it is possible that subjects will improve clinically which that endotherapy is no longer appropriate. The decision to proceed with endotherapy will be based on usual clinical care, but primarily related to the persistence of abdominal pain with an average daily pain score $\geq 4$ as per study enrollment criteria. However, we are reluctant to have additional pre-specified criteria since

the decision to proceed with procedural intervention is nuanced. These subjects will continue to be followed systematically as an observational cohort but not undergo the randomization procedures. If the subject continues to meet enrollment criteria after the 14-day run in period, the subject will proceed to the randomization procedures. The observational cohort will be capped at n=15 and will follow the same data collection schedule as the randomized cohort.

**Table 1. Summary of Study procedures***

| Visit | Details |
|---|---|
| Screening visit | • Patient seen in pancreatobiliary clinic for painful chronic pancreatitis<br>• Review eligibility criteria |
| Informed consent | • Obtain informed consent |
| Run-in period (approximately -14 to 0 days) | • Subject provides daily diary for approximately 14 days (Ecological Momentary Assessment) |
| Quantitative Sensory Testing | • Complete Quantitative Sensory Testing prior to randomization procedure |
| Randomization visit (day 0) | • Confirm eligibility criteria<br>• Finalize completion of baseline assessment instruments<br>• Randomization procedures |
| Randomization procedures (day 0) | • Complete EUS + sham or EUS + ERCP with pancreatic endotherapy<br>• *No randomization procedure if observational subject.* |
| Telephone contact (day 7) | • Telephone contact to confirm no procedure-related adverse events |
| Telephone contact (day 30) | • Telephone contact to confirm no procedure-related adverse events |
| Complete Daily Diary (days 0-30 and 76-90) | • Subject will complete daily diary for 30 days after randomization procedures (Ecological Momentary Assessment)<br>• Subject will complete daily diary for the 14-day period leading up to their follow-up visit (days 76-90), which will be scheduled on day 90 |
| Follow-up visit (day 90) | • Subject returns for in- person follow-up assessment (repeat baseline assessment instruments and quantitative sensory testing).<br>o *Observational subject may complete visit by telephone*<br>• Repeat ERCP with pancreatic endotherapy if applicable (if stents are in place and require removal or upsizing)<br>• Perform ERCP if failure to improve, subject is unmasked and found to be in sham group, and subject wishes to proceed with pancreatic endotherapy<br>• ***Complete primary outcome measures*** |
| Follow-up visit (day 180) | • Subject completes follow-up assessment (abbreviated version of the baseline assessment)<br>• Repeat pancreatic endotherapy scheduled, if applicable<br>• Referral for pancreatic surgery, if applicable |
| Follow-up visit (day 270) | • Subject completes follow-up assessment (abbreviated version of the baseline assessment)<br>• Repeat pancreatic endotherapy scheduled, if applicable<br>• Referral for pancreatic surgery, if applicable |
| Follow-up visit (day 360) | • Subject completes follow-up assessment (abbreviated version of the baseline assessment)<br>• Repeat pancreatic endotherapy scheduled, if applicable<br>• Referral for pancreatic surgery, if applicable |
| Study completion visit (day 360) | • Complete all study-related activities |

* All visits are research-related visits. Please note that endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) are not experimental procedures since they are used in clinical practice. Given the randomized nature of the study design, the costs for the randomization procedures will be covered by the grant. All follow-up procedures will be billed per usual clinical care.

### 10.1.2 Baseline and randomization procedures

The subject will complete baseline instruments detailed in ***table 2.*** The subject will return on study day 0. Patients will be compensated $75 for their time completing the baseline assessments. Women of childbearing potential will be administered a urine pregnancy test. If the result is positive for pregnancy, the patient will be excluded from the study. After confirmation of meeting eligibility criteria, the subject will undergo the randomization procedures (endoscopic ultrasound + sham pancreatic endotherapy or endoscopic ultrasound + ERCP with pancreatic endotherapy).

All subjects will undergo anesthesia administered sedation and endoscopic ultrasound (EUS). The endoscopist will assess the pancreas for parenchymal and ductal features of chronic pancreatitis and confirm the absence of exclusion criteria (such as the presence of an occult pancreatobiliary malignancy). Following the completion of the EUS, assuming that eligibility criteria are still met, and while the subject remains under anesthesia, the subject will be randomized to ERCP with pancreatic endotherapy or EUS only (sham). If randomized to sham, the endoscopist will not perform ERCP. To maintain the blind, the patient and clinical team will stay in the endoscopic suite for at least 45 minutes after randomization. This is the average length of time the ERCP with endotherapy could take if randomized to this group.

