Dartmouth-Hitchcock

Identifiers: NCT02160808
Unique Protocol ID: D13208 TBG-01
Brief Title: Secretin Infusion to Prevent Pancreatic Leaks Following Pancreatic Resection

Dartmouth College and Dartmouth-Hitchcock Medical Center
Committee for the Protection of Human Subjects

CPHS Study Plan for Full Committee Review

Template v. 2.24.2011

Instructions:

*The following information in the format provided below is an application for CPHS review. Read through each section and **respond to each item (even if to indicate NA - not applicable)**. Please also review the CHECKLIST for Full Committee Submission. We have provided some guidance information under each question.*

Please define all acronyms at first use and attach a glossary if more than 3 acronyms are used in this application.

When revising a CPHS reviewed Study Plan for further review, please track the changes. To turn on tracking in this document in Microsoft Word:

1) Display the forms and reviewing toolbars.
2) Unlock the form by clicking on the lock icon on the forms toolbar.
3) Turn on change tracking by clicking the icon on the reviewing toolbar.
4) Lock the form by clicking again on the lock icon on the forms toolbar.

Attachments:

Complete and submit Attachment(s) if applicable to the research study.
Attachments may be downloaded from this webpage:
http://www.dartmouth.edu/~cphs/tosubmit/forms/StudyPlanAttach

- ☐ *Attachment A: Nonsignificant Risk Devices*
- ☒ *Attachment B: Placebo*
- ☐ *Attachment C: Genetic Research*
- ☐ *Attachment D: Employees and Students*
- ☐ *Attachment E: Illiterate Participants*
- ☐ *Attachment F: Research Involving Children*
- ☐ *Attachment G: Research Involving Individuals With Impaired Decision-Making Capacity (formerly referred to as incompetent)*
- ☐ *Attachment H: Request for Waiver of Participant Consent*
- ☒ *Attachment I: Request for Waiver of Participant Signed Consent Form*
- ☐ *Attachment J: Drugs or Biologics*
- ☐ *Attachment L: International Research*
- *Attachment M: Pregnant Women, Fetuses and Neonates*

==========

Local Principal Investigators: **Kerrington D. Smith and Timothy B. Gardner**

Secondary Investigators: **Thomas Colacchio MD, Christina Angeles MD and Richard Barth MD**

Department: **Departments of Medicine and Surgery**

Study Title: **Secretin Infusion to Prevent Pancreatic leaks Following Pancreatic Resection**

Funding Source (Sponsor): **ChiRhoClin, Inc, and ChiRhoClin Research Institute. This is an investigator-initiated project. ChiRhoClin, Inc. will supply the drug, Secretin. Dr. Gardner will also receive a small grant from the ChiRhoClin Research Institute to support the research coordinator's salary.**

1. *Abstract.*

Provide an abstract of the proposed research ***in language that can be understood by a non-scientist****. The abstract should summarize the objectives of this project and the procedures to be used, with an emphasis on what will happen to the subjects.* ***(Maximum 250 words)***

Pancreatic ~~anastomotic~~ leaks complicate pancreatic resection in approximately 20% of cases. The pancreatic anastomosis or repair has been referred to as the Achilles heel of pancreatic surgery. Unfortunately, despite recognition of this problem and multiple operative techniques proposed to prevent this complication, leaks continue to represent a major cause of morbidity for patients undergoing pancreatic surgery. Treatment of leaks often requires nutritional support with total parenteral nutrition to diminish the leak in addition to invasive interventions to contain the leak with drains, stents or in severe cases, reoperation. Experiential data suggest that intra-operative infusions of secretin, a naturally occurring hormone that stimulates bicarbonate release from the pancreas, following resection but just prior to abdomen closure, may identify a leak if present. If secretin can demonstrate evidence of leaking intra-operatively, the pancreatic duct leak may be able to be fixed prior to abdominal closure. We aim to determine if giving an intra-operative infusion of secretin will allow for identification and treatment of leaks after pancreatic reconstruction and prior to abdominal closure, leading to a reduction in the rate of pancreatic ~~anastomotic~~ leaks requiring intervention. We will perform a double-blind, randomized pilot study of 176 patients undergoing pancreatic resection (pancreaticoduodenectomy and distal pancreatectomy) at Dartmouth-Hitchcock Medical Center. 88 of those patients will receive an intraoperative secretin infusion prior to abdominal closure and 88 will receive a saline placebo. Our primary outcome of interest will be the rate of pancreas duct leaks in each group as measured by the amount of amylase present in the surgical drains on or after post operative day (POD)# 3 following surgery.

2. *Objectives & Hypotheses:*

List your research objectives and hypotheses.

We hypothesize that intra-operative, intravenous secretin administration will decrease the rate of pancreatic leaks in patients undergoing pancreatic resection. Our primary objective is to determine if intravenous secretin administration will decrease the amount of pancreatic leaks as defined by the 2016 ISGPS definition of postoperative pancreatic fistula, measured by drain fluid amylase on or after POD#3days following resection. Our secondary objectives are to determine if intra-operative intravenous secretin administration changes the management of the pancreatic resection margin intraoperatively or impacts length of stay (LOS)

3. *Introduction:*

a) Explain the background of this project so that we will understand why it is important to perform this research project. b) Summarize previously published data and pilot studies. Be sure to include a discussion of any data that do not support the study hypothesis. If a study similar to the one being

proposed has already been completed, explain why the proposed study is necessary. c) For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternative modes of therapy. d) If not obvious, explain why human subjects are necessary. Include references for all published data cited. If a formal protocol for the study exists, page references to the protocol are acceptable.

