Full Study Title:	A Phase II Trial of Pre-operative Endoscopic Botulinum Toxin Injection in the Prevention of Postoperative Pancreatic Fistula following Distal Pancreatectomy
Protocol Number:	IRB # 22619
ClinicalTrials.gov ID:	NCT04965311
Investigational Product:	Botulinum Toxin (OnabotulinumtoxinA; Botox)
Version Number:	2.0
Version Date:	10/2/2023
Replaces:	1.5
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SUMMARY OF CHANGES

#	Section	Summary of Changes	Justification
1	3.1, 11.4.5	Changed the protocol driven DSMC review to be done following the completion of the first **three** participant's safety evaluations periods (30 days following BTX injection or 30 days following surgery, whichever is longer). The study DSMC review was originally planned following the completion of 6 patients, however due to the slow study accrual we have revised it to be following the completion of three patients.	Clarification was requested by Knight DSMC.

SYNOPSIS

Full Study Title	A Phase II Study of Pre-operative Endoscopic Botulinum Toxin Injection in the Prevention of Postoperative Pancreatic Fistula following Distal Pancreatectomy
Protocol #	22619
Coordinating Center	OHSU, Knight Cancer Institute
Clinical Phase	Phase II - Single Agent
Study Description	Pancreatic resections are inherently morbid operations with complication rates of approximately 40%, the most feared of which is leakage of pancreatic digestive enzymes into the abdominal cavity, termed postoperative pancreatic fistula (POPF). POPF occurs in approximately 30% of distal pancreatectomies, and can dramatically alter the recovery pathway. Pre-operative endoscopic botulinum toxin (BTX) injection into the Sphincter of Oddi has been hypothesized to reduce the rate of POPF following distal pancreatectomy. The present study is a single-arm Phase II interventional study investigating the use of endoscopic botulinum toxin injection into the Sphincter of Oddi prior to distal pancreatectomy to prevent POPF. Intervention will occur 7-14 days prior to planned distal pancreatectomy, and further data collection/treatment will occur per standard of care. Safety of the intervention will be assessed, and patients will be compared to matched historical patients for analysis of POPF rates.
Primary Objective	To determine the effect of pre-operative endoscopic BTX injection on clinically relevant POPF rates following distal pancreatectomy
Secondary Objectives	1) To determine the safety of pre-operative endoscopic BTX injection 2) To determine the effect of pre-operative endoscopic BTX injection on the rate of all POPF (biochemical and clinically relevant) following distal pancreatectomy
Exploratory Objectives	To evaluate differences in: 1) crPOPF, 2) POPF, 3) postoperative length of hospital stay, 4) rate of Clavien-Dindo grade III or greater complications, 5) rate of percutaneous drainage, 6) rate of unplanned re-operation, using a historical population matched for potential confounding clinicopathologic variables.
Primary Endpoint	Rate of clinically relevant POPF (crPOPF) in intervention group
Secondary Endpoints	1) Rate of serious adverse events following endoscopic BTX injection (e.g., clinical pancreatitis, bleeding, perforation, or other events delaying time to surgery or receipt of surgery) 2) Rate of any POPF in intervention group
Exploratory Endpoints	1) Clinically relevant POPF (binary) 2) Any POPF (binary)

	3) Postoperative Length of Hospital Stay (continuous) 4) Clavien-Dindo III or greater postoperative complications (binary) 5) Rate of percutaneous drainage procedure (binary) 6) Rate of unplanned re-operation (binary)
Key Inclusion Criteria	1. Patient scheduled for elective distal pancreatectomy or radical antegrade modular pancreatosplenectomy (RAMPS), via open or laparoscopic technique 2. Participant aged ≥ 18 years 3. Ability to understand nature and individual consequences of clinical trial 4. Written informed consent 5. For participants of childbearing potential, a negative pregnancy test and adequate contraception until 14 days after trial intervention
Key Exclusion Criteria	1. Known hypersensitivity to any BTX preparation or to any of the components in the formulation 2. Infection at the proposed injection site, including cholangitis 3. Anatomy incompatible with planned intervention (e.g., Roux-en-Y gastric bypass, distal gastrectomy with Roux-en-Y or Billroth II reconstruction) 4. Acute pancreatitis within 2 weeks of planned study intervention 5. Pancreas divisum 6. ASA score > III 7. Serious cardiovascular disease (e.g., Myocardial infarction in the past year, NYHA III/IV congestive heart failure, unstable angina). 8. Creatinine clearance <30mL/min 9. Liver cirrhosis (of any Child-Pugh grade) 10. Neuromuscular or any neurological disease with associated increased risk for a participant undergoing BTX injection 11. Prior BTX administration 12. Inability to obtain informed consent from participant or legally authorized representative. 13. Inability to comply with study and/or follow-up procedures 14. Pregnancy or lactation 15. Any condition that could result in undue risk for the participant and/or influence outcome measures (in the opinion of the investigator)
Number of Participants	Up to 64 participants will be consented. Up to 55 patients will undergo the study intervention such that 50 patients will undergo the study intervention and complete 30-day postoperative follow-up.

Duration of Therapy	A one-time endoscopic injection of BTX with no further study interventions
Duration of Follow Up	Up to 30 days following distal pancreatectomy.
Description of Study Intervention	Preoperative endoscopy with Sphincter of Oddi BTX injection will be the only trial-related intervention for patients participating in this trial. All the other procedures, including assessment of laboratory parameters, belong to the standard perioperative and postoperative procedures performed in patients undergoing distal pancreatectomy. In patients with childbearing potential, a pregnancy test will be performed during the routine preoperative laboratory examinations.
Statistical Analyses	This is a single arm, open-label, Phase II study to estimate the rate of clinically relevant POPF in participants that receive pre-operative endoscopic BTX injection. Using a Simon's 2-stage, a total of 50 evaluable participants will achieve an 88% power to detect a difference in crPOPF rate of 9.2% (H0: $\pi = 0.112$ versus Ha: $\pi = 0.02$; with a one-sided alpha level of 0.05). The trial will be continued following stage 1 if there is one or fewer crPOPF among the first 25 participants. If the study proceeds to stage 2, a total of 50 participants will be evaluated towards the primary endpoint, and the intervention considered promising if there are two or fewer cases of crPOPF.

SCHEMATIC OF STUDY DESIGN

	BTX Injection		Surgery and Postoperative Period				
Procedure	**Day 1**	**Day 7-14 (Pre-operative Medicine Appointment)***	**Day 1 (Day of Surgery)**	**Day 4 (Postoperative Day 3)**	**Day of Discharge**	**Discharge + 7-14 Days (Post-Operative Follow-up)**	**Day 30**
Physical exam	X		X*	X*	X*	X*	
Vital signs[1]	X	X*	X*	X*	X*	X*	
ECG (if indicated)		X*	X*				
Routine blood draw[2] (1 tablespoon)		X*	X*	X*			
Drain Fluid Analysis				X*			
Pregnancy test (if indicated)	X	X*	X*				
Review any adverse events		X	X				X
Review all other medications	X	X	X				
BTX Injection	X						
Distal Pancreas Resection			X*	X*			
IN THE EVENT OF OPERATIVE DELAYS, PATIENTS STILL EVALUABLE FOR EFFICACY IF RECEIVING SURGERY UP TO 28 DAYS FROM BTX INJECTION. A PRE-OPERATIVE MEDICINE APPOINTMENT PRIOR TO BTX INJECTION IS GENERALLY NOT NEEDED, BUT MAY BE REQUESTED FOR SOME PATIENTS DEPENDING ON HEALTH STATUS AND CLINICIAN DISCRETION							

* Interventions/monitoring per standard of care

[1] Can include heart rate, blood pressure, height, weight, oxygen saturation, temperature

[2] Can include CBC with differential, chemistry, magnesium, uric acid

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LIST OF ABBREVIATIONS

AE	Adverse event
ASA	American Society of Anesthesiologists
BTX	Botulinum Toxin
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRC	Clinical Research Coordinator
CRMS	Clinical research management system
crPOPF	Clinically-relevant postoperative pancreatic fistula
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG, EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FDA	United States Food and Drug Administration
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IND	Investigational new drug application
IRB	Institutional Review Board
ISGPF	International Study Group of Pancreatic Fistula
IV	Intravenous
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
NYHA	New York Heart Association
NSQIP	National Surgical Quality Improvement Project
OHSU	Oregon Health & Science University
PDAC	Pancreatic Ductal Adenocarcinoma
PI	Principal Investigator
PO	*Per os* (by mouth, orally)
POPF	Postoperative pancreatic fistula
RAMPS	Radical antegrade modular pancreatosplenectomy
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SNAP	Soluble N-ethylmaleimide sensitive fusion protein
SNARE	Soluble N-ethylmaleimide sensitive fusion protein receptors
TSMP	Trial Specific Monitoring Plan
ULN	Upper limit of normal
UP	Unanticipated Problem
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND

Over 50,000 new cases of pancreatic cancer are diagnosed in the United States each year,[1] with 96% being pancreatic ductal adenocarcinoma (PDAC).[2] PDAC carries a dismal prognosis with an overall 5-year survival of 7.2%,[2] however patients with resected disease can achieve 5-year survival rates of up to 30%.[3] Pancreatic resections are inherently morbid operations with complication rates of approximately 40%; one of the most feared complications by clinicians and patients is leak of pancreatic digestive enzymes from the cut pancreas into the abdominal cavity, termed a postoperative pancreatic fistula (POPF).

