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TITLE: Pancreatic Endotherapy for Refractory Chronic Pancreatitis

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13. SUPPLEMENTARY NOTES

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 1, the study protocol was finalized and approved by the Human Subjects Research Protection Office at the Medical University of South Carolina. A Data and Safety Monitoring Board was established and convened its first meeting. The Statistical Data and Coordinating Center finalized the case report forms and electronic database. The Electronic Momentary Assessment tool was developed; this will be used to monitor pain and other metrics throughout the clinical trial. Screening for eligible subjects commenced in June 2020; the ongoing COVID-19 pandemic presents an added challenge with coordination of screening and baseline visits, since most non-procedure clinical care has shifted temporarily to a virtual format. Efforts are now focused on screening and recruitment for the end of year 1 and beginning of year 2

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

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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

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

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.

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 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.

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			0%
Subtask 1: Complete enrollment in pilot randomized trial			0%
Finalize assessment measurements	1-4	GC/VM/JB/KM	6/15/2020
Milestone Achieved: 1st participant consented, screened, and enrolled			0%
Milestone Achieved: Study 1 begins	7-30		0%
Begin subject recruitment	6-9	GC/KM/JB/VM	0%
Complete enrollment	30	GC/TBD	0%
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 are now 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 will be approached in the ambulatory clinic by a physician investigator and research coordinator. We began screening in June 2020; the ongoing COVID-19 pandemic has created some additional challenges, since many patients are being seen in a virtual telehealth format. We will monitor the impact of COVID-19 recruitment in the early months of year 2.

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:

Changes in approach and reasons for change

As reported in the year 1, third quarter technical report, the protocol has been amended as detailed below. These changes are minor in nature and do not change the outcomes of the trial. These amendments were reported to the HRPO and at the time of annual HRPO renewal.

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

We encountered delays in the development of an Electronic Momentary Assessment tool to measure pain and other patient-centered outcomes as per study protocol. This was due to university policies regarding procurement services. As discussed in our year 1, third quarter progress report we elected to develop and validate this tool internally.

The ongoing COVID-19 pandemic has impacted clinical services, requiring our ambulatory clinics to shift a large component to a telehealth format. Since we have just commenced screening for this trial, we have not elected to pursue a protocol amendment to allow for telephone/telehealth consent. If it appears as though recruitment is significantly impacted by this shift in ambulatory practice, we may pursue this modification during the next 1-2 quarters. In the meantime, we are encouraging all physician investigators

None

formally considering the PERCEPT trial.

- Added additional details in Table 2. Baseline assessments
- Added 3 questionnaires to Table 3: follow-up assessments
- Opioid utilization, Pain catastrophizing, and Patient Global Impression of Change
- Minor grammatical edits

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 on 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

- Minor grammatical edits

- 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*

See attached appendix with includes the book of case report forms associated with the study database.

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:	Lauren Wakefield, MS No change
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:	Andre Thornhill No change
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

See attached study book of case report forms