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Per-oral Pancreatoscopy-guided Lithotripsy vs. Extracorporeal Shock Wave Lithotripsy For Treating Symptomatic Main Pancreatic Duct Stones in Chronic Pancreatitis: A Multicenter Randomized Clinical Trial

Lead Site: University of Colorado

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Synopsis

Title	**Per-oral Pancreatoscopy-guided Lithotripsy vs. Extracorporeal Shock Wave Lithotripsy in Chronic Pancreatitis: A Multicenter Randomized Clinical Trial**
Investigative sites	University of Colorado The Ohio State University Baylor St. Luke's Medical Center Methodist Dallas Medical Center University of Minnesota University Health, San Antonio Indiana University Washington University School of Medicine
Hypothesis	The central hypothesis is that per-oral pancreatoscopy- guided lithotripsy is superior to extracorporeal shock wave lithotripsy in clearance of main pancreatic duct stones, thereby improving pain levels and quality of life in patients with chronic calcific pancreatitis.
Primary Objective	To demonstrate the superiority of per-oral pancreatoscopy over extracorporeal shock wave lithotripsy in clearance of main pancreatic duct stones in patients with chronic pancreatitis. Failure to remove any or all stones with the initial intervention will be an outcome recorded for the study.
Secondary Objective	To demonstrate the effect of stone clearance to reduce pain and opiate use and improve quality of life.
Timeline	Enrollment will be performed over a 24-month time period with follow-up performed at 1, 3, 6, 12, 18, and 24 months after ductal clearance.
Primary Endpoint	Main pancreatic duct stone complete clearance rate
Secondary Endpoints	• Change in quality of life • Change in pain scores • Change in opiate use • Number of procedures • Adverse Events related to therapies
Study Design	Multicenter randomized trial
Sample Size	150 patients

List of Abbreviations

PD: pancreatic duct

PPL: per oral pancreatoscopy-guided lithotripsy

ESWL: extracorporeal shock-wave lithotripsy

EHL: electrohydraulic lithotripsy

LL: laser lithotripsy

ERP: endoscopic retrograde pancreatography

ERCP: endoscopic retrograde cholangiopancreatography

AE: adverse event

EUS: endoscopic ultrasound

CT: computed tomography

MRCP: magnetic resonance cholangiopancreatography

KUB: kidneys-ureters-bladder radiograph

Study Protocol

1. Research Questions and Hypothesis

Pain relief poses a significant challenge in patients with chronic pancreatitis given the paucity of effective medications and interventions. Approximately 50-90% of patients with chronic pancreatitis develop pancreatic duct (**PD**) stones which can obstruct the PD, causing ductal hypertension that can lead to severe pain.[1] This pain is frequently treated with opiates, which not only pose a risk of addiction but are also associated with increased hospitalization rates.[2] Traditional methods to remove PD stones include endoscopic retrograde pancreatography (**ERP**) with sphincterotomy, stricture dilation, and balloon or basket extraction and extracorporeal shock-wave lithotripsy (**ESWL**) for larger stones.[3, 4] A potential benefit of ERP techniques over ESWL alone is the ability to treat underlying pancreatic duct strictures with therapeutic PD stenting to not only facilitate stone removal but potentially to help reduce stone recurrence by improving pancreatic juice flow.[5, 6] As shown previously, use of ESWL alone without treatment of strictures is associated with a significantly higher stone recurrence rate.[7] Furthermore, ESWL does not remove stone fragments and ERP techniques are required for this aspect of stone clearance.[8] If ERP with PPL is performed it may obviate the need for ESWL except in special circumstance such as significantly impacted pancreatic stone burden in the head of the pancreas.

These methods, however, may be limited by imprecision, limited ESWL availability for PD stone therapy in the US, requirement of multiple treatment sessions, and decreased efficacy in removing larger, impacted stones.[9, 10] From a practical standpoint, the need to frequently outsource ESWL to urologists limits the ability of gastroenterologists to control the timing of these sessions and assess efficacy while potentially increasing patient costs, time commitment, and use of general anesthesia.[11] If ineffective in stone clearance, surgery remains a last-resort option that is associated with high morbidity (18-53%) and mortality (0-4.55%).[12] The introduction of per oral pancreatoscopy, or direct endoscopic visualization of the PD, has enabled targeted intraductal therapy, including electrohydraulic lithotripsy (**EHL**) and laser lithotripsy (**LL**) for these stones.[13] None of these treatment methods have been studied in prospective trials and there is a lack of comparative data between ERCP techniques and ESWL in removing stones, whether they improve pain and quality of life, and reduce opiate use along with assessing financial costs. There is, therefore, a *critical need* to compare the efficacy of per oral pancreatoscopy-guided lithotripsy (**PPL**) with ESWL and determine which therapy provides better outcomes with a goal of less procedures and that is more cost-effective in removing difficult PD stones. Without such information, the treatment of main pancreatic duct stones associated with chronic pancreatitis will likely remain limited anecdotal and consisting of retrospective case series.