If randomized to ERCP with pancreatic endotherapy, the endoscopist will proceed with this intervention immediately following the completion of EUS and treatment allocation (during the same anesthesia). Pancreatic endotherapy may include any or all of the following maneuvers: pancreatic endoscopic sphincterotomy, stricture dilation using a bougie or hydrostatic balloon catheter, pancreatic stone extraction with or without mechanical or electrohydraulic lithotripsy, extracorporeal shock wave lithotripsy, and stent placement. Overall technical success will be defined by the ability to insert at least one pancreatic stent across the dominant main pancreatic duct obstruction. Technical success for pancreatic stone treatment will be defined by the ability to remove all fluoroscopically visible main pancreatic duct stones.

At the discretion of the treating physician, patients may be given a medication called an indomethacin suppository to help prevent post-ERCP pancreatitis. Indomethacin is commonly used to prevent post-ERCP pancreatitis in clinical practice based on previous studies, but is not FDA approved for this specific purpose.

**Table 2. Baseline assessment in the PERCePT trial**

| Potential covariate(s) | Instrument(s) | Explanation and estimated completion time |
|---|---|---|
| Patient characteristics | PERCePT study case report forms<br>TIGAR-O [33] | • Data will be collected as applicable and available: history of acute pancreatitis episodes, date of chronic pancreatitis diagnosis, duct and parenchyma characteristics on prior imaging, anthropomorphic data, chronic pancreatitis risk factors (TIGAR-O)<br>• 5-minutes |
| Harmful alcohol drinking | Alcohol Use Disorders Test (AUDIT) [34] | • Screening instrument for hazardous and harmful alcohol drinking<br>• 2-minutes |
| Current pain disability | RAPID [35] | • Pain-related disability (90-day recall); developed, validated, |

| | | |
|---|---|---|
| | | and used for the EPISOD study<br>• 3-minutes |
| Average daily pain, mood, activity-level, sleep and analgesic medication use | Ecological Momentary Assessment (EMA) | • Ecological daily diaries designed to capture repeated measures of average daily pain using an 11-point Numeric Rating Scale<br>• Repeated measures of activity level, sleep, and use of opioid medications<br>• Assessed from day -14 to day 0 |
| Pain Severity and Functional Impairment | Brief Pain Inventory (BPI) | • Measures pain at its worst, least, average, and at time of evaluation<br>• Measures patient perception of effectiveness of current pain medications<br>• Measures functional impairment due to pain<br>• 7-minutes |
| Pain Character | PROMIS Pain Quality - Neuropathic and Nociceptive | • Assessment of pain quality<br>• 5-minutes |
| Pain Catastrophizing | Pain Catastrophizing Scale (PCS) | • Measurement of negative cognitive-set brought to bear during painful experiences<br>• Predictor of functional impairment due to pain and pain-related depression<br>• 5-minutes |
| Quality of life | PROMIS 29 Profile | • Assessment of anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, ability to participate in social roles and activities, and a single pain intensity item<br>• 5-minutes |
| Somatization | Brief Symptom Inventory – 18 (BSI-18)** | • Assessment of psychological distress and somatization<br>• 5-minutes |
| Patient expectation of response | Questions Before ERCP-Endotherapy | • Quantitative measure of the degree to which a patient expects to improve after pancreatic endotherapy<br>• 1-minute |
| Opioid utilization | - Current Opioid Misuse Measure (COMM)<br>- Baseline Opioid Medication For Abdominal Pain Form | • Self-report measures of risk for aberrant medication-related behavior in patients prescribed opioids for chronic pain<br>• 3-minutes |
| Laboratory Pain and Central Sensitization | Quantitative Sensory Testing (QST) | • Thermal and mechanical pain threshold, pain tolerance, as well as wind-up and conditioned modulation testing to assess central pain facilitation and inhibition<br>• 1-hour baseline visit |
| **The study investigator or their staff will respond to any subjects presenting suicidal ideations by using standard psychiatric procedures for safety purposes. If the BSI -18 Question 17 is answered low (1-2), the Coordinator will refer the subject to a mental health specialist for follow up. If the risk is considered moderate to high (3-4), the Coordinator will page the PI or a clinician and seek guidance for possible admission to mental health services without leaving the subject alone. | | |