A) Pancreatic duct leaks represent a major complication of pancreatic resection surgery. With a rate of between 20% even at expert, high-volume centers, this dreaded complication causes significant morbidity for patients with associated increased hospital costs. Treatment of pancreatic duct leaks often requires pancreatic rest with intravenous nutrition, endoscopic placement of pancreatic duct stents, and/or repeat surgical operation to close the leak. Despite many advancements in terms of leak closure techniques (duct to mucosa pancreaticojejunostomy, roux-en-Y reconstruction, devices (automatic staplers/ pledgets/stents) pancreatic leaks continue to be a major problem and pancreatic surgeons continue to search for methods to prevent or diminish the severity of pancreatic leaks.

B) Currently, there are no pilot studies which have specifically addressed whether secretin therapy can help to identify pancreatic duct leaks intra-operatively. While the drug has been used to identify leaks post-operatively using MRI (Gillams AR, Kurzawinski T, Lees WR. Diagnosis of duct disruption and assessment of pancreatic leak with dynamic secretin-stimulated MR cholangiopancreatography. AJR 2006) no previous studies have been performed. Secretin is widely available and used to stimulate pancreatic secretions from the ductal cells for many indications such as identifying the minor papilla, obtaining pancreatic fluid for cytokine analysis, and diagnosing pancreatic cancer. (Levenick JM, Andrews CL, Purich, Ed et al. A Phase II Trial of Human Secretin Infusion for Refractory Type B Pain in Chronic Pancreatitis. Pancreas 2013) It is also used to treat autism in select patients and diagnose the presence of a gastrinoma. (Williams K, Wray JA, Wheeler DM. Intravenous Secretin for Autism Spectrum Disorders. Cochrane Database Reviews 2012; Imamura M, Komoto I, Ota S. Changing treatment strategy for gastrinoma in patients with Zollinger-Ellison syndrome. World J Surg 2006).

Since 2011, patients at DHMC treated with pancreatic resection have occassionally been given intraoperative intravenous secretin to diagnose pancreatic duct leaks. While this technique has not been specifically studied in a prospective fashion, anecdotal expereince demonstrates that secretin infusion can identify leaks in the operating room prior to abdominal closure. Identifying the leaks intraoperatively then allows the surgeon to alter the technique of closure or suture placement directed at the site of leakage. Our hypothesis is that secretin-assisted leak identification with localization will allow for intraoperative closure and decreased incidence and severity of clinically significant leaks in the post-operative period.

C) This would be a randozimed, double-blind, placebo controlled trial. 1/2 of the patients would receive intra-operative secretin, the other half would receive saline placebo. Both the surgeon and patient would be blinded to the randomization assignment. The advantage of giving secretin would be that it may allow for the indentification of a leak intra-operatively and subsequently allow for repair if the leak was identified prior to abdominal wall closure. While the safety profile of the drug is excellent, receiving the medication could theoretically cause an increased intraductal pressure which may cause a leak when one was not already present.

D) Human subjects are needed to evaluate intra-operative, intravenous secretin in patients undergoing pancreatic duct resection.

4. *Design, procedures, materials and methods:*

Use a level of detail similar to what would be used when submitting an article for publication in a peer reviewed journal. Explain the study procedures, data collection, and analysis process. Please define terms and explain concepts which might be confusing to reviewers who are not expert in the area of the study. If a formal protocol for the study exists, page references to the protocol are acceptable.

This study design is a prospective, double-blind, randomized-controlled trial. We will enroll patients in our institution undergoing pancreatic resection to receive either 1) one dose weight-based Secretin to be given once the closure of the pancreatic resection margin is complete 2) saline placebo.

Consent and basic demographics will be garnered by the physician in an office visit once the surgery has been scheduled and consent for the surgery is being obtained. The consent will be validated by the treating surgeon in the pre-procedure area on the day of the surgery.

The patient will undergo the scheduled surgery. Once the pancreatic anastomosis has been deemed acceptable by the attending physician, but prior to abdominal closure, the patient will be randomized to receive either Secretin (0.2 mcg/kg) or saline placebo. The attending surgeon will be blinded to this assignment.
10 minutes after receiving the Secretin or placebo, the attending surgeon will examine the anastomosis or repaired cut edge of the pancreas to determine if leakage of pancreatic fluid is noted, leak location(s), type (side branch/main duct), color of the fluid and whether any further intervention was performed in an effort to close the leak. Specifics of operative intervention will be documented. The patient will then undergo standard surgical closure of the abdomen.

As is standard of care at DHMC, surgical drains will be placed adjacent to the anastomosis and drain amylase output will be checked on POD #1 through POD#5. Pancreatic leak is defined according to the International Study Group of Pancreatic Fistula (ISGPF) definition as a clinically relevant postoperative pancreatic fistula is now redefined as a drain output of any measurable volume of fluid with an amylase level >3 times the upper limit of institutional normal serum amylase activity, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula. Randomization assignments will be revealed once the patient has been discharged from the hospital following their initial surgical intervention. A follow-up visit with the patient two weeks following discharge, will evaluate for any evidence of ongoing pancreatic duct leak.