POPF occurs in approximately 13% of pancreaticoduodenectomies and up to 30% of distal pancreatectomies,[4] and can dramatically alter the recovery pathway. In pancreatic cancer, major postoperative complications (including POPF) are associated with non-receipt and delays to adjuvant chemotherapy, significantly reducing long-term survival following a curative-intent resection.[5] Interventions to reduce the rate of POPF therefore have the potentially to dramatically improve both short and long-term outcomes in patients undergoing distal pancreatectomy.

One proposed mechanism for POPF following distal pancreatectomy is that the Sphincter of Oddi, which normally regulates the flow of pancreatic secretions into the intestine, continues to serve as a barrier and acts like a dam, promoting pancreatic fluid exit from the cut edge of the pancreas, causing a POPF. Pre-operative endoscopic injection of botulinum toxin (BTX) into the Sphincter of Oddi has been suggested to lower the rate of POPF after distal pancreatectomy,[6] as paralyzing the muscle theoretically removes this resistance and would promote normal flow of pancreatic fluids into the duodenum until healing is complete. These results have not been uniformly reproduced, with one study performing BTX injection at a median of 1 day pre-operative not demonstrating a difference in POPF rates, possibly due to the delayed onset of BTX efficacy[7, 8] Additionally, this intervention has never been studied in an American population, though a randomized trial is accruing patients in Europe.[9] Of note, endoscopic BTX injection into the Sphincter of Oddi has previously been shown to be efficacious for abdominal pain resulting from Sphincter of Oddi dysfunction[10, 11] and post-cholecystectomy biliary pain[12], suggesting that the paralysis afforded by BTX can be therapeutic.

Endoscopic BTX administration is an innovative method to reduce POPF, as previously investigated strategies for POPF prevention have primarily been either intraoperative (such as absorbable mesh placement[13]) or postoperative medication-based interventions (such as pasireotide or hydrocortisone).[14, 15] Additionally, while external pancreatic duct stenting has shown efficacy in preventing POPF in patients undergoing pancreaticoduodenectomy[16], prophylactic endoscopic stenting and sphincterotomy has not been well-studied in the prevention of POPF following distal pancreatectomy[17], though prospective trials are accruing (NCT03314337). Importantly, sphincterotomy and instrumentation of the pancreatic duct during stent placement imparts a higher risk of acute pancreatitis than BTX administration, which does not instrument the duct itself.

In short, the present study represents a novel application of an established technique, and may have a significant positive impact on clinical practice by improving the perioperative care and outcomes of patients undergoing distal pancreatectomy. In the case of pancreatic cancer, a reduction of POPF rates may translate to higher receipt and fewer delays to adjuvant chemotherapy and improved survival.

1.1.1 OVERVIEW OF STUDY TERMS

Distal Pancreatectomy. Distal pancreatectomy (removal of the distal pancreas +/- spleen) is indicated in nonmetastatic PDAC, and other neoplasms when disease is localized in the pancreatic tail, as well as in certain patients with chronic pancreatitis.[18] A variant technique of distal pancreatectomy, termed radical antegrade modular pancreatosplenectomy (RAMPS) is often used specifically for malignancies of the pancreas.[19] Pancreatic surgery is technically difficult and highly morbid, with POPF being the most feared complication by clinicians and patients.

Postoperative Pancreatic Fistula (POPF). POPF results when digestive enzymes normally secreted by the pancreas leak into the abdominal cavity following an operation, leading to a wide range of inflammatory and auto-digestive complications. POPF is defined by the International Study Group of Pancreatic Fistula (ISGPF) as an amylase level obtained from drainage fluid or abscess of greater than three times the upper limit of normal, starting from the third postoperative day (POD3).[20, 21] POPF is further classified by the ISGPF into biochemical leaks (asymptomatic elevations in amylase from surgical drain fluid that do not require additional treatment), Grade B POPF (requiring percutaneous or endoscopic drainage), or Grade C POPF (resulting in organ failure); together, Grades B/C constitute clinically-relevant POPF (crPOPF). Rates of POPF following distal pancreatectomy range from 20-50% with an average of 30%,[22, 23] with a 10-year average of at OHSU of 30.9% for all POPF and 11.3% for crPOPF.

Sphincter of Oddi. The Sphincter of Oddi is a smooth muscle valve located at the Ampulla of Vater that regulates the flow of bile and pancreatic secretions into the duodenum.[24] Following distal pancreatectomy, the resting muscle tone of the Sphincter of Oddi may act as a dam, causing the "path of least resistance" for pancreatic secretions to be the cut edge of the pancreas, resulting in POPF as secretions exit into the abdominal cavity and cause and intense autodigestive and inflammatory reaction.

1.1.2 OVERVIEW STUDY INTERVENTION(S)

Botulinum Toxin (BTX). BTX is a neurotoxin produced by the bacterium *Clostridium botulinum,* which secretes eight exotoxins, (A, B, C(1), C(2), D, E, F, G), all of which block the release of acetylcholine (the primary neurotransmitter at the neuromuscular junction) by cleaving soluble N-ethylmaleimide sensitive fusion protein (SNAP) Receptors (SNARE), leading to muscle paralysis.[25] A commercial formulation of BTX (onabotulinumtoxinA; Botox) has been used for decades with great efficacy in multiple conditions, including strabismus, dystonias, spastic movement disorders, headaches, hyperhidrosis, as well as innumerable cosmetic applications such as reducing the prominence of wrinkles.[25, 26] BTX has an excellent safety profile, with one systematic review of 36 randomized controlled trials noting no serious adverse events.[27]

Botulinum Toxin Injection to Sphincter of Oddi: Endoscopic injection of BTX into the lower esophagus is a well-described and FDA-approved treatment for achalasia, and BTX injection into the Sphincter of Oddi is a well-described treatment for Sphincter of Oddi Dysfunction.[10, 11, 28] Injection of BTX into the sphincter of Oddi (**Figure 1)** performed a median of 6 days prior to distal pancreatectomy reduced POPF rates,[6] but not when performed at a median of one day pre-operatively.[7] This is suspected to be due to the fact that BTX reaches maximal paralytic efficacy at one week.[8]