### 10.1.3 Follow-up visits, day 0 -90

The subject will be contacted by telephone at day 7 and 30, and complete the Ecological Momentary Assessment during this 30-day period. After the 30 day follow up phone call is complete, the participant will be compensated $50 for their time. Thereafter, follow-up will

be on an as-needed basis until the subject returns on day 90 for the first formal follow-up assessment (details in ***table 3***). The discussion regarding next steps in treatment will occur between the subject, a blinded gastroenterologist, and a blinded pancreatobiliary surgeon. A multidisciplinary discussion between patient, endoscopist, and surgeon complies with society guidelines. In the case of medical management, this will be directed by the blinded physicians. In the event of an emergency room or inpatient hospitalization due to abdominal pain or other symptoms potentially attributable to chronic pancreatitis, a blinded physician will determine whether repeat endoscopic or surgical intervention is warranted before the 90-day outcome assessment. In the event that the patient is referred for repeat endoscopic or surgical intervention before reaching the 90-day outcome assessment, the Ecological Momentary Assessment tool will be reactivated in order to capture pain data for up to 14 days leading up to and including the day of intervention, as feasible. Rather than assuming no change from baseline in pain scores for those that have a re intervention prior to day 90, we will capture the pain score prior to re intervention and use these data to calculate the change score for the primary analysis.

The day 90 follow-up assessment will include completion of selected instruments and a discussion with blinded physician investigators about their clinical course. It is not realistic to assign a threshold pain score above which further intervention should be offered, so it is expected that the blinded physicians and patient will decide whether an intervention is required to treat pain; this highlights the importance of the study's sham design. Potential scenarios are detailed in ***figure 2.*** Although not incorporated into this study's pilot primary outcome, is it expected that a decision to proceed with an intervention to treat pain would be considered a "failure" of pancreatic endotherapy in a definitive clinical trial. Each of the groups in figure 2 are explained in further detail below. The design of the hierarchical diagram is deliberate and intends to illustrate that management options for groups 3 and 4 are the same. In addition, follow-up is in part dependent on the original treatment allocation. So, after all blinded assessments have been completed and a decision regarding intervention determined, an unblinded investigator will need to advise the subject regarding next steps. Participants will be compensated $75 after completing the 90-day follow up visit. If participants complete all visits, they will be compensated a total of $200.

1. **Sham group, no intervention advised.** In this scenario, the subject is doing well enough that no intervention is advised. Since no procedures have been performed until this point, continued medical management is reasonable. The subject would be followed through day 360 for relevant changes in clinical course and to assess secondary endpoints.
2. **Endotherapy group, no intervention advised.** In this scenario, the subject is doing well enough that no intervention is advised. Since pancreatic endotherapy had been performed during the randomization procedure, the subject would be advised to undergo repeat pancreatic endotherapy to remove pancreatic duct stents. In some cases, the treating endoscopist may recommend replacing or upsizing stents in an effort to minimize stricture recurrence. This will be determined by the unblinded treating physician per standard of care. Follow-up procedures would be open-label, although it is possible that the subject remain blinded to their original treatment allocation.
3. **Sham group, intervention advised.** In this scenario, the subject is doing poorly, and an intervention is advised. The blinded physicians will discuss three options with the patient: 1) further medical management, including the initiation or titration of analgesics; 2) pancreatic endotherapy; 3) consideration of surgical interventions.
4. **Endotherapy group, intervention advised.** In this scenario, the subject is doing poorly, and an intervention is advised. The blinded physician investigator will discuss three options

with the patient: 1) further medical management, including the initiation or titration of analgesics; 2) pancreatic endotherapy; 3) consideration of surgical interventions. Since the subject had previously undergone pancreatic endotherapy, the unblinded physician investigator will need to be informed of the recommendation and proceed endoscopy to remove pancreatic duct stents if necessary and applicable.

All procedures performed during the day 90 visit and thereafter will be open-label and are within the spectrum of routine clinical procedures.