Within the field of pancreatology, there exists legitimate equipoise regarding which treatment is more effective in removing pancreatic duct stones. ESWL has been performed for a longer period of time with a meta-analysis including 27 studies and 3189 patients demonstrating a 70% complete duct clearance rate with the use of ESWL.[14] There have been far fewer studies involving PPL with a recent meta-analysis involving 302 patients in 10 studies found a 86% success rate in stone clearance.[15] Importantly, a randomized study comparing the two techniques has not been performed and the only randomized study

comparing ESWL with endoscopy was completed in 2007 prior to the use of PPL.[9] Therefore, while PPL appears to be safe and effective in the treatment of these stones, there are no prospective studies evaluating its efficacy and given the relative efficacy of both techniques, a head-to-head randomized study is needed to determine which modality is optimal for patients with chronic pancreatitis.

Currently, treatment of these PD stones in the US is often dictated by the resources and expertise available at each center. Both ESWL and PPL are considered standard of care treatments with the European Society for Gastrointestinal Endoscopy (ESGE) recommending endoscopic therapy and/or ESWL as first-line therapy in patients with chronic pancreatitis who have a PD obstruction in the head or body of the pancreas.[3] In regards to size, the ESGE also recommends ESWL for stones > 5 mm in diameter and ERCP for stones < 5 mm in diameter, but clarifies that PPL be performed when ESWL is not available or for stones that are not adequately fragmented by ESWL.[3] In the US, ESWL is primarily performed by urologists for treatment of kidney stones, and the lack of familiarity with chronic pancreatitis has led to a general reservation by urologists in performing ESWL for pancreatic duct stones.[11] Furthermore, the difficulty in coordinating the schedules of anesthesia, urology, and gastroenterology together to perform ESWL for this disease has discouraged the use of the ESWL in the US.[16]

Therefore, our *long-term goal* is to determine the optimal treatment regimen for chronic pancreatitis-related pain associated with main pancreatic duct stones. Our *overall objectives* in this application, which is the next step toward attainment of our long-term goal, are to (**i**) determine whether PPL is superior to ESWL in removing main pancreatic duct stones, and (**ii**) ascertain the effectiveness of PPL or ESWL in improving pain and quality of life. Our *central hypothesis* is that PPL is superior to ESWL in removing difficult PD stones, thereby improving pain levels and quality of life in patients with chronic calcific pancreatitis. Our hypothesis has been formulated based on previous retrospective studies from our group demonstrating a higher stone clearance rate with PPL compared to published stone clearance rates for ESWL.[6, 13, 14, 16, 17] The *rationale* for this project is that the determination of the superior lithotripsy method and its effect on pain and quality of life is likely to guide clinical decision-making in patients with PD stones whereby optimal strategies for the treatment of chronic pancreatitis can be developed. To attain the overall objective, the following two *specific aims* will be pursued:

1. **Perform a multicenter randomized clinical trial to compare the efficacy of per oral pancreatoscopy-guided lithotripsy with extracorporeal shock-wave lithotripsy in the removal of pancreatic duct stones**. Based on preliminary data, our *working hypothesis* is that PPL is superior to ESWL in the clearance of PD stones.
2. **Compare the effect of per oral pancreatoscopy-guided lithotripsy with extracorporeal shock-wave lithotripsy in reducing pain and improving quality of life in patients with chronic pancreatitis.** Based on preliminary data, our *working hypothesis* is that stone clearance will reduce pain levels, decrease opiate use, and improve quality of life.

At the completion of the proposed research, our *expected outcomes* are to have determined which lithotripsy method is clinically superior in PD stone removal. We also expect to demonstrate the effect of PD stone removal on pain and quality of life. These results are expected to have an important *positive impact* because they will provide a strong evidence-based support for endoscopic therapies to ultimately

treat chronic calcific pancreatitis more effectively.