Figure 1: Botulinum Toxin Mechanism and Endoscopic Injection Method

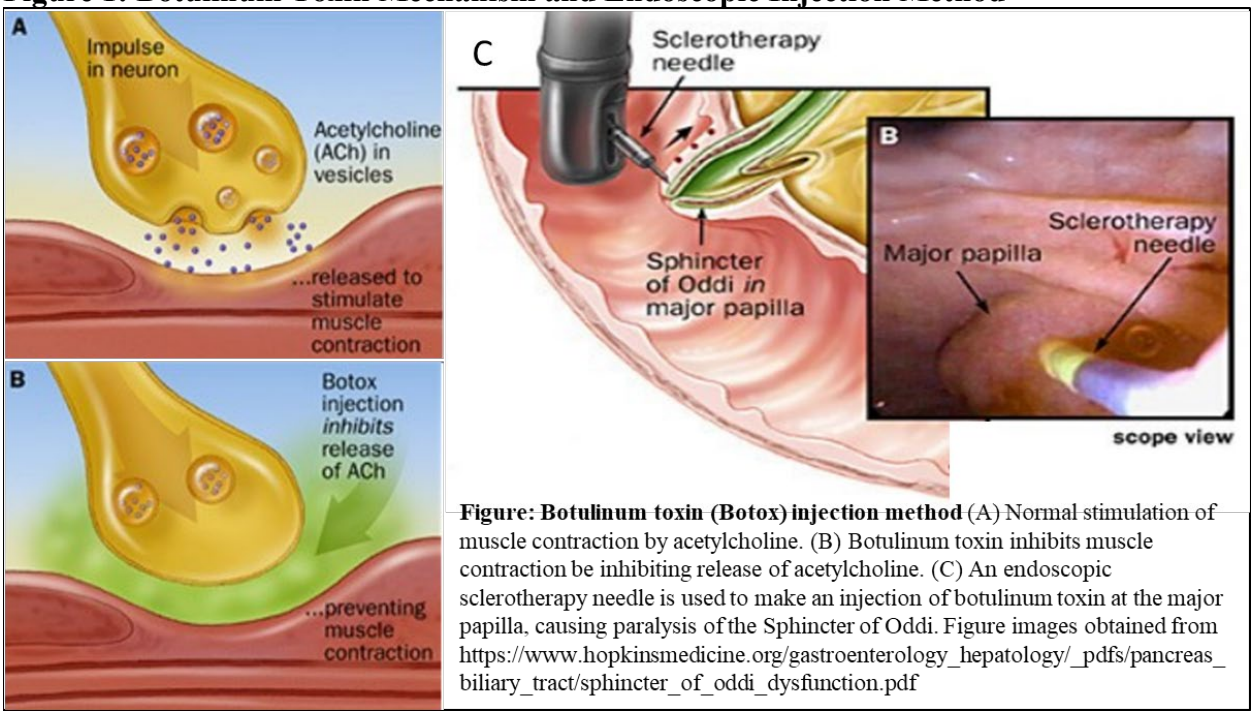

Figure: Botulinum toxin (Botox) injection method (A) Normal stimulation of muscle contraction by acetylcholine. (B) Botulinum toxin inhibits muscle contraction be inhibiting release of acetylcholine. (C) An endoscopic sclerotherapy needle is used to make an injection of botulinum toxin at the major papilla, causing paralysis of the Sphincter of Oddi. Figure images obtained from https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/pancreas_biliary_tract/sphincter_of_oddi_dysfunction.pdf

1.2 STUDY RATIONALE

The overall objective of this application is to establish the preliminary efficacy and safety of Sphincter of Oddi BTX injection in the prevention of POPF in the setting of a phase II clinical trial. The central hypothesis is that BTX injection is both safe and efficacious in the prevention of POPF. The rationale for this study is that prevention of POPF would enhance postoperative recovery and quality of life in patients undergoing distal pancreatic resections. These results are expected to have a significant positive impact on clinical practice by improving the perioperative care of patients undergoing distal pancreatectomy for pancreatic cancer and other nonmalignant conditions.

1.3 RISK/BENEFIT ASSESSMENT

1.3.1 KNOWN POTENTIAL RISKS

Botulinum toxin (onabotulinumtoxinA; Botox) has been used for decades with great efficacy in multiple conditions.[25, 26] BTX has an excellent safety profile, with one systemic review of 36 randomized controlled trials noting no serious adverse events, with focal weakness at/around the injection site being the only mild-moderate adverse event that occurred more often than controls, which is not a relevant risk for endoscopic injection.[27] Post-marketing reports indicate that the effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties, depending on the site of injection. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

In cases of endoscopic BTX injection, side-effects apart from asymptomatic serum lipase elevations or mild pancreatitis have not been previously reported when administered for Sphincter of Oddi dysfunction[10, 11], post-cholecystectomy biliary pain[12], or for prevention of POPF.[6, 7]

Risks specific to endoscopy represent additional study-related risks, and include postinterventional pancreatitis defined by the Atlanta criteria which includes two of the following: 1) abdominal pain consistent with acute pancreatitis; 2) serum lipase > 3 ULN; 3) characteristic imaging findings).[29] Rare risks with the upper endoscopy procedure include cardiopulmonary compromise with procedural sedation, intraprocedural hemorrhage, and bowel perforation.[30]

1.3.2 KNOWN POTENTIAL BENEFITS

Immediate potential benefits include a reduced risk of POPF per other studies, which may result in shorter hospital stay and quicker postoperative recovery on average. Long-term potential benefits include the possibility of a higher chance of receiving life-prolonging adjuvant chemotherapy with the avoidance of POPF (due to the study intervention), which would otherwise have delayed or disqualified a patient from adjuvant chemotherapy.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Primary Objective	Endpoint	Start	End
Evaluate the efficacy of pre-operative BTX injection compared to no therapy for the prevention of clinically relevant	Rate of clinically relevant (Grade B and Grade C) POPF following distal pancreatectomy/RAMPS,	Day of Surgery	Postoperative Day 30

POPF	defined by standard biochemical definitions of POPF per the ISGPF criteria		

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary Objective	Endpoint	Start	End
Evaluate the safety of pre-operative BTX injection into the Sphincter of Oddi	Rate of serious adverse events following BTX injection defined as: pancreatitis requiring hospitalization, gastrointestinal hemorrhage or perforation, other events delaying time to surgery or receipt of surgery, or grade 3 or higher AEs attributable to BTX	Day of study intervention	30 days following surgery or study intervention or until date of surgery
Evaluate the efficacy of pre-operative BTX injection compared to no therapy for the prevention of all POPF	Rate of any POPF following distal pancreatectomy/RAMPS, defined by standard biochemical definitions of POPF per ISGPF criteria	Day of Surgery	Postoperative day 30

2.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory Objective	Endpoint	Start	End
Using a historical population matched for potential confounding clinicopathologic variables, evaluate differences in POPF,	Rate of POPF	Day of Surgery	Postoperative Day 30
Using a historical population matched for potential confounding clinicopathologic variables, evaluate differences in crPOPF.	Rate of crPOPF	Day of Surgery	Postoperative Day 30
Using a historical population	Postoperative length of	Day of Surgery	Postoperative

matched for potential confounding clinicopathologic variables, evaluate differences in postoperative length of hospital stay.	hospital stay		Day 30
Using a historical population matched for potential confounding clinicopathologic variables, evaluate differences in rate of Clavien-Dindo grade III or greater complications	Clavien-Dindo grade III or greater complications	Day of Surgery	Postoperative Day 30
Using a historical population matched for potential confounding clinicopathologic variables, evaluate differences in rate of percutaneous drainage,	Postoperative percutaneous drainage	Day of Surgery	Postoperative Day 30
Using a historical population matched for potential confounding clinicopathologic variables, evaluate differences in rate of unplanned re-operation.	Unplanned re-operation	Day of Surgery	Postoperative Day 30

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 11*, Statistical Analysis for additional information regarding statistical methods used in this study.*

This is a Phase II, open-label study to estimate the rate of crPOPF in patients that receive pre-operative endoscopic BTX injection into the sphincter of Oddi as a single agent prior to undergoing distal pancreas resections. The study design consists of a single arm intervention group (n=50) with comparison to historical rates for crPOPF. BTX injection will occur 7-14 days before the planned date of surgery as an outpatient endoscopic procedure. Thereafter, participants will receive all surgery and postoperative treatment in accordance with institutional standards.

The trial will commence with the enrollment of the first six patients for a safety-run in of the endoscopic BTX injection technique. During the safety run-in, the PI will evaluate patient safety outcomes including grade 3 or higher adverse events. Additionally, the study will be evaluated by the DSMC following the completion of the first three participant's safety evaluation periods (30 days following BTX injection or 30 days following surgery, whichever is longer). Progressive study enrollment will continue throughout the safety run-in, and enrollment will be halted if recommended by the DSMC after completion of the run-in. If 2 or more of the first 6 participants enrolled experience delay in planned surgery ≥ 14 days (due to significant GI hemorrhage, perforation, or adverse reaction to BTX) or pancreatitis requiring hospitalization,

then the study will be halted for safety. A total of 25 patients will be enrolled prior to a planned interim analysis for the primary endpoint of interest (crPOPF). If sufficient number of participants have experienced crPOPF (2 or greater), the trial will be prematurely terminated. If the interim analysis does not result in study termination, enrollment of the remaining participants will resume to enroll a total of 50 patients completing study intervention and follow-up.

