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TITLE: Pancreatic Endotherapy for Refractory Chronic Pancreatitis

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14. ABSTRACT

The Pancreatic Endotherapy for Refractory Chronic PancreaTitis (PERCePT) trial is a single center, pilot, sham controlled trial of pancreatic endoscopy therapy for painful chronic pancreatitis. During year 2, subject recruitment and follow-up continued (this began at the end of year 1). To date, 13 (of 30 planned) subjects have been randomized. The contact PI changed institutions at the onset of year 3, compounding delays in enrollment attributable to the COVID pandemic.

15. SUBJECT TERMS
Chronic pancreatitis; pain; endoscopic retrograde cholangiopancreatography; extracorporeal shock wave lithotripsy

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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TABLE OF CONTENTS

1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose, and scope of the research.

Pancreatic duct obstruction causing pancreatic duct hypertension is one of several mechanisms of pain for patients with chronic pancreatitis. Pancreatic endotherapy, including main pancreatic duct stone lithotripsy and extraction as well as dilation and stenting of pancreatic duct strictures, are commonly offered in clinical practice despite limited data supporting their efficacy; there have been no sham comparative effectiveness studies. 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 endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic endotherapy is often performed in clinical practice despite limited data and potential negative short- and long-term consequences on the natural history of chronic pancreatitis. The PERCePT trial is a pilot, sham-controlled clinical trial of ERCP with pancreatic endotherapy for pain secondary to chronic calcific pancreatitis with main pancreatic duct obstruction. The overarching goals of this pilot study are to: 1) determine the feasibility of a sham-controlled pancreatic endotherapy trial and 2) optimize enrollment criteria and outcome measures for a subsequent, definitive study.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Chronic pancreatitis; pain; endoscopic retrograde cholangiopancreatography; extracorporeal shock wave lithotripsy

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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 using 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.

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) 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. In addition to measuring several patient-centered outcomes during the follow-up period, we will work with the National Pancreas Foundation to query its membership regarding outcomes of greatest importance to patients with painful chronic pancreatitis.

What was accomplished under these goals?

Milestone	Timeline	MUSC	MUSC completion date or % completed	OHSU	OHSU completion date or % completed
Major Task 1: Finalization of study protocol and regulatory documents for pilot randomized clinical trial	**Months**		**100%**		**100%**
Subtask 1: Prepare Regulatory Materials and Research Protocol for Study					
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	GC/VM/JB/KM	6/1/2019	N/A	N/A
Finalize consent form & human subjects' protocol	1-3	GC/LW	6/1/2019		6/1/2019
Finalize Ecological Momentary Assessment programming for PERCePT study	3-6	GC/JB/TBD	6/1/2020	N/A	N/A
Establish Data & Safety Monitoring Board, and complete first meeting	3	GC/VM/JB/KM	1/15/2020	N/A	N/A
IRB protocol submission	3	GC/LW	6/18/2019	GC/HK	10/15/2021
Department of Defense Human Research Program Office (HPRO)	6	GC/LW/AW	12/27/2019	GC/HK	4/7/22
Submit amendments, adverse events, and protocol deviations as needed	As Needed	JE/TBD	As needed	GC/HK	As needed
Annual IRB report for continuing review	Annually	N/A	Annually	GC/HK	Annually
Milestone Achieved: Local IRB approval	6	GC/LW	6/18/2019	GC/HK	2/11/2022
Major Task 2: Training investigators and research coordinator				100%	100%
Subtask 1: Hiring and Training of Study Staff					
Job description design for research coordinator	1	LW	8/1/2019	GC/HK	1/1/2022
Advertise, interview, and hire research coordinator	2-4	LW/GC	10/1/2019	GC/HK	1/15/2022
Train physician investigators	3-6	LW/GC	6/1/2020	GC/HK	3/1/2022
Milestone Achieved: Research staff trained	6	LW/GC	6/1/2020	GC/HK	3/1/2022
Major Task 3: Participant Recruitment				43%	43%
Subtask 1: Complete enrollment in pilot randomized trial		JE/TBD	43%		43%
Finalize assessment measurements	1-4	GC/VM/JB/KM	6/15/2020	N/A	N/A
Milestone Achieved: 1st participant consented, screened, and enrolled			10/9/2020	GC/HK	7/14/22
Milestone Achieved: Study 1 begins	7-30		10/9/2020	GC/HK/CP	2/15/2022
Begin subject recruitment	6-9	JE/TBD	09/15/2020	GC/HK/CP	2/15/2022
Complete enrollment	30	JE/TBD	43%	GC/HK/CP	43%
Complete follow-up assessments 12 months after completion of randomization procedures	42	JE/JB/TBD/KM	30%	GC/HK/CP	30%
Milestone Achieved: Complete follow-up assessments	42	JE/JB/TBD/KM	30%	GC/HK/CP	30%
Major Task 4: Analyze results			0%		0%
Subtask 1: Report Findings from pilot randomized trial			0%		0%
Analyze, measure, and report the results from the PERCePT trial		VM/JE/JB/KM	0%	GC/HK	0%
Milestone Achieved: Report findings from overall studies	48	JE/VM/JB/KM	0%	GC/HK	0%