2. **Basic Design of the Study**

This study is a multicenter randomized trial comparing per oral pancreatoscopy-guided lithotripsy (**PPL**) using either laser lithotripsy (**LL**) or electrohydraulic lithotripsy (**EHL**) with extracorporeal shock wave lithotripsy (**ESWL**) in removing main pancreatic duct (**PD**) stones from patients with chronic calcific pancreatitis. Specific aims for this trial include:

- **SA1**: To determine whether PPL is more effective than ESWL in removing PD stones in terms of main pancreatic duct stone clearance rate in patients with chronic calcific pancreatitis.
- **SA2**: Evaluate the effectiveness of main pancreatic duct stone removal in reducing pain and improving quality of life in patients with chronic calcific pancreatitis.
    - **SA2a**: To determine whether a greater clearance of PD stones via PPL or ESWL will improve quality of life to a greater extent.
    - **SA2b**: To determine whether a greater clearance of PD stones via PPL or ESWL will reduce pain and opiate requirements to a larger extent.

The primary endpoint of this trial will be complete clearance of main PD stones in eligible patients. This study will be statistically powered to detect superiority of PPL over ESWL in this primary endpoint. Major secondary endpoints will include: 1) change in quality of life after PD stone removal; 2) change in pain levels after PD stone removal; 3) change in opiate use after PD stone removal; 4) comparison of total number of procedures in both arms, and 5) PD stone recurrence rate.

3. **Sample and Methodology**

We will enroll 150 subjects (**Figure 1**) with chronic pancreatitis who have symptomatic main PD stones identified by non-invasive imaging, endoscopic ultrasound or prior endoscopic retrograde pancreatography (**ERP**).

Following baseline assessments and identification of main PD stones, patients will be randomly assigned to receive either PPL or ESWL as the primary lithotripsy method to fracture PD stones. Both these procedures represent potential next steps in the algorithm of managing PD stones.[3] If partial clearance (removal of some, but not all stones) of PD stones is achieved as determined by the performing endoscopist, subjects can receive repeated PPL or ESWL sessions (for a maximum of 4 sessions total as is commonly practiced before referral for alternative therapy) until complete removal of stones is achieved.[5] Failure to remove any main PD stones will be considered a failure of the treatment. Additionally, failure to achieve complete clearance within a maximum of 4 sessions of either PPL or ESWL will be considered a treatment failure, even if partial clearance is achieved.

Cross-over and/or combination therapy will be allowed at the discretion of the endoscopist after treatment failure. As described in the statistical analysis, under the intention-to-treat (primary) analysis, should cross-over occur, the final outcome of complete stone clearance will be attributed to the initial therapy. Under the per-protocol (secondary) analysis, in the case of cross-over, the final outcome of complete stone clearance will be attributed to the combination of ESWL and PPL. Similarly, in terms of survey collection, should cross-over occur, the analysis of the survey results will be attributed to the

originally assigned intervention in the intention-to-treat (primary) analysis. In the per-protocol (secondary) analysis, the outcomes will be attributed to the combination of both interventions resulting in technical success.

Patients who are randomized and subsequently found to have an exclusion criteria identified will continue follow-up per study protocol.

Stone clearance will be determined by occlusion pancreatography showing the absence of main PD stones. Complete stone clearance will be defined as the absence of stones in the head or body of the main PD. Partial stone clearance will be defined as the removal of more than 50% but less than 100% of stone/stone fragments in the head or body of the main PD.

Recurrence will be defined as the presence of stones following confirmed clearance in the final pancreatogram. To be considered as recurring, the stone must require intraductal lithotripsy for removal.