The study schedule will be divided into 2 periods: (1) the post-treatment period which starts at the time of BTX injection and ends on the day of surgery (2) the postoperative period which begins at the time of surgery and ends 30 days postoperatively.

In addition to comparing study patients with the historical rate of POPF, exploratory analysis will be performed by matching study patients with historical patients on relevant clinicopathologic characteristics that are associated with risk of POPF. Historical controls are appropriate, as the study could not be completed in a timely and cost-efficient manner with prospective enrollment of both study groups. Additionally, many surgeons involved in the present study would not support enrollment of a placebo group as many currently utilize preventive medications such as pasireotide or hydrocortisone.

At the completion of the proposed study, the expected outcomes are to have evaluated the safety and efficacy of pre-operative BTX administration in the prevention of POPF.

3.2 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events (Section 7.11).

3.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification that documents the reason for study suspension or termination will be provided by the suspending or terminating party to OHSU Coordinating Center, local IRB, and other regulatory authority (if required). If the study is prematurely terminated or suspended, the Investigator must promptly inform the IRB and provide the reason(s) for the termination or suspension. The OHSU Coordinating Center will notify sub-site(s) of any study suspension or discontinuation.

Reasons for terminating the study may include the following:

- Unfavorable assessment of risk/benefit ratio
- Incidence or severity of adverse events, in this or other studies, that indicates a potential health hazard to participants
- Demonstration of lack of efficacy that warrants stopping
- Data that are not sufficiently complete and/or evaluable
- Investigator not adhering to the study protocol or applicable regulatory guidelines in conducting the study
- Participant enrollment is unsatisfactory
- Submission of knowingly false information from the study site to OHSU Coordinating Center or regulatory authority
- Upon instruction by local or other regulatory or oversight authority.

The study may resume once concerns about safety, protocol compliance, and/or data quality are addressed as applicable and requirements of the OHSU Coordinating Center, funder, IRB and/or

other applicable regulatory authority are satisfied.

4. STUDY POPULATION

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all following criteria:

1. Participant scheduled for elective distal pancreatectomy or radical antegrade modular pancreatosplenectomy (RAMPS), via open or laparoscopic technique
2. Participant ≥ 18 years of age
3. Ability to understand nature and individual consequences of clinical trial
4. Written informed consent from participant or legally authorized representative.
5. For participants of childbearing potential, a negative pregnancy test and adequate contraception until 14 days after trial intervention

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Known hypersensitivity to any BTX preparation or to any of the components in the formulation
2. Infection at the proposed injection site, including cholangitis
3. Anatomy incompatible with planned intervention (e.g., Roux-en-Y gastric bypass, distal gastrectomy with Roux-en-Y or Billroth II reconstruction)
4. Acute pancreatitis within 2 weeks of planned study intervention
5. Pancreas divisum
6. ASA score > III
7. Serious cardiovascular disease (e.g., Myocardial infarction in the past year, NYHA III/IV congestive heart failure, unstable angina).
8. Creatinine clearance <30mL/min
9. Liver cirrhosis (of any Child-Pugh grade)
10. Neuromuscular or any neurological disease with associated increased risk for a participant undergoing BTX injection
11. Prior BTX administration
12. Inability to obtain informed consent due to comprehension or language barrier.
13. Inability to comply with study and/or follow-up procedures
14. Pregnancy or lactation
15. Any condition that could result in undue risk for the participant and/or influence outcome measures (in the opinion of the investigator)

4.3 LIFESTYLE CONSIDERATIONS

During this study, participants are not asked to modify lifestyle or diet apart from standard of care peri-procedural measures prior to upper endoscopy or distal pancreatic resection.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will be conducted in the United States. Participants for this study will primarily be recruited from surgical clinics within OHSU, but additional collaborative study sites may also be invited to participate in this trial. Participants may be identified and referred to this study by their primary treating physician from within OHSU/CHO, collaborating study sites, or from the outside community. Participants may be identified by a member of the participant's treatment team, the PI, research team, or medical and surgical oncology clinics part of OHSU/CHO or collaborating study sites. As a member of the treatment team, the investigator(s) will screen their participant's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Referral of potential participants to investigator(s) of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of the participant's malignancy.

The investigator(s) may also screen the medical records of potential participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of participating in the study. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

In the event of an insufficient rate of accrual at OHSU, additional patients undergoing distal pancreas resections at Legacy Good Samaritan will be enrolled. If accrual remains insufficient, patients undergoing distal pancreas resection at Providence Portland will be enrolled. Should either of these events occur, a modification to the study protocol will be submitted and approved prior to enrollment of patients at sites outside of OHSU.

4.4.1 ACCRUAL ESTIMATES

Total accrual of all participants is anticipated to take a total of 36 months.

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

Table 1. Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**				
	Females		Males		Total
Hispanic or Latino		6.6		6.5	13.1
Not Hispanic or Latino		43.8		43.1	86.9
Ethnic Category: Total of all participants*					100*
Racial Category					
American Indian or Alaskan Native		0.9		0.9	1.8
Asian		2.4		2.3	4.7

Table 1. Population Demographics - Oregon (%)

Ethnic Category	Sex/Gender				
	Females		Males		Total
Black or African American		1.1		1.1	2.2
Native Hawaiian or other Pacific Islander		0.2		0.2	0.4
White		43.9		43.2	87.1
Two or more races		1.9		1.9	3.8
Racial Category: Total of all participants*					100*
TOTALS		50.4		49.6	100*
Source: Adapted from U.S. Census Bureau, 2017. *Totals may not equal 100 due to rounding.					

Table 2. Projected Accrual for the Present Study

Prospective Cohort:

Ethnic Category	Sex/Gender			
	Females	Males	Other/Unknown	Total
Hispanic or Latino	4	4	0-1	6
Not Hispanic or Latino	26	26	0-1	44
Unknown	0-1	0-1	0-1	0
Ethnic Category: Total of all participants*	30-31	30-31	0-3	63
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0-1	0-3
Asian	1	1	0-1	2-3
Black or African American	1	1	0-1	2-3
Native Hawaiian or other Pacific Islander	0-1	0-1	0-1	0-3
White	27	27	0-1	54-55
More than one race	1	1	0-1	2-3
Unknown	0-1	0-1	0-1	0-3
Racial Category: Total of all participants*	30-31	30-31	0-7	63
Source: Adapted from U.S. Census Bureau, 2017. *Totals may not equal 100 due to rounding.				

While malignant histology or chronic pancreatitis are associated with lower odds of crPOPF in proximal pancreas resections, this has not been shown to be the case for distal pancreas resections.[23] Nevertheless, we will attempt to enroll an approximately equal proportion of patients with PDAC or chronic pancreatitis as the operative indication as historical patients at OHSU (130 of 353 distal pancreas resections since 2011, 37%). Due to the lack of evidence that this impacts crPOPF in distal pancreatectomy, however, no enrollment thresholds will be set.

4.4.2 INCLUSION OF CHILDREN

This protocol does not include children for the following reason:

1. The number of children with this type of cancer/condition is limited

5. PARTICIPANT SCREENING, ENROLLMENT, AND WITHDRAWAL

This is a single-arm phase II clinical trial (without randomization).

Each individual that consents to participate in this study must be entered into OHSU's electronic clinical research information system, eCRIS, regardless of Screening outcome.

5.1 CONSENT AND SCREENING

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current IRB approved informed consent form must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study. The informed consent discussion must be documented, and a copy of their signed IRB approved informed consent form must be scanned in the participant's medical record.

Each site must maintain a screening log of all participants who are approached for the study, as well as source documentation related to the consent and screening outcome for each, including an explanation for exclusion due to screen failure where applicable. Each site is required to retain, in a confidential manner, sufficient information on each participant so that the participant may be contacted should the need arise.

5.1.1 SCREENING PERIOD

The screening period begins once the participant has provided written informed consent to participate in the study and ends once BTX injection is initiated. All screening and baseline evaluations will be performed during the screening period. Day 1 of the clinical trial will be when participants are started on the study intervention.

5.1.2 RE-TESTING DURING SCREENING

Re-testing of laboratory parameters and/or other assessments within the Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Enrollment is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments may be repeated in an effort to find all possible well-qualified participants. Consultation with the Principal Investigator may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 ENROLLMENT PROCEDURES

This is a Phase II trial, and there is no randomization for treatment.