The patient will also be followed for thirty (30) days after secretin/placebo administration by the research team to assess for a pancreatic leak and sequelae of a leak, - intra abdominal deep soft tissue infection, surgical site infection, hemorrhage, IR (interventional radiology) drain placement, or reoperation. This will be accomplished by telephone and/or by chart review Patients discharge date will be followed for the study. If no secretin/placebo is administered, the patient will not be followed on the study.

If any of the above are noted during the 30 days following secretin/placebo administration the following will be used to assess causality:

Causality

The following 4-point scale will be used for rating the causal relationship of the AE to the investigational product:

Unrelated: Clearly and incontrovertibly due to extraneous causes, and does not meet criteria listed under unlikely, possible, or probable.

Unlikely: Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state or by environmental factors or other therapies administered.

Possible: Follows as reasonable temporal sequence from administration. May have been produced by the patient's clinical state or by environmental factors or other therapies administered.

Probable: Clear-cut temporal association with improvement or cessation of test drug or reduction in dose. Reappears upon re-challenge. Follows a known pattern or response to test drug.

The primary outcome of interest will be the presence of pancreatic leaks based on the amount of drain amylase on or after POD#3. Secondary outcomes will include: 1) technical interventions intraoperatively directed to leak closure or manipulation of the anastomosis following Secretin or placebo stimulation 2) length of stay as a surrogate to complication severity after pancreatic surgery.

Patient demographics, risk factors, operative technique, randomization assignment and outcome data will be recorded on standard case report forms – **See Case Report Forms in Appendix.** Data will be stored in an encrypted hard-drive by a single agent (Gardner) who is the only researcher who has access to the randomization data.

5. *Inclusion/Exclusion Criteria:*

Please provide detailed description of inclusion and exclusion criteria. If a formal protocol for the study exists, page references to the protocol are acceptable.

Inclusion criteria:

1. Scheduled for pancreatic surgery requiring pancreatic resection at DHMC
2. Age greater than 18 years old
3. Ability to provide written informed consent

Exclusion criteria:

1. Inability to provide written informed consent
2. Current ongoing acute pancreatitis
3. Pregnant or nursing mothers
4. Any medical condition which in the judgment of the Investigator renders participation in this study medically inadvisable.
5. Participation in an investigational clinical study for a drug or medical device within 30 days prior to Visit 1.
6. Any known allergy to methylene blue.

6. *Financial Considerations:*

Disclosure of financial impact on the participant is critical to informed consent. Insurance cannot be billed for research-related services outside the standard of care or paid for by the funding agency for

the study. The department, the study or the participant may be responsible for payment for researchrelated services. Participants should know which tests, visits, or procedures will be billed to them or their insurance and which ones will be paid by the funding agency for the study or the department.

a) *List tests, visits, and procedures performed for only research purposes. These services are outside the standard of care. They would not be performed if the individual were not a research participant, and may not be billed to a health insurance plan.*
Note: 6a information must also be in "How is this different . . ." section of the consent form.

The administration of Secretin or placebo is for research purposes only and will not be billed to the patient. Drain placement, drain amylase measurement and the two week follow-up visit are per standard of care and will be billed directly to the patient.

b) *List the tests, visits, and procedures that may be standard care, but for which the funding agency for the study is paying.*

None

c) *Will the funding agency for the study be responsible for the above costs?* ☒ *Yes* ☐ *No*
If No, describe who will be responsible (i.e., department or participant).

Secretin will be supplied by ChiRhoClin, Inc and saline placebo will be supplied by the Section of Gastroenterology and Hepatology out of research funds maintained by the primary investigators. No additional tests, visits, or procedures will be performed for research purposes only.

PLEASE ENCLOSE THE DHMC BILLING GRID/PLAN. Also enclose the schedule of events or table listing all procedures from the sponsor protocol.

7. Statistical Methods and Review Statement:

a) *Specify the primary endpoint, as well as other endpoint(s).*

Primary Objective:

1. Pancreatic leak as defined by the ISGPF definition of post-operative pancreatic leaks

Secondary Objective:

1. Assess whether intervention is performed intra-operatively on the pancreatic anastomosis following Secretin or placebo injection.
2. Assess degree to which leakage severity, as a complication, increases length of stay.

b) *State the statistical analysis plan, including all hypothesis tests (e.g., t-test, chi-square), and estimation methods related to the primary endpoint. If a formal protocol for the study exists, page references to the protocol are acceptable.*

For the analysis of the primary endpoint, a categorical variable, we will use a two-tailed Fisher's Exact test to determine a p-value. We will then be able to calculate an absolute and relative risk reduction. We will also evaluate this variable using a student's t-test for means of amylase levels in the drain fluid. We will plan on performing univariate analysis of all of the potentially contributing variables outlined in the

CRF, and then building a multivariable logistic regression model using the categorical variable of drain amylase >3x the upper limit of normal. The data from the multivariate regression will be reported as Odds Ratios.

The secondary outcomes are both categorical and continuous variables and thus we will use the Fisher's Exact test as well as the two-tailed student's t-test. A multivariable analysis is not planned for evaluating the secondary variable.

Randomization will occur in a block format of 5 and will be generated by the primary investigators.

c) *Justify the sample size, using the concepts of power, type I error, and effect size if applicable. If a formal protocol for the study exists, page references to the protocol are acceptable.*

A clinically significant absolute decrease of 15% (20% to 5%) in the pancreatic duct leak rate. Based on these estimates and a two-tailed test comparing proportions using the statistical calculator (http://homepage.stat.uiowa.edu/~rlenth/Power), we project an estimated sample size of **176 participants (88 per arm)** to demonstrate an absolute 15% reduction in the leak rate with 80% power at a two-sided alpha level of 0.05.