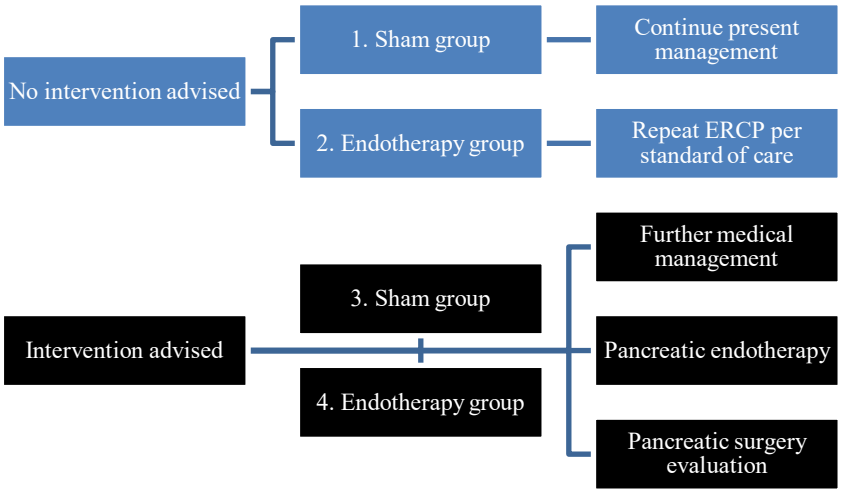


**Figure 2. Potential scenarios during the 90-day follow-up visit**

### 10.1.4 Follow-up visits, day 91-360

Every effort will be made to preserve the integrity of the original treatment allocation, recognizing the need for a pragmatic approach to the follow up period. Although 90-day outcomes will be the focus of this pilot study, all subjects will be followed for 12 months after randomization at which point the same outcome measures will be assessed. These data will be used to examine changes in the 90-day and 12-month outcomes, recognizing that interventions performed after 90 days will be unblinded.

The content of follow-up visits at days 180, 270, and 360 are detailed in **table 3** *and* may be *completed* by *telephone* or in-person.

**Table 3. Follow-up assessments in the PERCePT trial**

| Outcome measures | Instrument(s) | Follow-up visit | | | | Explanation and estimated completion time |
|---|---|---|---|---|---|---|
| | | 90 | 180 | 270 | 360 | |
| Clinical evaluation | Blinded physician evaluation | X | | | | • Assessment by a blinded gastroenterologist and pancreatobiliary surgeon |
| Patient characteristics | PERCePT study follow-up case report forms | X | X | X | X | • Data will be collected as applicable and available: history of acute pancreatitis episodes, opioid utilization, interventions performed and hospital encounters during the interval follow-up period<br>• 5-minutes |
| Harmful alcohol drinking | Alcohol Use Disorders Test | X | X | X | X | • Screening instrument for hazardous and harmful alcohol drinking |

| | | | | | | |
|---|---|---|---|---|---|---|
| | (AUDIT) [34] | | | | | • 2-minutes |
| Current pain disability | RAPID [35] | X | | | X | • Pain-related disability (90-day recall); developed, validated, and used for the EPISOD study<br>• 3-minutes |
| Average daily pain, mood, activity-level, sleep and analgesic medication use | Ecological Momentary Assessment (EMA) | X | | | | • Electronic daily diaries designed to capture repeated measures of pain, activity, sleep, and opioid use<br>• Daily from days 0-30 and 76-90 |
| Pain Severity and Functional Impairment | Brief Pain Inventory (BPI) | X | X | X | X | • Measures pain at its worst, least, average, and at time of evaluation<br>• Measures patient perception of effectiveness of current pain medications<br>• Measures functional impairment due to pain<br>• 7-minutes |
| Quality of life | PROMIS 29 Profile | X | X | X | X | • Assessment of anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, ability to participate in social roles and activities, and a single pain intensity item<br>• 5-minutes |
| Laboratory Pain and Central Sensitization | Quantitative Sensory Testing (QST) | X | | | | • Thermal and mechanical pain threshold, pain tolerance, as well as wind-up and conditioned modulation testing to assess central pain facilitation and inhibition<br>• 1-hour follow-up visit |
| Opioid Utilization | Current Opioid Misuse Measure (COMM) | X | X | X | X | • Self-report measures of risk for aberrant medication-related behavior in patients prescribed opioids for chronic pain<br>• 3-minutes |
| Pain Catastrophizing | Pain Catastrophizing Scale (PCS) | X | X | X | X | • Measurement of negative cognitive-set brought to bear during painful experiences<br>• Predictor of functional impairment due to pain and pain-related depression<br>• 5-minutes |
| Patient Global Impression of Change | PGIC | X | X | X | X | • Patient's assessment of efficacy from the index ERCP procedure<br>• 1 minute |