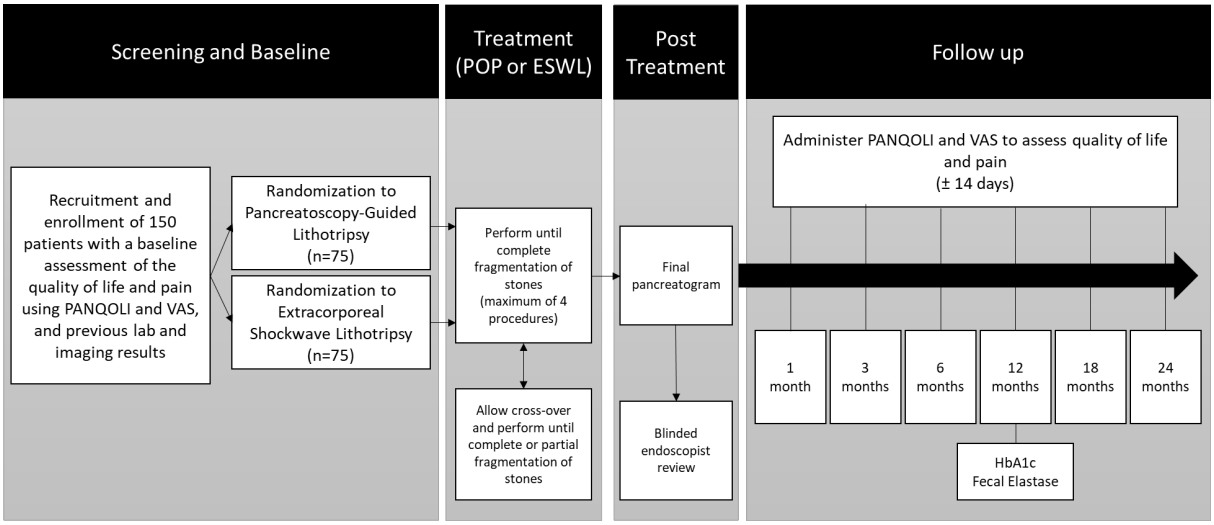
Following complete PD stone removal, patients will be given a validated quality-of-life instrument, the PANQOLI[18], at 1, 3, 6, 12, 18, and 24 months post-treatment. Similarly, the visual analog scale will also be given at 1, 3, 6, 12, 18, and 24 months post-treatment. Lastly, daily opiate use will be recorded at 1, 3, 6, 12, 18, and 24 months post-treatment. The 1, 3, 6, 12, 18, and 24-month assessments will have a ± 2 weeks window to be completed.

In order to ensure that subjects respond to the questionnaires as required, REDCap will be programmed to automatically send three reminders to the participants' email when the questionnaires are due. Furthermore, the study coordinator will make three separate attempts to contact non-responding patients within the designated timeframe. If a patient remains unresponsive, these instances will be documented as protocol deviations.

Documentation on interventions for chronic pancreatitis occurring outside of scheduled appointments will be recorded a separate CRF (“non-scheduled chronic pancreatitis interventions”). This CRF will encompass any pancreatic interventions (other than POP x ESWL planned visits) taking place between the subject's consent form signature and their final follow-up.

All patients will have a HgbA1c and fecal elastase drawn at baseline (within 12 months prior to treatment initiation) and at the 1-year mark from treatment completion. Laboratory tests will be drawn per standard of care, and tests results will be added to the REDCap database.

Figure 1: Study Flowsheet



4. Subject Inclusion and Exclusion Criteria

4.1 *Inclusion Criteria:*

1. Subjects aged 18-89
2. Subjects with abdominal pain secondary to chronic calcific pancreatitis and main pancreatic duct stones found on cross-sectional imaging, EUS, or ERP with upstream PD dilation
3. Main PD stones in the head or body that are greater than 50% in size of the immediate downstream diameter of the pancreatic duct
4. Stones ≥ 5 mm in diameter or impacted in the main PD on cross-sectional imaging or EUS

4.2 *Exclusion Criteria:*

1. Subjects who have previously received PPL or ESWL for PD stones within 12 months of enrollment
2. Patients with PD stones isolated in the tail or side branches of the main duct
3. Pancreatic tail stones comprising more than one-third of the stone burden within the main PD, if multiple locations of stones are noted within the main PD
4. Nontraversable ansa loop with upstream stones
5. Inability to place a transpapillary pancreatic duct stent during ERP
6. Patients with prior pancreatic surgery or surgically altered gastroduodenal anatomy, such as Roux-en-Y surgery

7. Acquired pancreas divisum
8. Significant cardiopulmonary co-morbidities precluding general anesthesia
9. Patients with coagulation disorders that cannot be corrected to an INR below 2.0
10. Patients with ongoing alcohol abuse and/or illicit drug use, except products containing THC
11. Pregnancy
12. Patients in active treatment for malignancy other than non-melanoma skin cancer or papillary thyroid cancer

5. Study Steps

5.1 *Screening/Baseline Evaluation*

Potential eligible patients will undergo an initial visit in which eligibility will be confirmed and the trial protocol explained in detail. All willing and eligible patients providing informed consent will have baseline data obtained including detailed history of chronic pancreatitis (i.e. disease duration, etiology, drug use, and family history of pancreatic disease), endoscopy history, and current medication use. Baseline quality of life and pain levels will also be obtained. Laboratory tests: HbA1c and Fecal elastase will be drawn per standard of care within 12 months prior to enrollment, and tests results will be documented in the study.

The National Institute of Alcohol Abuse and Alcoholism (NIAAA) defines binge drinking as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 percent - or 0.08 grams of alcohol per deciliter - or higher. For a typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours.[19]

Patients of childbearing potential will undergo a serum/urine pregnancy test based on each site practice, as per the standard of care.