8. *Data and Safety Monitoring:*

Describe plans for data and safety monitoring to ensure the safety of subjects and the quality of the data. As described in federal guidance "... a variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the trial. In many cases, the principal investigator would be expected to perform the monitoring function." This plan should include monitoring to determine:

The progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. Monitoring should also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

Note: This section does not request information related to sponsor study monitor visits. This section requires a description of an adequate data and safety monitoring plan.

Interim analysis will be performed once 50% (88) patients have been enrolled. If more than 66% of cases of duct leak are in a particular study group, a formal comparison between groups will be performed with the use of a two-sided stopping boundary of 0.005%.

The co-heads of the DSMB will be Dr. Theodore Trus and Dr. Stuart Gordon, in the Section of General Surgery and Gastroenterology and Hepatology. Drs. Trus and Gordon will not be participating in the trial.

9. *Genetics:*

Does any part of the study involve genetic analysis of biological specimens? ☐
Yes x☒ *No*
If yes, respond to ***Genetics Attachment C***

10. *Instruments:*

Describe each instrument, if any, used to collect data in this study.

Please see the CRF included in the appendix.

11. Deception.

Will deception of participants, including withheld information, be used in this research? ☐ *Yes* ☒ *No*

If yes, complete a-d.

12. *Enrollment:*

a) *Estimated number of participants for duration of entire study:*

At Dartmouth or associated sites: ***Female:*** **88** ***Male:*** **88**

If Multi-center study: Estimated total number at all sites: 0

b) *Estimated age range of participants:* Age >18

13. *Timetables:*

a) *Indicate length of participant involvement in the study:*

Participation will involve enrollment at the time of surgery and discharge following surgery. Patients will then be seen in the clinic two weeks following the procedure.

b) *Estimate how long it will take to enroll enough participants to complete this study:* At DHMC, approximately 120 major pancreas surgeries are performed annually. If 80% of patients agree to participate in the study, the enrollment should be complete after **24 months**.

14. *Risks:*

The purpose of this section is to determine if subjects will be placed "at risk," which in general means exposed to the possibility of physical, psychological, social, economic, legal, dignitary or other harm as a consequence of any activity proposed in the research project.

a) What is the overall risk classification of the research?

☒ *Minimal*
☐ *Greater than minimal*
☐ *Significant*
☐ *Unknown*

Note: In the federal regulations on human subjects protection minimal risk means "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

b) Describe any potential risks (physical, psychological, social, legal, economic, or other) and assess their likelihood and seriousness. Describe the procedures for protecting against or minimizing these risks, including risks to confidentiality, and assess their likely effectiveness. Please list risks from most severe/likely to least severe/unlikely.

Synthetic secretin is FDA approved to diagnose exocrine pancreas dysfunction by the functional secretin stimulated pancreas function test and to facilitate pancreatic duct cannulation during ERCP. It is identical in amino acid sequence to native human secretin.

There has not been any reported adverse drug reaction to human secretin stimulation. Rarely, in over 1000 patients who have undergone Secretin-enhanced pancreatic function tests, there is transient vasodilatory effect resulting in flushing of the face and lips with stable vital signs. Therefore, the risks of administrating intravenous secretin are modest as described in the package label.

In doses (800cu SQ bid x 7 days) given in clinical studies greater than those offered in the current study, there were no adverse events reported

Secretin is not known to increase the risk of acute pancreatitis episodes in patients with chronic pancreatitis not presently having an acute pancreatitis attack. No allergic reactions have been reported with secretin in commercial use although the administration of a test dose 0.2 mcg IV is still recommended. No significant hemodynamic effects have been observed following administration of secretin. Otherwise, the risks of administering secretin are modest as described in the package label.

The risk of confidentiality should be low given the case report form will be only available to Dr. Gardner and will be kept in a locked cabinet. All data will be entered on a password-protected Microsoft Excel spreadsheet. Any statistical analysis will be done with patient study numbers and initials for identification of patient.

15. *Risk/Benefit analysis:*

Describe why the risks to subjects are reasonable in relation to the anticipated benefits to participants and in relation to the importance of the knowledge that may reasonably be expected to result from the study.

A potential risk reduction of up to 15% for pancreatic duct leaks outweighs the given theoretical risks of one time Secretin administration.

16. *Research Setting*

a) *Is this a multi-center study?*

☐ *Yes* ☒ *No*

If yes: Are you the lead investigator? ☐ *Yes* ☐ *No If you are NOT the lead investigator:*

Name of lead investigator:

Institution where the lead investigator is located:

b) *List all sites where research will take place and the CPHS at Dartmouth College is the reviewing IRB (e.g. DHMC Alliance Hospitals, DHMC Clinics, WRJ VAMC):*

Dartmouth-Hitchcock Medical Center

c) If you are the lead investigator of a multi-center study, *list all sites where research will take place and the CPHS at Dartmouth College is* ***NOT*** *the reviewing IRB: or check* ☒*N/A*

NA

☐ ☒ ***d)*** *Does this study involve sites outside of the United States and Canada? Yes No*
If yes, are arrangements for the international site(s) being made by a multinational pharmaceutical or device sponsor or a cooperative oncology working group? Yes No
☐ ☒ *If no, please* ***complete Attachment L****.*

17. ***Adequacy of Resources to Protect Subjects:***

a) Investigator (including co-investigators) has sufficient time to conduct and complete the research. ☒ *Yes* ☐ *No*

b) Adequately qualified (including experience, training, supervision, and familiarity with the protocol) staff are available for this research. ☒ *Yes* ☐ *No.*

c) Describe availability of psychological, social, or medical services, which include counseling or social support services, that may be required as a consequence of research participation.