5.2.1 ENROLLMENT PROCEDURES FOR THE OHSU SITE

Eligibility must be confirmed and documented by the Principal Investigator prior to enrollment.

Materials required to complete the eligibility review include, at minimum:

- Current IRB-approved consent form and HIPAA Authorization for the study signed & dated by the participant
- Documented (signed and dated) attestation by the PI confirming participant's eligibility based on available source documentation and authorizing enrollment
- Endoscopic evaluation at the time of planned study intervention to verify anatomic eligibility for BTX injection

Once eligibility is confirmed, the participant is considered 'enrolled' once study intervention is performed.

5.2.2 ENROLLMENT PROCEDURES FOR SUB-SITES

The OHSU Coordinating Center oversees the participant enrollment process for all sub-sites.

When a potential participant is identified, a sub-site must notify the Coordinating Center of their intent to consent and screen the individual for study participation. The Coordinating Center will inform the site in writing whether or not they may proceed.

The sub-site investigator, or study team designee, must send source documents that support eligibility to OHSU for review and verification before the sub-site may enroll the participant.

- Current IRB-approved consent form and HIPAA Authorization for the study signed & dated by the participant;
- Completed eligibility checklist signed and dated by the site investigator or designee; and
- Source documents that support eligibility.

The OHSU Coordinating Center team is responsible for verifying completeness of documents, entering participant information into OHSU's clinical research information system (eCRIS), and assigning a study number/identifier for each individual participant. The Coordinating Center will notify the sub-site in writing to indicate whether or not a participant is eligible and will assign a participant number/identifier.

Once the OHSU Coordinating Center confirms a subject's eligibility, the participant is considered 'enrolled' and study intervention may begin. If the OHSU Coordinating Center deems the participant ineligible, this participant is considered a screen failure.

For any participant deemed locally by the sub-site as a screen failure, the sub-site must still provide sufficient documentation to the Coordinating Center for entry into eCRIS.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a failing to meet eligibility criteria may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

Any participant that has signed the consent form (for either screening or study participation) but does not meet all of the study eligibility criteria, or meets study eligibility criteria but terminates their participation prior to receiving study treatment, will be considered a screen failure and not counted towards total number of planned enrollments. The reason for screen failure should be captured in the research record for each participant who fails to meet all of the eligibility criteria.

5.3.1 RE-SCREENING ALLOWANCE / PROCEDURES

This study permits the re-screening of a participant that has discontinued the study as a screen failure (i.e., participant has not been treated). If re-screened, the participant must be re-consented.

5.4 PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. If a participant no longer wants to receive investigational product, but is willing to come for follow-up appointments, the participant's request should be honored, if possible.

If a participant withdraws consent, they should be asked to specify if they are withdrawing consent to all further participation in the study, including any further follow up (e.g., survival contact telephone calls) or if they are choosing to withdraw only from further study intervention, meaning that further follow-up and data collection about their disease and health status is allowable. The participant should also be asked about their consent to the future use of their study-generated data and any biological samples, as applicable.

No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation and collection of any new or ongoing AEs should be collected at the time the participant withdraws consent.

A participant may also be withdrawn from the study by the Sponsor/Sponsor-Investigator, Investigator, local IRB, or regulatory authorities.

Reasons for a participant to discontinue the study may include the following:

- Participant dies or is lost to follow-up
- Participant withdraws consent for any further participation
- The end of study is reached
- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

In the event of a pregnancy, the study treatment will not be administered. Refer to Section 10.6.5 regarding reporting of pregnancy. Participants who withdraw or discontinue after receiving study intervention count towards the enrollment total.

5.4.1 HANDLING PARTICIPANT DISCONTINUATION FROM STUDY

When a participant discontinues participation in the study, the reason the participant is no longer participating, the study name, IRB study number, and the date of discontinuation must be documented in the participant's medical record. The change in study status must be documented in the appropriate clinical trial management system (e.g., eCRIS) per OHSU policy.

For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 8, STUDY PROCEDURES/EVALUATIONS AND SCHEDULE.

Participants enrolled in this study who withdraw prior to initiating their treatment will be replaced.

Participants who sign the informed consent form, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study prior to undergoing planned pancreatic surgery will count towards enrollment totals
.

5.5 LOST TO FOLLOW-UP

A participant will be considered "lost to follow-up" if the participant:

1. Undergoes BTX injection and does not present for planned surgical intervention and is unable to be contacted by study staff for 30 days following BTX injection
2. Undergoes BTX injection and planned surgical intervention, but does not present for planned post-operative follow-up appointment and is unable to be contacted by study staff for 30 days following postoperative hospital discharge.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within two weeks, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if

necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6. STUDY INTERVENTION

A list of the adverse events and potential risks associated with the study intervention administered in this study can be found in Section 10.4, Adverse Events.

6.1 ONABOTULINUMTOXINA

6.1.1 STUDY INTERVENTION DESCRIPTION

Botulinum Toxin (BTX). BTX is a neurotoxin produced by the bacterium *Clostridium botulinum,* which secretes eight exotoxins, (A, B, C(1), C(2), D, E, F, G), all of which block the release of acetylcholine (the primary neurotransmitter at the neuromuscular junction) by cleaving soluble N-ethylmaleimide sensitive fusion protein (SNAP) Receptors (SNARE), leading to muscle paralysis.[25] BTX (onabotulinumtoxinA; BTX) has been used for decades with great efficacy in multiple conditions, including strabismus, dystonias, spastic movement disorders, headaches, hyperhidrosis, as well as innumerable cosmetic applications such as reducing the prominence of wrinkles.[25, 26] BTX has an excellent safety profile, with one systematic review of 36 randomized controlled trials noting no serious adverse events.[27]

6.1.2 ACQUISITION

OnabotulinumtoxinA (BTX) will be obtained from OHSU research pharmacy services. Where possible, a single manufacturer of generic BTX (Allergan, Dublin, Ireland) will be used throughout the conduct of this trial. However, BTX may be sourced from alternative manufacturers.

6.1.3 FORMULATION, APPEARANCE, PACKAGING AND LABELING

BTX (onabotulinumtoxinA) is an FDA approved drug and available for human use. Each vial of Botox® Cosmetic contains either 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride or 50 Units of Clostridium botulinum type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride in a sterile, vacuum-dried form without a preservative

6.1.4 PRODUCT STORAGE AND STABILITY

BTX (onabotulinumtoxinA)

6.1.5 COMPATIBILITY

BTX (onabotulinumtoxina) may only be reconstituted with 0.9% sodium chloride.

6.1.6 PREPARATION

The commercial preparation of BTX (onabotulinumtoxinA) is supplied in vials containing 100 U of the lyophilized powder. The entire required dose of BTX (onabotulinumtoxinA) will be withdrawn from the vial and reconstituted in 1 mL of 0.9% sodium chloride. During this time period, unused reconstituted BTX (onabotulinumtoxinA) should be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use. BTX (onabotulinumtoxinA) vials are for single-dose only. Used vials of BTX will be discarded. For this trial, the entire required dose of BTXTX will be withdrawn from each vacuum-dried vial and reconstituted in 1 mL of 0.9% sodium chloride. Endoscopic administration of the drug will be performed by trained endoscopists within 24 hours of reconstitution.

6.1.7 ADMINISTRATION

Endoscopic injection of BTX into the lower esophagus is a well-described treatment for Sphincter of Oddi Dysfunction.[10, 11, 28] Subjects will undergo an outpatient upper endoscopy with injection of BTX into the sphincter of Oddi (**Figure 1).** The endoscope is introduced through the mouth and advanced to the duodenum. At the level of the ampulla of the Vater, the injection needle will be inserted into the upper margin of the papillary orifice. Then 1 mL of the properly reconstituted BTX (onabotulinumtoxinA) solution will be injected as a single deposit. Then the endoscope will be removed to complete the procedure. Acceptable window of time for administration of agent is the total procedural time during endoscopy. No special IV tubing or filtration is needed.

6.1.8 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

All subjects will have their heart rate, respiratory rate, oxygen saturations, blood pressure and ventilation will be monitored throughout and after the procedure. If subjects develop hypersensitivity symptoms like rash, wheezing, or pruritus, hypersensitivity medications should be administered.

There are no other special considerations, including hydration, steroids, special IV tubing, filtration, or special equipment required.

6.1.9 ACCOUNTABILITY

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The Investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the site.
- Use by each participant including pill/unit counts from each supply dispensed.
- Return of investigational product to the Investigator or designee.
- Destruction or return of investigational product for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the participants were provided the correct study medication specified.