## 11.0 Data Management

### 11.1 Data Monitoring Plan

*The below applies to the PERCePT pilot trial and subsequent multicenter, definitive trial, as applicable.*

The purpose of clinical trial monitoring is to ensure that: 1) the rights and well-being of human subjects are protected; 2) trial data are accurate, complete, and verifiable from source documents; and, 3) the trial is conducted in compliance with the current approved protocol, with GCP, and applicable regulatory requirements. In accordance with the FDA's "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring", the study team will adopt a dynamic approach to data monitoring, which focuses on critical risks and utilizes centralized monitoring, and on-site site monitoring to increase data quality, maximize efficiency, reduce

redundancy, and better utilize monitoring resources. The DCU which is serving as the statistical and data management center for the proposed trial are highly experienced in providing centralized and risk-based monitoring for clinical trials. As data are submitted by the enrolling site during the course of the study, the data manager carefully reviews the data for errors or omissions within or across forms. Meanwhile, the study statistician carefully reviews the eCRF data in aggregate and across CRFs to identify errors and trends. As errors are identified by the data manager and statistician, the data manager generates Data Clarification Requests (DCRs) to the site using the DCU's clinical trials management system, referred to as WebDCU™. Critical or systemic errors identified by central monitoring are shared with study team members so that swift and appropriate action can be taken including the development of a corrective action plan when needed.

The DCU's risk-based monitoring approach is based upon the premise that a certain level of random error in non-critical data is acceptable and that efforts should be focused on decreasing errors in data associated with the planned analysis and human subject protection. The level of risk is affected by factors including study design, study endpoints, study population, experience of investigators, data collection methods, safety profile of an investigational product/intervention, stage of the study, and quantity of data. Prior to the start of the study, the study team will identify the risks associated with the trial. This monitoring plan is then developed to most effectively mitigate these critical risks, if the source of risk cannot be eliminated entirely.

**11.2 Sample Size**. A total of 30 subjects will be randomized (15 per arm) within a 21-month period. In a recent retrospective cohort study including patients undergoing first-time pancreatic endotherapy for chronic pancreatitis at the Medical University of South Carolina, the average number of new patients/year undergoing pancreatic endotherapy was 22, and > 30 in recent years. This is above our estimated enrollment rate for this pilot study.

**11.3 Data Management**. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU and MUSC. All clinical data on enrolled subjects will be data entered by study personnel into a web-based clinical trials management system, WebDCU, which is managed by the Data Coordination Unit (DCU), Department of Public Health Sciences at MUSC. This user friendly, secure web-based database system, developed by the DCU, will be used for subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer. Access to data will be restricted to study personnel. All study team members will receive a unique user account and ability to set up their own private password. The system has an audit trail to track all logins and enter/edit of study data.

De-identified data from the study will be stored indefinitely. In the event of a screen failure of a consented subject, data collected during screening will be retained for separate analysis.

**11.4 Statistical Analysis**. The analysis will be conducted according to the intention-to-treat (ITT) principle wherein subjects will be analyzed according to the assigned treatment. Several exploratory analyses and descriptive statistics will be examined, including covariates. Secondary analyses of additional outcomes, including change in QOL scores, disability, and depression, will be approached in a similar manner and considered exploratory using confident intervals rather than p values.

**11.5 Data Security and Confidentiality**. During the course of the trial, user access to the files with subject identifiers, and the 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.

**11.6 Quality Control**. 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. The site will be monitored by the DCU and the site monitor 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.

**11.7 Web Based System**. Because the DCU uses a web-based system, source documents and CRFs will remain at the study site. This 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.

## 12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

**12.1 DoD Independent Research Monitor**. The Research Monitor, **the PERCePT Data and Safety Monitoring Board**, is responsible to oversee the safety of the research and report observations and findings to the IRB. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB and the HRPO.

**12.2 PERCePT Data and Safety Monitoring Board Members**

12.2.1 Walter Park, MD (Chair)– Assistant Professor of Medicine, Stanford University School of Medicine

12.2.2 Nicholas Zyromski, MD – Professor of Medicine, Indiana University School of Medicine

12.2.3 Hyungjin Kim, Sc. D – Adjunct Professor of Biostatistics, University of Michigan School of Public Health

## 13.0 Withdrawal of Subjects

- 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, 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.
- If the 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 quality of life.