Dartmouth-Hitchcock Medical Center provides adequate access to mental health services, including social and behavioral counseling. Secretin is already being used on patients at *high risk* for pancreatic duct leaks, and we have in place the medical ability to treat a complication of this therapy in the rare event that one would occur.

d) Describe psychological, social, or medical monitoring, ancillary care, equipment needed to protect participants (e.g. close proximity to resuscitation equipment or a plan for monitoring of emotional state during study procedures).

None

e) Describe other resources needed for the protection of subjects in the conduct of this research (e.g. language translation services).

None

f) Explain how the investigator has access to a population that would allow recruitment of the required number of subjects.

DHMC performs about 120 major pancreatic surgeries annually.

18. ***Participant Population:***

Certain populations are considered vulnerable to coercion and undue influence. These populations are provided with additional protections when participating in a research study. The populations include:

- *prisoners*
- *human embryos*
- *fetuses*
- *elderly people*
- *people with an cognitive disability (also see #24 below)*
- *people with a disabling psychiatric illness*
- *people who are economically disadvantaged persons*

- *people who are illiterate*

Refer to: *Students, Employees* ***Attachment D***
Illiterate Subjects ***Attachment E***

a) *List vulnerable groups: or check None* ☒

b) *Describe additional protections: or check N/A* ☒

19. *Gender and Racial/Ethnic distribution:*

NIH guidelines state that research involving human participation should include minorities and both genders.

Note: If one gender or minorities are excluded or are inadequately represented in this research, particularly in proposed population-based studies, a clear and compelling rationale for exclusion or inadequate representation should be provided.

Will eligibility for the study be based on gender, race, or ethnicity? ☐ *Yes* ☒ *No If yes, explain:*

20. *Pregnant Women:*

Are pregnant women eligible for enrollment into this study? ☐ *Yes* ☒ *No*

If yes, respond to ***Research Involving Pregnant Women, Fetuses and Neonates:*** ***Attachment M*** *If no, explain and include a process to determine pregnancy status. If a pregnancy test is required, note who will pay:*

They will not be included as pancreatic surgery is contraindicated, with very rare exceptions, in pregnancy.

21. *Fetuses and Neonates:*

Are fetuses and neonates participants in the research?

☐ *Yes* ☒ *No*

If yes, respond to ***Research Involving Pregnant Women, Fetuses and Neonates: Attachment M***

22. *Children:*

Are children eligible for enrollment into this study? Under state law, a child is a person less than 18 years old.

☐ *Yes* ☒ *No*

If yes, respond to ***Children:*** ***Attachment F***

If no, present an acceptable justification for the exclusion:

Note: NIH guidelines state that research involving human participation should include children unless there is appropriate justification for their exclusion. The investigator should address the rationale for selecting or excluding a specific age range of children, or an explanation of the reasons for excluding children as participants in the research. When children are included, the plan should also include a description of the expertise of the investigative team for dealing with children at the ages included, of the available facilities to accommodate the children, and a sufficient number of children to contribute meaningfully to the study analysis.

23. *Women of Child-Bearing Capability*

Are women of child-bearing capability eligible for enrollment into this study? ☒ *Yes* ☐ *No*

If yes, describe potential harm to an unborn fetus from study activities and the process for determining pregnancy status if necessary. If a pregnancy test is required, note who will pay. If there is potential harm to an unborn fetus, the investigator should review with each individual a plan to avoid pregnancy. If the investigator regards these contraceptive plans as inadequate, the individual should be advised on how to achieve adequate contraception or should be excluded from the study.

Since the standard of care when performing surgery in patients with potential child-bearing capability is to perform pregnancy tests, we will require them for this study.

24. *Individuals With Impaired Decision-Making Capacity:*

a) Will participants potentially lacking capacity to provide informed consent be eligible to enroll in this study? ☐ *Yes* ☒ *No*

b) Is it likely study participants may lose their capacity to provide informed consent during the conduct of the study? ☐ *Yes* ☒ *No*

If yes to a or b, respond to ***Research Involving Individuals with Impaired Decision-Making Capacity: Attachment G***

25. *Recruitment:*

Describe how subjects will be recruited for participation in this study:

Eligible participants may be identified from medical record information as a "preparatory to research" activity under the HIPAA Privacy Rule. Protected health information obtained as a preparatory to research activity may not be removed by a researcher from DHMC, including on mobile electronic storage devices. Contact with the identified participants, however, may not occur without prior CPHS approval of the recruitment plan for the study. This plan should describe how initial contact with participants will be made and by whom. Please note in general, individuals should not be contacted for recruitment into a research study by someone unknown to the individual.

a) Will subjects be recruited by searching records
☐ *(e.g., school records, medical records)? Yes* ☒ *No*

If yes, will this search include paper files? ☐ *Yes* ☐ *No*

If yes, where will these paper files be located?