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

- We have been granted a no-cost extension through June 2024 to increase our recruitment time.
- We will complete enrollment for the study by fall/winter 2023; the study DSMB requested extending recruitment through December 21, 2023 although this would require truncated follow-up for the last subject(s) enrolled since the no-cost extension ends in June, 2024.
- We are hopeful to achieve 50% of our original enrollment target (15/30). Since this is the first attempt at a sham intervention trial in painful chronic pancreatitis, this will be an important contribution to pancreatology as we learn about barriers to participation in intervention trials and the placebo effect – two key feasibility parameters to a larger scale study
- Physician investigators and the PERCePT research coordinators at OHSU are screening all new referrals and ambulatory clinic schedules for patients referred for "chronic pancreatitis," "pancreatitis," "abdominal pain," "pancreatic stone," and other keywords that suggest potential eligibility. Potential subjects are approached in the ambulatory clinic by a physician investigator.
- Finalize database and analyze pilot study results by the end of the no-cost extension

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

6.

Changes in approach and reasons for change

- This was originally designed as a feasibility pilot study since there have been no sham intervention trials in painful chronic pancreatitis to date. Recruitment has been very challenging because:
    - COVID pandemic disrupted referral patterns and closed them completely for stretches in 2020-2021
    - PI transition to OHSU resulted in a reduction in referrals at his prior institution (MUSC) and caused delays in on boarding the study at his new institution (OHSU)
    - Identifying patients who are eligible, agreeable, and able to participate in a fairly complex study protocol have been challenging. As part of our qualitative analysis of this study, we will examine potential protocol revisions to improve feasibility of a follow-up sham intervention trial studying patients with painful chronic pancreatitis.

Actual or anticipated problems or delays and actions or plans to resolve them

Recruitment remained the principal challenge in meeting the enrollment target due to:

1. Time needed to complete regulatory requirements at OHSU
2. COVID pandemic and modification in research activities as well as clinical practice as detailed in earlier reports
3. Stringent enrollment criteria; as this is a pilot trial, we elected to restrict the population to patients who have never undergone pancreatic endotherapy in the past. Since these patients are having significant pain, recruitment in this sham-controlled trial is challenging.

Changes that had a significant impact on expenditures

None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

- Protocol amendments have been approved by the IRB at MUSC and OHSU. USAMRMC HRPO was notified of these minor changes.
    - September 2021 - Removed Gregory Cote's name from ICF and added Joseph Elmunzer's name and contact information. The IRB required us to send all patients a letter explaining the change in PI.
    - October 2021 - Protocol Amendment: Removed exclusion criteria stating that patients with a Current Opioid Misuse Measure (COMM) score greater than or equal to 9 will not be included. This is because the COMM score may be inflated due to comorbidity unrelated to opioids and artificially even in patients not taking opioids.
    - March 2022 – Add OHSU Prep to Research form. Update protocol to reflect that study will be conducted at two sites – OHSU and IRB.
- There were no significant changes in this grant year (July 2022 – June 2023)

Significant changes in use or care of vertebrate animals

None

Significant changes in use of biohazards and/or select agents

N/A

7. PRODUCTS:

- *Publications, conference papers, and presentations*

Nothing to report

- *Books or other non-periodical, one-time publications.*

Nothing to report

- *Other publications, conference papers and presentations.*

Nothing to report

- *Website(s) or other Internet site(s)*

Nothing to report

- *Technologies or techniques*

Nothing to report

- *Inventions, patent applications, and/or licenses*

Nothing to report

- *Other Products*

None.

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Gregory Cote, MD, MS (GC) Principal Investigator, OHSU No change
Name: Project Role: Research Identifier Nearest person month worked Contribution to project	B. Joseph Elmunzer Principal Investigator, MUSC No change
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Valerie Durkalski-Mauldin, PhD Co-investigator, MUSC No change
Name: Project Role: Researcher Identifier: Nearest person month worked: Contribution to Project:	Jeffrey Borckardt, PhD Co-investigator, MUSC No change
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Haley Nitchie, MHA Consultant, MUSC No change
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Patty Hutto Data Manager, MUSC No change
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	April Williams Project Manager, MUSC No change
Name: Project Role: Research Identifier Nearest person month worked Contribution to project	Heather Katcher, PhD, RD Research Manager, OHSU No change

Name: Project Role: Research Identifier Nearest person month worked Contribution to project	Czarinna Posadas Research Coordinator, OHSU No change
Name: Project Role: Research Identifier Nearest person month worked Contribution to project	Ann Jeline Manabat Research Coordinator, OHSU 2 • Identify and screen eligible patients • Coordinate study visits; conduct data entry • Liaise with the Data Coordination Unit and MUSC clinical center to coordinate study activities • Assist with maintenance of study documents, policies and procedures • Regulatory compliance
Name: Project Role: Research Identifier Nearest person month worked Contribution to project	Alexander Waters Research Coordinator, OHSU 1 • Identify and screen eligible patients • Coordinate study visits; conduct data entry • Liaise with the Data Coordination Unit and MUSC clinical center to coordinate study activities • Assist with maintenance of study documents, policies and procedures • Participate in the process of IRB submission

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to report

9. SPECIAL REPORTING REQUIREMENTS: N/A

10. APPENDICES: N/A