5.2 *Consent*

Patients will be provided the necessary information regarding the study and consent will be obtained either in person and/or electronically through medical records depending on specific site IRB approval guidelines. Consent for the study will be obtained by a member of the study team either in person or electronically through medical records depending on specific site IRB approval guidelines.

5.3 *Randomization*

Randomization will occur after informed consent is obtained and prior to receiving lithotripsy. Once enrolled, the research coordinator will enter the patient into the REDCap database, at which randomization will occur via computer algorithm.

Randomization will be performed using a 1:1 ratio. The investigator will then inform the patient which lithotripsy therapy will be subsequently performed.

5.4 *Treatment Regimens*

<u>Per oral pancreatoscopy-guided lithotripsy</u>

Standard ERP will be performed to cannulate the PD, perform pancreatic sphincterotomy, and stricture

dilation as necessary. A pancreatoscope (Spyglass Digital System, Boston Scientific, Marlborough, MA) will then be inserted through the duodenoscope into the PD. For PPL, electrical pulses will be delivered through an aqueous medium by EHL or LL with the probe tip in contact with or 1-2mm away from the stone.

For EHL, the Nortech bipolar biliary EHL probe (1.9 Fr, 0.66 mm) will be used and lithotripsy will start at medium power and can be increased to high power (maximum of 100 Joules). In terms of frequency, the maximum frequency allowed will be 30 pulses/second. There will be no limit to the number of EHL probes used during a session of lithotripsy, but the maximum time of lithotripsy allowed will be 1 hour.

For LL, Holmium laser will be utilized with energy ranging from 1 to 10.5 Joules, a frequency of 8-14 Hz and a power from 5-25W. LL fibers will include 200, 272, and 365 µmeter fibers. Similar to EHL, a maximum of 1 hour of intraductal lithotripsy will be allowed. Both forms of intraductal lithotripsy can be performed during the same treatment session.

EHL and/or LL will be continued until stone fragments are ≤ 3 mm or a maximum of 1 hour of lithotripsy.

Extracorporeal shock wave lithotripsy

Stone localization will first be performed by obtaining high-quality plain films of the pancreatic area in left and right oblique positions using a two-dimensional radiologic targeting system.

Depending on the stone localization, ESWL will then be performed with the patient in either slight left or right lateral decubitus with shock waves entering the body from the ventral side. The shockwaves will be focused first on the most downstream located stone within the main duct and then on other calculi moving from the head towards the body. If a stent has been inserted during preceding ERP then this may also serve as a guide to target main pancreatic duct stones by ESWL.

ESWL will start at the lowest power level and will gradually be increased until 25% of the shocks have been delivered to help create vascular constriction to minimize the risk of hematoma. The middle 50% of the shocks will be equally distributed between the 1st 25% of shocks and the final 25% of shocks at the top level of power. The final 1000 shocks should be administered at the highest power level number. The range of shocks delivered will be limited to 4000 to 6000 shocks. The rate of shocks will range from 70-90/minute.

A KUB (kidney-urether-bladder)-right posterior oblique X-ray will be done within 7 days after the ESWL session to determine the level of fragmentation of the stones. The goal will be to continue ESWL until stone fragments are felt to be ≤ 3mm.

Non-lithotripsy pancreatoscopy maneuvers will be permitted in the ESWL arm and not result in primary endpoint failure.

5.5 *Outcome Determination*

An occlusion pancreatogram following extraction of stone fragments will be obtained after the endoscopist/urologist has determined treatment completion. All patients will receive an ERP at the completion or either PPL or ESWL, with an occlusion pancreatogram performed to determine stone

clearance. An initial pancreatogram (or PD image from cross-sectional test – MRCP, MRI, CT scan, or EUS) with stone location and two representative final occlusion pancreatogram images will be uploaded to the REDCap database and will be reviewed by a blinded endoscopist to assess the level of stone clearance (complete or partial).

6. **Standard of Care/Research Procedure**

The current standard of care for the treatment of PD stones varies by region. In Europe, extracorporeal shock- wave lithotripsy (**ESWL**) is a primary method by which stones are fragmented. Once ESWL is performed, however, ERP is still performed to remove the stone fragments. In Europe, ESWL is frequently performed by gastroenterologists who can perform ERP as well.