If yes, will this search include electronic files?
☐ *Yes* ☐ *No*

If yes, who maintains these electronic files?

b) Will databases be utilized? ☐ *Yes* ☒ *No*

If yes, please specify types and locations of databases:

c) Will fliers or brochures be posted, mailed or otherwise distributed? Yes No

☐ ☒

d) Will letters be sent to potential participants?
☐ *Yes* ☒ *No*
If yes, please provide the letter(s) for CPHS review.

e) Will referral be utilized for recruitment? ☐ *Yes*
☒ *No*
If yes, please be aware patients should first be informed about the study and agree to the contact before any referral.

f) Will any other method be employed? ☒ *Yes* ☐ *No*
If yes, please specify, in detail, what those methods will be:
Patients will be identified as study subjects when they present to DHMC for consideration of pancreas surgery.
.

g) Does the research plan include "finder fees" or incentives (bonus payment, gift certificates) offered to study personnel for enrollment of participants? ☐ *Yes* ☒ *No*
Note: As a rule, finder fees or incentives are not acceptable. Please justify any offered incentives. If incentives become available during the course of the study, please notify the CPHS.

Attach copies of any proposed flyers, posters, pamphlets, print advertisements, and scripts for on-air advertisements or telephone calls. All recruitment materials should be approved by CPHS prior to use.

Note: Advertising should not use terms such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" implies that research participants will be receiving newly marketed products of proven worth. Advertisements should not promise "free medical treatment," when the intent is only to say participants will not be charged for taking part in the investigation. The CPHS will determine if the promise of treatment without charge is an inappropriate inducement for study participation. Advertisements may state that participants will be paid, but should not emphasize the payment or the amount to be paid. The advertisement should include: the name and address of clinical investigator and research facility; the condition under study or the purpose of the research; in summary form, the criteria that will be used to determine eligibility for the study; a brief list of participation benefits, if any (e.g., a no-cost health examination); the time or other commitment required of the participants; and the location of the research activities; and the person or office from whom to obtain further information.

26. *Consent Process:*

a) Informed Consent:

The Principal Investigator (PI) is responsible for ensuring all participants have provided informed consent to participate in this study unless the consent process is waived or altered by the CPHS. The PI may authorize other appropriately trained individuals to obtain consent from participants.

Please file the consent form in the medical record of each research participant if study participation may affect other medical treatment.

Explain how informed consent to research participation will be obtained. Please describe the consent process, including information about:

- *Who has been authorized by the PI to obtain consent*

- *The time interval between providing information potential participants about a study and having the consent form signed*
- *Any precautions taken to minimize the possibility of coercion or undue influence*
- *Plans for responding to a potential participant or a legally authorized representative who does not speak English, such as the use of a translator or a translated consent form*
- *Any aids used to simplify scientific or technical information, like a diagram*
- *Plans to accommodate the probable literacy level of potential participants*

Informed consent will be obtained by primary investigator in the clinic at the time of consent for surgery. Consent will be re-evaluated on day of surgery. We will use a translator for non English speakers and since the study is very simple, we will not use any aids. Literacy levels can be accommodated by having the consenting nurse or physician able to read the consent to the trial participants if necessary.

☐ *I intend to obtain consent for research participation but I am requesting a waiver for the use of a signed and dated consent form. Please respond to the criteria listed in* ***Attachment I*** *and include an information sheet based on the CPHS template.*

☐ *I am requesting an alteration of the consent process to exclude certain information that is ordinarily required. A list of the essential elements of consent to research participation is available on the CPHS website: http://www.dartmouth.edu/~cphs/tosubmit/ConsentElements.html. Please respond to* ***Attachment H.***

☐ *I am requesting a waiver of the entire consent process and use of a consent form. Please respond to* ***Attachment H.***

Explain why any alteration or waiver to the consent process or form is necessary.

b) Authorization: *Explain how an authorization for research use of protected health information (PHI) will be obtained. PHI is individually identifiable health information obtained from a health care provider or insurance plan. In general, the HIPAA Privacy Rule permits the use or disclosure of PHI for research purposes only with an authorization from each participant whose PHI will be involved. Only when certain criteria are satisfied can the CPHS grant a waiver of authorization or of the use of a signed and dated authorization form. A waiver of authorization is necessary for recruitment procedures when patient information is used to identify and contact potentially eligible research participants. A single form may combine the essential information for both consent and an authorization. The CPHS consent template contains this combination and is available on the CPHS website at www.dartmouth.edu/~cphs.*

Check all that apply:
☐ *This study does not involve PHI.*
☒ *A single form combining an authorization with the consent form and based on the CPHS template is included with this application.*
☐ *A separate authorization form is included with this application.*
☐ *I am requesting a waiver of authorization for only the recruitment procedure. Please respond to* ***Attachment H.***
☐ *I am requesting a waiver of signed and dated authorization. Please respond to* ***Attachment I.***
☐ *I am requesting a waiver of authorization for the use or disclosure of PHI in this entire study. Please respond to* ***Attachment H.***

In your explanation of the consent process above, please include information about obtaining authorization for the research use of PHI.

27. *Privacy and Confidentiality*:

Describe the plans to protect the privacy of subjects and maintain the confidentiality of the data.