- Investigators and/or the sponsor may stop a subject's participation in the study at any time if they decide it is in the subject's best interest. They may also do this if the subject does not follow the investigator's instructions.

## 14.0 Risks to Subjects

**14.1 Loss of Confidentiality**. All studies carry some risk for the potential loss of confidentiality. Every effort will be made to protect your information. 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 coded format with the key maintained with the local site PI. Furthermore, study binders will be maintained in locked physical facilities and only accessible to authorized study team members to protect patient privacy.

**14.2 Interviews & Questionnaires**. Some of the questions the researchers ask may be upsetting or may make patients feel uncomfortable answering. If the patient does not want to answer a question, they may skip it and go to the next question.

**14.3 Quantitative Sensory Testing**. The procedure proposed in this study are widely used to research and clinical practice and have been shown to be safe. For thermal pain procedures, the stimulator will be set with a limit of 50ºC which is well below the threshold for causing any damage to the subject's skin or nerve endings. However, it is not unusual to experience some tenderness, redness or inflammation in the heated skin area after completion of the thermal pain procedures. These symptoms subside within a few hours with no intervention. For mechanical stimulation procedures, the range of von Frey Hair weights (digital and analog) to be used for stimulation will be incapable of breaking the skin or doing any tissue damage.

**14.4 Endoscopic ultrasound (EUS)**. Risks of EUS include bleeding, heart or lung problems, infection, or inflammation at the intravenous (IV) site, perforation and adverse reaction to medication.

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

**14.6 Blinding**. To keep free from bias, the protocol has been carefully developed to minimize 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 provider through the Statistical and Data Coordination Center (SDCC).

**14.7 Sham**. Subjects in the sham group will not receive ERCP with endotherapy. 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.

**14.8 ERCP**. If randomized to ERCP plus endotherapy, the procedure will be performed immediately after EUS and under the same anesthetic. Subjects undergoing ERCP will be at risk for the ERCP specific complications which includes post-ERCP pancreatitis (5-10%).

**14.9 Indomethacin**. Indomethacin is used in clinical practice to prevent post-ERCP pancreatitis, but is not FDA approved for this indication. Long or medium-term use of non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, is associated with several adverse events including peptic ulcer disease, kidney failure, heart attack, strong, and worsening of congestive heart failure or high blood pressure. The risk of these adverse is related to the duration of use. A single dose of indomethacin is extremely unlikely to cause the biochemical, hormonal, and physiological changes necessary to induce such events.

**14.10 Endotherapy**. The risks of endotherapy involve bleeding around the site, infection, or obstruction caused by the fragments of material created by the endotherapy that may require more endotherapy to remove.

**14.11 Stent Placement**. There is a chance that the stent placement could be placed within or migrate into the duct and cause pancreatitis, infection, or perforation. Migrated stents can be difficult to retrieve and may require an operation.

## 15.0 Potential Benefits to Subjects or Others

**15.1 Potential benefits to the study subjects.** If ERCP with pancreatic endotherapy improves pain, quality of life, or other outcome measures of interest, then subjects randomized to the treatment arm (EUS + ERCP with pancreatic endotherapy) will have benefited from this intervention. If this hypothesis is refuted, then subjects randomized to EUS alone (EUS + sham) will have avoided a potentially harmful intervention (ERCP with pancreatic endotherapy).

**15.2 Potential benefits to science and society**. The results of this study are expected to provide preliminary data required to plan a definitive clinical trial evaluating pancreatic endotherapy. Such a trial would be expected to have a direct and immediate impact on patient care irrespective of the final outcome. Currently, the decision to perform ERCP with pancreatic endotherapy is physician-specific and a topic of repeated controversy among experts. If the study proves that ERCP with pancreatic endotherapy improves pain (or other relevant outcomes), then this practice will be adopted more widely across the world. However, if the study refutes the hypothesis that ERCP with pancreatic endotherapy reduces pain, then the practice of performing ERCP with pancreatic endotherapy for painful chronic pancreatitis would be expected to diminish significantly.

## 16.0 Sharing of Results with Subjects

The results of the initial randomization procedures will not be shared with the participants until completion of the study. However, if the subject's doctor recommends additional procedures during the course of the study, the results of these procedures will be shared with the participant.

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