In the United States, however, ESWL is primarily performed by urologists for the treatment of kidney stones. Few gastroenterologists have direct access to ESWL and urologists remain hesitant to use ESWL for non-kidney stones. Therefore, in the United States, standard therapy has become ERP.[4] In ERP, pancreatography is performed by cannulating the PD and then injecting radio-opaque iodine contract into the PD. Pancreatography allows for radiographic visualization of a stone and associated strictures; stone removal can be achieved by sweeping the PD with either a balloon or basket after performing a pancreatic sphincterotomy where the sphincter opening the PD is cut and coagulated. This is often followed by balloon or catheter dilation of any downstream pancreatic duct strictures. ERP is typically made more difficult by strictures downstream of the stones and the presence of numerous, large (>5mm in diameter) or hard stones.

In this study, per-oral pancreatoscopy-guided lithotripsy (**PPL**) will be compared with ESWL. Pancreatoscopy, the placement of a small endoscope directly into the PD, allows for direct visualization of the PD and stones. This allows for intraductal lithotripsy to be performed while directly visualizing the stones. Briefly, EHL, one version of intraductal lithotripsy, creates high-frequency shock-wave pulses which generate energy that can result in the fragmentation of stones. LL, on the other hand, involves the focusing of laser light on the surface of a stone which can induce wave-mediated stone fragmentation. Both techniques can fragment stones into smaller pieces, which can then be swept out of the PD using standard techniques such as balloon or basket sweeping.

Upon completion of the procedure, all patients will be observed in the post-anesthesia care unit for 1 hour as is the current standard of care. Following the index ERP session and sphincterotomy, extended recovery in the hospital or discharge will be planned per institutional practice. If patients exhibit symptoms such as intractable abdominal pain or severe N/V, they will be admitted for overnight observation. All patients will receive a phone call within 48 hours of discharge as is standard practice to identify any short-term AE's.

7. **Subject and Study Stopping Criteria**

Subjects may withdraw from the study at any time for any reason. Subjects can also be withdrawn from the study at any time at the discretion of the investigators for breach of study protocol or emergence of an exclusion criteria (i.e. pregnancy).

The study can be stopped at any point should the Data Safety Monitoring Board (DSMB) request cessation

of the trial based on any compilation of adverse events or clear demonstration of superiority of one technique. Similarly, should the interim analysis reveal futility in that the study hypothesis is deemed unprovable within the constraints of the study, the study may be stopped. The study will also be stopped once the intended sample size goal is reached and 6-month follow-up has been obtained. Lastly, the study can be stopped should study costs exceed the allotted budget.

8. **Data Collection Tool**

A comprehensive system has been previously developed at this institution, and will support the data collection and reporting needs of this project which includes:

(i) streamlining data collection from the participating centers,

(ii) creating a secure database from which statistical analysis can be performed. Data will be stored at the University of Colorado instance of REDCap15, which resides on a local secure server. Data regarding stone clearance rates and adverse events will be entered by investigators at each center. Using an Application Programming Interface (API), data can be transferred to and from REDCap to SAS software (v.9.3, SAS Institute, Cary, NC) used to export data from REDCap to SAS to conduct analysis. SAS software interfaces seamlessly with REDCap-produced syntax files (i.e. SAS code) and SAS-ready CSV (comma separated variables) data files. Results of these analyses will be imported back into REDCap, using the API, for long-term storage, reference, and further analysis. Access to these data will be controlled by a custom module and all users of the site will be required to log in. No protected health information will be collected or displayed and data stored in our HIPAA compliant serve environment to ensure privacy.

9. **Data Analysis Plan**

Statistical Analysis: Comparison of technical success rate, defined as the rate of complete clearance of PD stones, between PPL and ESWL will be performing using the chi-squared test or Fisher's exact test. Secondary outcomes including adverse event (both overall and serious adverse event) rates, procedure length, and number of procedures will be compared using a chi- square test or Fisher's exact test for categorical variables and the Student's t test will for continuous variables. A p value <0.05 will be considered significant. In the primary analysis, all results will be analyzed under an intention-to-treat protocol. A per-protocol (secondary) analysis will also be performed where the technical success will be attributed to the combination of modalities resulting in achieving the primary outcome should cross-over occur.

To identify predictors for technical success, a multivariable logistic regression will be performed incorporating variables that were associated ($p<0.2$) with technical success on univariate analysis.