Note: Under certain circumstances, an invasion of privacy or breach of confidentiality may present a risk of serious harm to subjects (e.g., as when the research obtains information about subjects that would, if disclosed by the researcher, jeopardize jobs or lead to prosecution for criminal behavior). Under other circumstances, an invasion of privacy or breach of confidentiality can be a moral wrong

a) *Will any study activities involve an interaction or reveal information for which protection of participant privacy is necessary?* ☐ *Yes* ☒ *No*
If yes, please identify the activities and describe the plan to protect the privacy of participants. For example, a plan for protection of privacy might consist of conducting the assent process for an adolescent minor in a private setting, rather than in the presence of the minor's parent.

b) *Will the data collected in the course of the study be considered sensitive, e.g., include information about a mental health disorder, HIV status, or SS#?* ☐ *Yes* ☒ *No*
If yes, provide the rationale for why these data are needed:

If yes, could any of these data, if disclosed, damage financial standing, employability, insurability, or reputation?
☐ *Yes* ☐ *No*
☐ *If yes, will a Certificate of Confidentiality be obtained? Yes* ☐ *No*

Any person engaged in research collecting information about illegal conduct from human research subjects may apply for a Certificate of Confidentiality. NIH provides detailed instructions for investigators wishing to make an application at http://grants.nih.gov/grants/policy/coc/index.htm.

c) *Describe specific physical, administrative, and technical safeguards employed to secure data, e.g., limitation of access to data, use of locked file cabinets, protection of computer-based data systems.* Data will be kept by one investigator (Dr. Gardner) on a password-protected hard drive that only he has access to. No other investigators will have access to this data.

d) *Will data that identify individual subjects be published or in any way be disclosed to third parties other than project personnel?*
☐ *Yes* ☒ *No*
If yes, please explain here and incorporate the information in consent form:

28. *Responsibility for costs of injury or illness related to research:*

Will the sponsor or other funding agency be responsible for costs of injury or illness related to the research?
☐ *Yes* ☒ *No*

If applicable, describe whether or not the sponsor will be responsible for investigational device removal if required:

If the sponsor or other funding agency will not be responsible for costs of injury or illness related to research, please complete:

a) *The reasons why the sponsor or funding agency is not accepting responsibility for research-related injury.*

All procedures for Secretin stimulation are standard of care

b) *Summary of risks as related to potential costs that could be incurred as a result of research-related injury or illness.*

The risk of using one dose of Secretin are extremely rare. Please see above.

c) *Describe reasons for requesting that DHMC or Dartmouth College provide coverage for research-related injury or illness, which is not standard policy.*

NA

29. *Participant Remuneration:*

Will participants be paid for their time, reimbursed for travel or meal expenses, or receive any sort of "gift" for participating in this study?

☐ *Yes* ☒ *No*

If yes, please describe in detail:

Note: Participant remuneration is not considered a benefit of being in a research study. CPHS will consider the amount of payment in relation to the time needed and any inconvenience to participants. Payment, reimbursement, or gifts should not be in an amount that would be coercive to the participant population.

If study is to be done at the VA, specific questions need to be answered if a participant is being paid "in excess of reimbursement for travel." Please contact the CPHS office if you need more information.

30. *Use of Drug or Biological Agent:*

Respond to items below or check x No drug or biological agent involved.

List the drugs and biologic agents to be used in this study: Secretin (0.2 mcg/kg) in a single dose

Is each drug or biological agent approved by the FDA for the specific indication for which it is used in this study?

Drug or Biologic Agent: ~~Secretin~~ ☐ *Yes* ☒ *No* **This drug is an FDA designated orphan drug "for use in conjunction with diagnostic procedures (excluding ERCP) for pancreatic disorders to increase pancreatic fluid secretions." In this study, secretin is being used under an IND granted to ChiRhoClin.**

Drug or Biologic Agent: _____ ☐ *Yes* ☐ *No*

If no, respond to a and b for each drug or biologic agent used for an unapproved indication:

a) *Briefly discuss the plan for the storage, dispensing, handling, and disposal of investigational and FDA-approved drugs, devices, and biologics. When these activities are being done by the investigator, include a description of the procedures for inventory control and documentation.*

DHMC Investigational Pharmacy is managing all study drugs.

☒ *Yes* ☐ *No*

If No please describe management plan below.

b) *Check and respond to one of the following statements for each drug or biologic agent:*
☒ *If this study is being done under an Investigational New Drug (IND) application to the FDA please provide: IND # (Investigational New Drug):* ***# 56821*** *and specify who holds the IND#:* ***ChiRhoClin, Inc.***

OR

☐ *If a drug or biologic agent or the combination of drugs or agents is not FDA approved for the indication for which it is used in this study, but an IND # has not been obtained, please* ***complete Attachment J***

31. ***Placebo vs. Standard Care:***
Does any part of the study involve use of a placebo or procedures that are inconsistent with the standard of care at DHMC?
☒ *Yes* ☐ *No*
If yes, respond to ***Placebo: Attachment B***

32. ***Medical Device:***
Respond to items below or check x No devices involved.

List the devices to be used in this study: NA

Is each device approved by the FDA for this indication?
Device: _____ ☐ *Yes* ☐ *No*
Device: _____ ☐ *Yes* ☐ *No*

If no or if FDA approval is pending, respond to a, b, and c for each device used for an unapproved indication.

a) *Is the device provided free of charge by the sponsor?* ☐ *Yes* ☐ *No*

b) *Where are the devices used in the study stored? Who controls their use?*

---

c) *Respond to (1), (2), (3), or (4)*

(1) *If this study is being done under an Investigational Device Exemption (IDE) from the FDA please provide: IDE#: #___ or check here if the IDE is pending:* ☐
Also check the FDA Device HCFA Reimbursement Category:
☐ *A* ☐ *B2* ☐ *B3*
Please note: CPHS will not approve a study before an IDE # has been received.