Completed accountability records will be archived by the site. There are no study drugs that require shipment back to the manufacturer at the end of the study.

6.1.10 DESTRUCTION AND RETURN

At the completion of the study, the Investigator or designee will oversee the destruction of study agent per local institutional guidelines.

7. TREATMENT PLAN

7.1 DOSAGE AND ADMINISTRATION

Regimen Description					
Agent	*Premedication; Precautions*	*Dose*	*Route**	*Schedule*	*Cycle Length*
onabotulinumtoxinA	none	100 units in 1 mL of 0.9% NaCl solution	Endoscopic injection into intraduodenal sphincter of Oddi segment	Days 7-14 before surgery	Single injection administered once
**Specify route of administration (e.g., IVB, IVP, IVCI, PO, intra-arterial, peritoneal, intrathecal, intracavity, etc.) and duration (e.g., IVP over 10 seconds), including any allowable time windows (+/- minutes).*					

Subjects will undergo an outpatient upper endoscopy for administration of a single BTX injection. The endoscope will be introduced through the mouth and advanced to the duodenum. At the level of the Ampulla of the Vater, the injection needle will be inserted into the upper margin of the papillary orifice. Then 1 mL (100 units) of the properly reconstituted BTX solution will be injected as a single deposit. The volume in syringe will be checked to ensure the entire amount is delivered. Then the endoscope will be removed to complete the procedure. Acceptable window of time for administration of agent is the total procedural time during endoscopy. No special IV tubing or filtration is needed. The participant's heart rate, respiratory rate, oxygen saturations, blood pressure and ventilation will be monitored throughout and after the procedure. No additional BTX injection will be administered for each participant. Reported adverse events and potential risks are described in Section 10, SAFETY. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat

the participant's malignancy.

7.2 DISCONTINUATION FROM STUDY INTERVENTION

Study intervention is a one-time dose during endoscopic procedure, thereafter all other procedures and treatment will be in accordance with institutional standard of care.

7.3 TREATMENT PERIOD AND MAINTENANCE

Participants will receive BTX (onabotulinumtoxinA) on between 7 to 14 days prior to planned distal pancreas resection. No other study-specific interventions or maintenance dosing will occur.

7.4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and general medical guidelines for the care of participants undergoing distal pancreas resections.

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed in general. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment.

Other medications for the prophylaxis of POPF are disallowed, including hydrocortisone and pasireotide. These medications may be administered at the treating physician's discretion following diagnosis of any POPF.

All medications (other than investigational products) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered during the study must be listed on the case report form (CRF).

Treatment recommendations described in the following sections may be modified according to institutional standards and guidelines as appropriate.

7.4.1 NAUSEA / VOMITING

No routine prophylactic anti-emetic treatment is required at the start of treatment, however, participant should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter per institutional guidelines.

7.4.2 HYDRATION

Not applicable to the present study

7.4.3 OBSERVATION PERIOD – Patients will be observed and monitored according to the standard of care following upper endoscopy, generally 1-2 hours.

7.4.4 MANAGEMENT OF SERIOUS COMPLICATIONS FROM STUDY INTERVENTION

Pancreatitis: Any patient with abdominal pain, nausea, and intolerance to oral intake will be evaluated for pancreatitis and managed per the standard of care depending on severity of pancreatitis (see American Gastroenterological Association guidelines).[31]

Gastrointestinal Bleeding: Patients reporting hematemesis, hematochezia, or melena following study will be evaluated by phone, in clinic, or the emergency department as their clinical status dictates. Most gastrointestinal bleeding following endoscopy is self-limited and otherwise asymptomatic and not considered a serious complication. If clinically significant bleeding occurs, defined as that accompanied by new anemia, hypotension, or other signs/symptoms of significant blood loss, patients will be further evaluated in the emergency department and treated per the standard of care with serial evaluation of hemoglobin/hematocrit, PT/INR, vitals/physical exam, and receive endoscopic, intra-arterial, or surgical management as indicated.

Gastrointestinal Perforation: Patients experiencing new severe abdominal pain following discharge from the endoscopic procedural unit will be evaluated in clinic or in the emergency department as dictated by clinical status. Patients with gastrointestinal perforation will be treated as clinically indicated, typically with surgical intervention.

BTX-Specific Complications: Patients experiencing BTX-related complications will be managed according to the clinical scenario. Serious allergy-spectrum reactions (e.g., anaphylaxis) will be noted during the observation period and managed accordingly by the clinical staff. Other reactions such as local weakness are predominantly reported in cases of skeletal muscle-adjacent injections. No specific management is required in most cases, however new-onset symptoms following BTX injections will be evaluated by phone or in clinic as indicated, and managed appropriately.

Patients will be counseled on warning signs for the above serious complications prior to and after BTX injection.

7.5 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Patients will be asked to be *nil per os* starting at midnight prior to planned upper endoscopy.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

7.6.1 PROHIBITED THERAPIES

No concomitant therapy or investigational therapy aimed at preventing POPF is allowed during the study, including pasireotide.

8. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

8.1 STUDY-SPECIFIC PROCEDURES

8.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the participant's malignancy, when applicable, will be recorded separately and not listed as medical history (e.g., date of diagnosis, staging).

8.1.2 DISEASE ASSESSMENT

The investigator or qualified designee will obtain prior and current details regarding the participant's pancreatic cancer.

8.1.3 MEDICATION REVIEW

A complete medication history will be acquired concurrent with medical history.

8.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant, or Advanced Registered Nurse Practitioner as local law permits and per institutional standards. The physical examination to be conducted will include an evaluation of: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; lymphatic system, musculoskeletal system, and nervous system. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings. All physical examinations will also include:

8.1.4.1 *Vital signs*

Vitals to be collected include blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry. As part of screening/baseline visit, vitals should be obtained within 10 days prior to first dose of study agent. Vitals will also be obtained during treatment.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF page.

8.1.4.2 *Height and weight*

Height will be collected at screening only. Weight will be collected at each in person visit.

8.1.4.3 *Performance status*

Performance status (Eastern Cooperative Oncology Group) will be determined for all participants at screening.

8.1.5 ADVERSE EVENT EVALUATION

Toxicities and adverse experiences will be assessed using the NCI CTCAE 5.0. Safety will be monitored by assessing physical examination, vital signs, body height (screening only) and weight as clinically indicated. Additionally, hematology, chemistry, coagulation, urinalysis, thyroid function, and pregnancy will be assessed as clinically indicated.

Adverse events will be monitored from the time the participant receives treatment on study. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study, including and up to 30 days. Due to the known excellent safety profile of botulinum toxin and FDA-approval for endoscopic injection for achalasia, AEs grade 1-2 will not be collected during the study. AEs Grade 3 or higher must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug.

Abnormal laboratory values will only be recorded as an AE if determined to be clinically significant by the investigator.

For details on AE collection and reporting, refer to Section 10.

8.2 LABORATORY PROCEDURES AND EVALUATIONS

8.2.1 HEMATOLOGY
Only as clinically indicated per institutional standard of care.

8.2.2 COMPREHENSIVE METABOLIC PANEL
Only as clinically indicated per institutional standard of care.

8.2.3 COAGULATION PANEL
Only as clinically indicated per institutional standard of care.

8.2.4 PREGNANCY TEST
A serum or urine pregnancy test is required during screening for all persons of childbearing potential. The pregnancy test is required within 7 days prior to study intervention and results must be available prior to administration of study agent. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

8.2.5 AMYLASE ASSAY
Amylase levels will be drawn from all surgical drains, when present, on postoperative day 3 or 4, per standard of care prior following pancreas resections. In patients undergoing percutaneous drainage of a postoperative intra-abdominal fluid collection, amylase levels on the drained fluid will be drawn to evaluate for crPOPF. An amylase level >3 times the upper limit of normal from a surgical drain is sufficient for diagnosis of POPF, while an amylase level >3 times the upper limit of normal from a percutaneous drain is sufficient for a diagnosis of crPOPF.

8.3 SCREENING ASSESSMENTS

A screening (consultation) visit may occur as part of standard of care. If a participant is eligible for the study after review of key inclusion/exclusion criteria, additional screening visits will be scheduled while staff members are requesting insurance authorization to participate in a clinical trial.

