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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, 7 (of 30 planned) subjects have been randomized and 1 subject enrolled into the observational cohort; another subject is in the run-in phase. The contact PI is changing institutions so a proposal to allow for recruitment at two centers is detailed in this annual report and related documents.

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

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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

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

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.

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	Completion date or % completed
Major Task 1: Finalization of study protocol and regulatory documents for pilot randomized clinical trial	Months		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
Finalize consent form & human subjects' protocol	1-3	GC/LW	6/1/2019
Finalize Ecological Momentary Assessment programming for PERCePT study	3-6	GC/JB/TBD	6/1/2020
Establish Data & Safety Monitoring Board, and complete first meeting	3	GC/VM/JB/KM	1/15/2020
IRB protocol submission	3	GC/LW	6/18/2019
Department of Defense Human Research Program Office (HPRO)	6	GC/LW/AW	12/27/2019
Submit amendments, adverse events, and protocol deviations as needed	As Needed	GC/LW/AW	As needed
Annual IRB report for continuing review	Annually	GC/LW	Annually

Milestone Achieved: Local IRB approval at MUSC	6	GC/LW	6/18/2019
Major Task 2: Training investigators and research coordinator			100%
Subtask 1: Hiring and Training of Study Staff			
Job description design for research coordinator	1	LW	8/1/2019
Advertise, interview, and hire research coordinator	2-4	LW/GC	10/1/2019
Train physician investigators	3-6	LW/GC	6/1/2020
Milestone Achieved: Research staff trained	6	LW/GC	6/1/2020
Major Task 3: Participant Recruitment			15%
Subtask 1: Complete enrollment in pilot randomized trial			23%
Finalize assessment measurements	1-4	GC/VM/JB/KM	6/15/2020
Milestone Achieved: 1st participant consented, screened, and enrolled			10/9/2020
Milestone Achieved: Study 1 begins	7-30		10/9/2020
Begin subject recruitment	6-9	GC/KM/JB/VM	10/9/2020
Complete enrollment	30	GC/TBD	23%
Complete follow-up assessments 12 months after completion of randomization procedures	42	GC/JB/TBD/KM	0%
Milestone Achieved: Complete follow-up assessments	42	GC/JB/TBD/KM	0%
Major Task 4: Analyze results			0%
Subtask 1: Report Findings from pilot randomized trial			0%
Analyze, measure, and report the results from the PERCePT trial		VM/GC/JB/KM	0%
Milestone Achieved: Report findings from overall studies	48	JC/BH/CP	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?

Efforts remain focused on screening and enrollment. Physician investigators and the PERCePT research coordinator 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 and research coordinator. We began screening in June 2020 with the first randomization in October 2020. To date, 7 of 30 (23%) planned subjects have been randomized; 1 additional subject screen failed after pain scores fell below the predefined threshold during the run-in period and remains in the observational cohort (1 of estimated 15 subjects). Another subject has consented to participate and is beginning the run-in phase prior to randomization at the time of drafting this document.

The study PI, Gregory Cote, has accepted a position as Division Head at Oregon Health &

Nothing to report

is a regional referral center for patients with chronic pancreatitis. Given delays caused by regulatory approval and finalization of the Electronic Momentary Assesment tool in year 1 and those caused by COVID-19 in years 1-2, we propose that this study continue at MUSC with a new PI (B. Joseph

Nothing to report

new budget to allow completion of subject recruitment at two sites is included in this annual report. We have not increased overall expenditures from the original budget.

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:

Changes in approach and reasons for change

Gregory Cote has accepted a position as Division Head and Professor of Medicine at Oregon Health & Sciences University (OHSU) effective September 1, 2021. After discussion with DOD grants management, it has been advised to keep the award at MUSC as the hosting institution. To that end, we recommend that B. Joseph Elmunzer, MD, MS assume the role as Principal Investigator at MUSC. Dr. Elmunzer is the overall PI for the Stent vs. Indomethacin study, a multicenter, randomized clinical trial funded by the NIH which is evaluating the role of prophylactic pancreatic duct stents in the prevention of post-ERCP pancreatitis. In addition, Dr. Elmunzer has been an active co-investigator for this project. He has served as the blinded and unblinded physician for different subjects who have already been randomized in this trial in addition to participating in the informed consent process.

Recruitment remains the principal challenge in completing this project due to:

1. Delays in study activation due to development of the electronic momentary assessment
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.

The expansion to a second medical center will increase the probability of achieving our target sample size within the 4-year grant period.

None

The GI team at OHSU offers a complete portfolio of interventions under the rubric of "pancreatic endotherapy," the topic of study in this pilot clinical trial. These interventions include ERCP with pancreatic sphincterotomy, pancreatic stone extraction, pancreatic stricture dilation and stenting, electrohydraulic lithotripsy, and extracorporeal shock wave lithotripsy (like MUSC but unique to many

Amendment #1 approved by MUSC IRB 2/12/2020, and USAMRMC HRPO notified of these minor changes:

ICF Changes:

- Clarified subject obligations when enrolled into the observational group
- Minor grammatical edits
- Edited the 180, 270, and 360-day follow-up visits to state they can be done in-person or via telephone and clarified that paragraph
- Edited duration paragraph specifying there are 8 visits, with minimum of 3 being in-person for the randomized group, and 2 in-person for the observational group
- Clarified what costs will be covered by the study

None

- Edits to Table 1. Summary of Study Procedures
- Specified observational subjects do not get randomized
- Made changes allowing for 180-day, 270-day, and 360-day follow up to be completed in-person or via telephone. 90-day visit stays in-person for randomized subjects, but observational subjects have option of completing it via telephone. This change was also made later in the protocol in section 10.1.4 Follow-up visits.
- Added additional details in Table 2. Baseline assessments
- Added 3 questionnaires to Table 3: follow-up assessments

N/A

- Removed Aurora Newman from study personnel, adding Lauren Wakefield

- *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.

7. 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) No change
Name: Project Role: Researcher Identifier: Nearest person month worked: Contribution to Project:	Jeffrey Borckardt, PhD No change
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Haley Nitchie, MS Research coordinator No change 6.0 Ms. Nitchie replaced Lauren Wakefield who found a position in a different department. She is primarily responsible for coordinator activities including: 1) facilitate subject recruitment; 2) complete baseline, randomization, and follow-up visits; 3) complete adverse event reporting; 4) work with data coordination unit and PI on IRB communications.
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Valerie Durkalski-Mauldin, PhD No change
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Sara Butler Data manager No change 2 Replaces Andre Thornhill who has left the data coordination unit. Overseeing data management aspects of trial including case report development.
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	Anh Phan Biostatistician N/A 1 Assists Valerie Durkalski with biostatistical responsibilities.
Name: Project Role: Researcher Identifier Nearest person month worked: Contribution to Project:	April Williams No change

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

8. SPECIAL REPORTING REQUIREMENTS

9. APPENDICES