In terms of secondary outcomes, change in PANQOLI scores, VAS scores, and opiate daily doses will be compared between subjects in the PPL group and ESWL group. Additional outcomes to be measured include stone recurrences and number of chronic pancreatitis-related hospitalizations during the follow-up period. Should cross- over occur, under the primary (intention-to-treat) analysis, the outcomes will be attributed to the initially randomized intervention. In the secondary (per-protocol) analysis, the outcomes will be attributed to the combination of treatments resulting in technical success. A subgroup analysis will also be performed on patients who achieved only partial stone clearance (thus considered a treatment

failure) in the above-mentioned outcomes. Comparisons will be made using a chi-squared test or Fisher's exact test for categorical variables and the Student's t test for continuous variables. Paired t tests will be performed to evaluate individual changes within each arm. A p value <0.05 will be considered significant.

Power analysis: A large meta-analysis by Moole et al found a complete stone clearance rate of 70% in patients who received ESWL in conjunction with ERCP.[14] In contrast, the largest studies examining pancreatoscopy-guided lithotripsy methods have found complete stone clearance rates ranging from 83-99%.[6, 17] Using a conservative stone clearance rate of 90% for pancreatoscopy- guided lithotripsy, a sample size calculation was performed using a two-sided test with 80% power and significance (α) of 0.05. This demonstrated the need for 124 subjects total, with 62 in each arm. Accounting for an expected dropout rate of 20%, the sample size needed would be a total of 150, or 75 subjects in each arm.

10. Data and safety monitoring plan

A Data and Safety Monitoring Board (DSMB) will be established to monitor the data and safety of this project. A DSMB will be appointed by the study team and will include at a minimum: A senior faculty member clinician with substantial research experience within the Division of Gastroenterology and Hepatology at the University of Colorado who is not involved in the study, and will serve as the group leader, a statistician, and a senior gastroenterologist from a non- participating academic institution. The DSMB will meet every six months. DSMB meetings will be only open to designated DSMB staff and other individuals who have been approved to have access to unblinded data. Any recommendations for alteration or termination for part or all of the trial shall be based on consideration of the accumulating data in the context of totality of evidence. Specific statistical monitoring guidelines for safety and efficacy concerning the primary and secondary endpoints will be developed in cooperation with the DSMB.

10.1 *Definition of AEs, serious AEs, and unanticipated problems*

AEs are defined as any undesired, harmful, or pathological change in a patient as indicated by signs, symptoms, or laboratory changes that occur in association with the use of the trial interventions, whether considered intervention-related or not. This definition includes intercurrent illness or injuries, exacerbation of existing conditions, psychological events, psychosocial events, and AEs as a result of the study intervention. All endoscopic AEs will be defined and classified as recommended by the American Society for Gastrointestinal Endoscopy (ASGE).[20]

The most common AEs for PPL are expected to include pancreatitis and bleeding. The most common infectious complications are expected to include cholangitis, cholecystitis, and less likely or rare duodenoscope-related infection transmissions and perforation. No differences in the types and proportion of AEs have been found in previous studies examining EHL and LL.[10]

The risks of ESWL include post-ESWL pancreatitis, bleeding, infection, steinstrasse, sepsis, and rarely, perforation, pancreatic duct leak and arrhythmias. An overall AE rate for ESWL is 6.7%.[21] The most common adverse event associated with ESWL remains pancreatitis with a meta-analysis finding a rate of 4.2%.[14] Mild skin erythema and tenderness also typically occurs at the region of contact with the shockwaves and other adverse events such as bleeding and infection occur in approximately 1% of cases.[3] Similarly, the primary risk of PPL is pancreatitis which in a meta-analysis was found to occur in 8.7% of cases.[15] Additional risks include incomplete fragmentation of the stone requiring alternative treatment,

stone migration, inability to access stones(s), no stones, need for further procedures, loss of pancreas and/or death. Machine malfunction may occur, necessitating rescheduling. In addition, the stones might not get removed completely. In comparison, surgery, an alternative treatment modality typically consisting of either a lateral pancreaticojejunostomy or a Frey procedure, has a higher rate of adverse events. In a randomized trial comparing surgery with endoscopy, the surgical treatment arm had a 27% adverse event rate with the main adverse events including anastomotic leakage (6.8%), bleeding (6.8%), incisional hernia (4.5%), pneumonia (4.5%), and severe delayed gastric emptying (4.5%).[22] Additionally, as these procedures would typically be performed as part of the management of patients with PD stones at the study sites, there are no separate research risks from the risks of standard care.

Worsening abdominal pain may occur after either of the procedures, with the potential need for prolonged observation. Abdominal pain may be related to ductal manipulation, stone mobility, or due to other adverse events.