The following will be reviewed at screening visit:
- Clinical history and physical exam (per standard of care)
- Informed consent obtained and documented

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedure that are performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

8.4 EARLY TERMINATION OR END OF STUDY VISIT

Any participant who undergoes early termination will undergo end of study visits depending on their progress in the protocol. Participants who have not received BTX injection are not considered enrolled, will not require a follow up visit and will be treated per standard of care.

Participants who have received injection but not yet had surgery will have a follow-up visit within 30 days of intervention to evaluate for adverse events. Participants undergoing termination following pancreatectomy will have an end of study visit at the time of their regular post-op visit and will be cared for per the standard of care.

8.5 FOLLOW-UP

Participants will be followed for 30 days following distal pancreas resection for efficacy. For safety, patients will be followed for 30 days following BTX injection if no surgery occurs or 30 days after surgery, whichever is longer. A follow-up visit will occur 14 days (± 7 days)-following hospital discharge, consistent with standard of care practices. Additionally, all subjects will be contacted by phone by the NSQIP Surgical Clinical Reviewer (Fouad Attia) or other study team member approximately 30 days following operation to collect standard NSQIP other study datapoints. If a participant is diagnosed with any BTX-related adverse event (of any grade), additional follow-up phone calls will be performed monthly for three months following BTX injection to ensure resolution at the end of BTX duration of action.

Subjects not undergoing pancreatectomy and those undergoing pancreatectomy greater than 6 weeks from the date of BTX injection will not be evaluable for assessing efficacy of the study intervention but will be evaluable for assessing safety. The 6 weeks timepoint is chosen because the maximal efficacy of BTX may begin to wane following this timepoint. In patients undergoing BTX injection but not undergoing planned pancreatectomy (or experiencing a delay in pancreatectomy due to an AE from BTX), data on the reason(s) for delay or cancelled operation will be recorded.

8.6 UNSCHEDULED VISITS

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (e.g., laboratory or clinical assessments) at those visits that, in the opinion of the investigator, are deemed related to this study should be recorded in the CRF.

8.7 SCHEDULE OF EVENTS

Visit Days (± 7 Days)	Screening	Days*		Day of Surgery	Follow-up
	Days -1 to -28	1	Days 2-14 (one pre-operative medicine visit within this time frame)		0-30 Days Post-Surgery or Two Weeks Post-Discharge (if LOS >30 Days)**
BTX Administration		X			
Informed consent	X				
Inclusion/exclusion criteria	X				
Medical history	X				
Prior/concomitant medications	X	X			
Standard of Care Pre-Intervention Labs	X		X		
Height and weight	X	X			
Comprehensive physical examination	X				
Physical Examination	X	X	X		X
Vital signs	X	X	X		X
Efficacy Assessments					X
AE assessment			X		X
Follow-up data collection					X
Amylase Measurement(s)					X
Phone call for efficacy evaluation					X
*Length dependent on scheduling of surgery, but will not be shorter than 7 days ** Follow-up event can occur two-weeks post discharge (if LOS > 30) but collects information related to first 30 days post-surgery					

Please note that patients will undergo an in-person pre-operative medicine exam prior to distal pancreatectomy/RAMPS per standard of care. Additionally, at the clinician's discretion patients may undergo pre-procedure medicine evaluation appointment prior to upper endoscopy and BTX injection.

9. EFFICACY MEASURES

Therapeutic efficacy will be evaluated in this study by the presence of any POPF, clinically relevant POPF, postoperative length of stay, and major postoperative complications.

9.1 DEFINITION OF EFFICACY MEASURES

9.1.1 ANY POPF

Amylase level >3x the upper limit of normal from a fluid specimen obtained on postoperative day 3 or later, from a surgical drain or intra-abdominal fluid collection.

9.1.2 CLINICALLY RELEVANT POPF (GRADE B AND C POPF)

1. Amylase level >3x the upper limit of normal from a fluid specimen obtained on postoperative day 3 or later from postoperatively placed percutaneous or endoscopic drain of an intra-abdominal fluid collection (Grade B POPF).

OR

2. Amylase level >3x the upper limit of normal from a fluid specimen obtained on postoperative day 3 or later from a surgical drain, postoperatively placed percutaneous or endoscopic drain of an intra-abdominal fluid collection, combined with organ failure clearly attributable to the POPF (Grade C POPF).

Major postoperative complications: Any postoperative complication filling criteria for Clavien-Dindo grade III or higher.

Length of stay: Number of midnights in-hospital following distal pancreas resection

Clavien-Dindo Complication Grades[32]:

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

10. SAFETY

10.1 SPECIFICATION OF SAFETY PARAMETERS

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 8.7, Schedule of Events. Any clinically significant adverse events persisting at the postoperative follow-up appointment will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

10.2 DEFINITIONS

10.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of

the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

10.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor-Investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.
- Pancreatitis requiring hospitalization
- GI bleeding requiring hospitalization
- GI perforation requiring hospitalization
- Any procedure-related complication resulting in delay of surgery

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or
- The development of drug dependency or drug abuse.

10.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets <u>all</u> of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

10.2.4 SEVERITY OF EVENT

Due to the known safety profile of botulinum toxin and FDA-approval for endoscopic injection for achalasia, AEs grade 1-2 will not be collected during the study. For serious AEs (Grade 3 or higher), the Investigator will grade its severity using, when applicable, the current version of the

CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Note: a semi-colon indicates 'or' within the description of the grade.

10.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Possibly Related:	There is some evidence to suggest a causal relationship.
Unrelated:	The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

10.3 EXPECTEDNESS

The Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

10.4 ADVERSE EVENT LIST(S)

10.4.1 ADVERSE EVENT LIST FOR BTX

Please refer to package insert for onabotulinumtoxinA for additional details.

Clinical Studies Experience: BTX (onabotulinumtoxinA) and BTX Cosmetic contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse events observed with the use of BTX Cosmetic also have the potential to be observed with the use of BTX and vice-versa. In general, adverse events occur within the first week following injection of BTX and while generally transient, may have a duration of several months or longer and include:

Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical

therapy. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin.

Post-Marketing Experience: There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established. New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. The following events, not already addressed elsewhere in the package insert, have been reported since the drug has been marketed: abdominal pain; anorexia; brachial plexopathy; diarrhea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoaesthesia; localized numbness; malaise; myalgia; paresthesia; pyrexia; radiculopathy; skin rash (including erythema multiforme, and psoriasiform eruption); tinnitus; vertigo; visual disturbances; and vomiting. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to botulinum toxin.

10.4.2 ADVERSE EVENT LIST FOR ENDOSCOPY

Overall, the rate of serious adverse events following endoscopy is less than 0.01%. Known risks associated with endoscopy are summarized in Table 3 have been extensively reported in large observational studies.[33]

Table 3. Adverse Events Associated with N=73029 Endoscopic Procedures[33]

Adverse event	Total	Percentage
Bleed	51	0.07
Cardiorespiratory arrest	21	0.03
Postprocedural pain	20	0.03
Pancreatitis	17	0.02
Arrhythmias	8	0.01
Febrile reaction	6	0.01
Non-cardiac chest pain	6	0.01
Perforation	5	0.01
Hypoxia	4	0.01
Iatrogenic	4	0.01
Hemodynamic	3	<0.01
Myocardial infarction	2	<0.01
Miscellaneous	2	<0.01
Obstruction	2	<0.01
Tooth break	2	<0.01
Anaphylaxis	1	<0.01
Aspiration pneumonia	1	<0.01
Cognitive dysfunction	1	<0.01
Dyspnea	1	<0.01

GI obstruction	1	<0.01
Seizures	1	<0.01
Sore throat	1	<0.01
Stricture	1	<0.01
Stridor	1	<0.01
Syncope	1	<0.01
Total	163	0.22

10.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, upon review by a study monitor, or during an audit. All AEs grade 3 or higher but not meeting the criteria for SAEs will be captured on the appropriate CRF. AEs of grade 1 and 2 will not be captured due to the well-characterized side effect profile of BTX for other indications, including endoscopic BTX injection which is FDA approved. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs grade 3 or higher occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE after treatment with study intervention begins.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will record all reportable events with start dates occurring after treatment with study intervention begins for 30 days (for AEs grade 3 or higher) after the intervention is performed or 30 days after date of surgery, whichever is longer. AEs will be evaluated using the current version of the CTCAE v5.0. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. Any SAE that occurs after treatment with alternative therapy

will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment.