OR

(2) *If 510(k) notification for a device has been sent to FDA check here ☐ and either: provide a copy of the documentation verifying 510(k) clearance, or check here if 510(k) clearance is pending ☐.*

OR

(3) *If a device is exempt from IDE requirements, check here ☐ and provide a copy of a letter from the FDA or sponsor stating that the device is exempt from IDE requirements under 812.2(c).*

OR

(4) *If you are requesting a* ***nonsignificant risk*** *determination for a device from CPHS, please check here ☐ and complete* ***Attachment A****.*

Please note: The CPHS may approve, disapprove, or require modifications in a protocol that has been approved or cleared by the FDA.

33. *Conflict of Interest Review:*

Dartmouth College, Dartmouth-Hitchcock Clinic, and Mary Hitchcock Memorial Hospital have adopted a policy on Conflict of Interest in Human Subject Research. Copies of the policy are available on the Dartmouth College, Office of Sponsored Projects web site at http://www.dartmouth.edu/~osp/policies.html.

Definitions:

"Conflict of interest" occurs when an independent observer may reasonably question whether an individual's professional actions or decisions are influenced by considerations of the individual's private interests, financial or otherwise.

Conflicting financial interests do not include:

- *salary and benefits from Dartmouth College, Dartmouth-Hitchcock Clinic, and Mary Hitchcock Memorial Hospital;*
- *income from seminars, lectures, teaching engagements, or publishing sponsored by federal, state, or local entities, or from non-profit academic institutions, when the funds do not originate from corporate sources;*
- *income from service on advisory committees or review panels for governmental or nonprofit entities;*
- *investments in publicly-traded mutual funds;*
- *gifts and promotional items of nominal value; and*
- *meals and lodging for participation in professional meetings.*

"Principal investigator or other key personnel" means the principal investigator and any other person, including students, who is responsible for the design, conduct, analysis, or reporting of research involving human subjects.

Instructions:

To assist institutional review of the proposed research for conflicts of interest, please respond to the question below.

With regard to this proposed research study, does the principal investigator or other key personnel, or any of their spouses, domestic partners, or dependent children, hold a financial interest that would

reasonably appear to affect or be affected by the proposed study, including but not limited to the following interests?

a. *compensation for services (e.g., consulting fees or honoraria), or in-kind payments, other than from the researcher's primary employer, in the prior calendar year or projected over the next twelve months;*

b. *royalty income or the right to receive future royalties under a patent license or copyright, when the proposed research is directly related to the licensed technology or work;*

c. *equity interests (e.g., stocks, stock options or other ownership interests), including equity holdings where the value cannot readily be determined by reference to public prices;*

d. *intellectual property rights (e.g., patents and copyrights), and royalties from such rights;*

e. *gifts or funds available to the researcher from the sponsor of this study beyond the current project;*

f. *funding expected to significantly exceed the projected costs of conducting this study; or*

g. *another financial or private interest that may present a conflict of interest.*

*No: The Principal Investigator or other key personnel **do not** have any financial interests listed in a. -g. above.*

*x Yes: The Principal Investigator or other key personnel **do** have financial interests listed in items a. -g. above.*

***Only if you have answered yes to the question above** about study-specific financial interests for a member of the research team, please provide the following additional information.*

Name of each individual with a listed financial interest: Timothy Gardner

Each individual on the above list should complete a Conflict of Interest Disclosure Form for Human Subject Research. The disclosure should include only those financial interests that are specifically relevant to this research study.

The Conflict of Interest Disclosure Form for Human Subject Research is available on the CPHS website at the following url:

http://www.dartmouth.edu/~cphs/tosubmit/forms/

Please complete and sign the Conflict of Interest Disclosure Form for Human Subject Research form. In an envelope marked "Confidential", send the form to the Director of the Office of Sponsored Projects, using the following address:

CPHS/COI-HS, Hinman Box 6254.

Attachment B
Placebo or Procedures that are Inconsistent with the Standard of Care

Consider the ethical implications of using a placebo or procedures that are inconsistent with the standard of care in this study. Specifically, explain what "standard of care" therapy is for this participant population and how the use of placebo therapy may affect risks for participants. Also discuss:

a) the safety and efficacy of other available therapies (if any),
b) the maximum total length of time a participant may receive placebo on study,
c) the greatest potential harm that may come to a participant as a result of not receiving effective therapy (immediate or delayed onset), and
d) safeguards for the participants receiving placebo.

Required comment from the local research team specifically addressing a-d above and in addition to any justification included in the study protocol. Information copied directly from the protocol is not acceptable in this section:

At this time, in average risk patients, we are unclear of giving Secretin intra-operatively will allow better identification and repair of pancreatic duct leaks. The dug is used occasionally in high risk patients to evaluate for duct leaks and we would like to see if this drug is universally useful in all patients undergoing pancreatic surgery. The patient will only be included in the study from the time of their surgery to initial hospital discharge. The risk of not receiving therapy is that they may have a higher risk of duct leak (we will know better after the study). Patients receiving placebo will receive the same standard of care post-operatively than those receiving Secretin stimulation.