The definition of a serious AE is any AE that results in any of the following outcomes:

> 1) death, 2) life-threatening, 3) persistent or significant disability/incapacity, or 4) requires or prolongs hospitalization. Serious AEs are expected to include perforation, air embolism, and cardiopulmonary AEs associated with the use of general anesthesia, which will be used in all procedures.

Unexpected AEs will be defined as any AEs with specificity or severity which is not consistent with the current risk information in this investigational plan as formulated from prior studies investigating the trial interventions.

Grading of severity of AEs will be done in accordance to the grading system proposed by the ASGE and the revised Atlanta classification.[20, 23] For pancreatitis, grading will be done according to the revised Atlanta classification as follows:

> 1) Mild – no organ dysfunction, 2) Moderate - transient organ failure <48 hours OR local or systemic AEs without persistent organ failure, and 3) Severe – persistent single or multi organ failure >48 hours OR present or persistent systemic inflammatory response syndrome (SIRS).

All other AEs will be classified as follows:

> 1) Mild – AE is usually transient, does not require any special treatment, and does not interfere with the patient's daily activities, 2) Moderate – AE usually introduces a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated with simple therapeutic maneuvers, and 3) Severe – AE interrupts a patient's usual daily activity and generally requires systemic drug therapy or other intervention.

10.2 *Procedures for documentation of adverse events*

All AEs are to be reported using the centralized online data collection system. All AEs must be entered within 14 days of occurrence. A standardized reporting system will be available on the REDCap system, which will be accessible to all study members at each site. AE reporting can be done by either site PIs or research coordinators.

All serious AEs that occur from initiation of the study to 14 days post final intervention are to be reported immediately (within 24 hours) using the electronic data collection system. All serious AEs will then be immediately relayed to the PIs. The PIs will first review the AEs to: 1) ascertain the seriousness, 2) ascertain the relationship between AE and intervention, 3) verify that all data are complete, and 4) follow-up with the specific site for incomplete data and/or data clarification. The PIs will then submit the AEs to the DSMB, who will then review the AEs to confirm the findings of the PIs.

All AEs from ESWL are ESWL-related. PPL is part of the ERCP procedure. Most AEs in this group will be related to the ERCP procedure itself. A potential rare AE specific to PPL (EHL or LL) is ductal perforation from the lithotripsy fiber and will be noted by the investigator. The investigator will determine the relationship of an AE specific to a lithotripsy device used to fragment the stones.

10.3 *Monitoring of Data*

The DSMB will be responsible for data and safety monitoring. All primary and secondary outcomes as well as data integrity and study progress along with all AEs will be reviewed by the DSMB.

The DSMB will meet at least twice a year to review the data mentioned above. These meetings will every six months.

An interim analysis will be performed at the halfway point of enrollment, which is expected to be at the 75th patient. Should the interim analysis reveal an unexpected accumulation of AEs or a clear superiority of one lithotripsy method over the other, the DSMB may recommend stopping the study, which will be reported to the PIs, IRB and the funding agency.

The DSMB will include at a minimum the following individuals:

- Frank Scott: Gastroenterologist, University of Colorado
- Jay Burton: Hepatologist, University of Colorado
- Biostatistician: Non-study Statistician
- Sunil Sheth: Gastroenterologist, Beth Israel Deaconess Medical Center

11. Feasibility/Recruitment Plan/Materials

The power analysis suggests that a total of 150 participants will need to be enrolled to achieve sufficient statistical power to compare the two lithotripsy methods. With a total of 8 recruitment sites, we anticipate complete enrollment within 5 years and with a follow-up of 12 months/patient post completion of treatment, the study is anticipated to be completed within 6 years.

All recruitment will be done at each study site by the site-specific PI. As each study site is a referral site for patients with chronic pancreatitis who have PD stones, no advertising will be performed. All patients will be recruited based on screening done prior to regularly scheduled clinic or procedural visits.

12. Training Plan

The PIs will be responsible for training all study staff. The initial training meeting will occur at the 1st Investigators Meeting involving all PIs, co-investigators, and the study coordinator. The protocol will be

reviewed in its entirety and all standard procedures will be reviewed. Informed consent will also be reviewed during this session to ensure consistency across the study sites. All questions from the study staff will also be answered during this time. The protocol will then be reviewed at each site with the site-specific PIs and research assistants.

Quarterly conference calls involving all PIs, study coordinator and research assistants will be held once enrollment begins to ensure that any questions the study group has are answered. In addition, all potential protocol changes will be discussed during these calls. Should an emergent protocol change be needed, an emergent conference call will be held to discuss the change and once agreed upon, the changes will be submitted to the respective Institutional Review Boards.

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