10.6 REPORTING PROCEDURES

10.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. Events that meet the criteria for OHSU RNI must be reported to the IRB within 5 days of learning of the event. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

10.6.2 CENTRAL REPORTING OF ADVERSE EVENTS FOR MULTI-SITE STUDIES

A sub-site must notify the OHSU Coordinating Center of any SAE by phone, fax, or email no later than 24 hours after learning of the event. The sub-site must also report each event to the institution's local IRB or other oversight entity per institutional policies/requirements. The sub-site will send the Coordinating Center supporting materials regarding the SAE, as well as [describe what sub-site must submit to coordinating center, for example: Knight SAE form, MedWatch form 3500, and/or any other trial specific reporting form (AESI, AECI)].

The Coordinating Center will review and submit SAE information to the FDA, OHSU IRB, sub-sites, and any other entities as required by federal and local policies/regulations, and any other applicable requirements.

The Coordinating Center is responsible for distributing IND and/or IDE Action Letters and/or Safety Reports, as applicable, to sub-sites for review and submission to their institution's local IRB as required per site policy.

10.6.3 FDA REPORTING

Some events must be reported to the FDA through the MedWatch Voluntary reporting program, even if the trial involves a commercially available agent. Events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the study intervention.

For studies conducted under an IND/IDE, the OHSU Coordinating Center Investigator is required to report certain events to the FDA per applicable regulations.

For multi-site investigator-initiated trials, the OHSU PI is the study sponsor and the following reporting responsibilities and requirements apply.

The sub-site investigator is required to report AEs to the Coordinating Center using a MedWatch report form and/or any trial-specific report form and supporting materials. Adverse events to be reported include any UPs (i.e., not listed in the package insert and/or IB) and any SAEs with a suspected association to the investigational product. The Coordinating Center will centrally assess all reported events and report any events to the FDA as warranted using the MedWatch 3500A Mandatory report form.

10.6.4 SUSPECTED UNEXPECTED ADVERSE REACTIONS (SUSARS)

Per regulatory requirements, if an event is assessed by the Sponsor Institution as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor Institution to submit the SUSAR to Regulatory Authorities according to applicable regulations. In addition, the SUSAR will be distributed to the Investigators/sites utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective IRB or IEC per the governing institutional requirements and in compliance with local laws and guidelines.

10.6.5 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy or suspected pregnancy in a participant during study participation must be reported within 24 hours of learning of its occurrence. The sub-site investigator is required to notify the OHSU Coordinating Center by phone, fax, or email no later than 24 hours of learning of a pregnancy. The sub-site must also report each event to the institution's local IRB or other oversight entity per institutional policies/requirements. The Coordinating Center will centrally assess the event and report to the manufacturer and any other entity as warranted. The sub-site will send the Coordinating Center information regarding the pregnancy using secure institutional email. Describe what sub-site must submit to Coordinating Center, for example: Knight SAE form template, MedWatch form 3500, and/or any other trial specific reporting form.

The investigator must follow the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications. The sub-site must report the outcome of the pregnancy to the Coordinating Center as defined above.

If during study participation a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

10.7 STUDY STOPPING RULES

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety

Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected.
- Death suspected to be related to BTX injection.
- As indicated by statistical stopping rules in this protocol per Section 11.4.5: 1) During safety run-in if two or more out of the first six participants experience a surgical delay ≥ 14 days past the previously scheduled date. 2) Interim analysis if two or more of the first 25 participants experience crPOPF. If either of these events are met the trial will be stopped. In the case of the safety run-in, the trial may be resumed if a correctable cause for the serious adverse events can be found or a prophylactic treatment administered.

11. STATISTICAL CONSIDERATIONS

11.1 STATISTICAL HYPOTHESIS

This study is a Phase II, open-label study to determine the effect of pre-operative endoscopic BTX injection on crPOPF rates following distal pancreatectomy. It is hypothesized that the rate of crPOPF in study participants will be significantly lower than the known historical rate of crPOPF.

11.2 SAMPLE SIZE DETERMINIATION

This will use a Simon's two-stage design. The two-stage design to test a difference of 9.2% (2% vs. 11.2%) has an expected sample size of 30.33 and a probability of early termination of 0.787. If the pre-operative BTX injection is effective, there is a 0.124 probability of concluding that it is not, equivalently 0.876 power. After the pre-operative BTX injection on 25 patients in the first stage, the trial will be terminated if 2 or more crPOPF. If the trial goes on to the second stage, a total of 50 participants will be studied. If the total number crPOPF is less than 3, the drug will be considered efficacious. Anticipating 10% drop-out (lost follow-up), up to 55 participants need to be enrolled to achieve 50 evaluable participants. The sample size and power analysis were conducted is conducted using PASS 15 software (http://www.ncss.com/software/pass/).

11.3 POPULATIONS FOR ANALYSES

11.3.1 Safety Population

The safety population includes all enrolled participants who received the single BTX injection. All safety analyses related to the intervention will be conducted using the population receiving BTX injection. Analysis for demographics, baseline characteristics, disease history, on-study treatment summaries, concomitant medications, and participant disposition will also be conducted using the safety population.

11.3.2 Efficacy Evaluable Population

The efficacy evaluable population includes all participants enrolled in the study who received the single BTX injection, underwent distal pancreatomy/RAMPS, and had up to 30 days or greater of postoperative follow-up for POPF assessment. Participants who experience surgical delay greater than 6 weeks are not evaluable. All efficacy analyses will be conducted using the efficacy evaluable population. Safety analyses related to surgery will use the efficacy population.

11.4 DESCRIPTION OF STATISTICAL METHODS

11.4.1 ANALYSIS OF PRIMARY ENDPOINT(S)

Using the efficacy analysis set, the estimate of clinically relevant POPF rate on pre-operative endoscopic BTX injection will be measured and reported with 95% exact confidence interval.

11.4.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

11.4.2.1 *Rate of serious adverse event*

Using the safety analysis set, the incidence of serious adverse events following endoscopic BTX injection into the sphincter of Oddi as a single agent will be determined for participants undergoing distal pancreas resections. The 95% confidence interval will be reported with the point estimate of SAE rate.

11.4.2.2 *Rate of any POPF*

Using the efficacy analysis set, the estimate of biochemically or clinically relevant POPF rate on pre-operative endoscopic BTX injection will be measured and reported with 95% exact confidence interval.

11.4.3 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

Exploratory analysis will be performed with historical patients accounting for the covariates that predict experiencing a crPOPF. That is, to estimate the effect of pre-operative endoscopic BTX injection on crPOPF for this non-randomized trial, we will use disease risk score matching[34] to pair treatment and control units with similar values on the disease riskscore with known risk factors for crPOPF with the following endpoints of interest at 30 days postoperatively. The disease risk score model will be derived from the historical control cohort, which consists of distal pancreas resections from 2013-2020 with pancreas-specific National Surgical Quality Improvement Program (NSQIP) information. The historical control group has experienced approximately 30 crPOPFs, which is sufficient for estimation of crPOPF risk using the predictive variables captured by NSQIP and supplemental chart review. Individual patients from the historical and intervention groups will be assigned disease risk scores, and matched according to scores.

As data allow, the benefit of pre-operative BTX injection for 30 days outcomes will be analyzed using disease risk score matching using known risk factors for crPOPF against historical patient controls for the following endpoints :

1) Clinically relevant POPF
2) Any POPF
3) Postoperative Length of Stay
4) Clavien-Dindo III or greater postoperative complications
5) Rate of percutaneous drainage procedure
6) Rate of unplanned re-operation

11.4.4 SAFETY ANALYSES

Adverse events will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1) preferred term and system organ class. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Using the safety analysis set, descriptive statistics will be used to summarize all on-study AEs, grade 3-4 AEs, treatment-related AEs, grade 3-4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to study therapy discontinuation. Grade 3-4 laboratory abnormalities will be summarized using worst grade NCI CTCAE v5.0 criteria.

11.4.5 PLANNED INTERIM ANALYSES AND STOPPING RULE

A safety-run in to test the endoscopic BTX injection technique will be performed. During the safety run-in, the PI will evaluate patient safety outcomes including grade 3 or higher adverse events. Additionally, the study will be evaluated by the DSMC following the completion of the first three participant's safety evaluation periods (30 days following BTX injection or 30 days following surgery, whichever is longer). Progressive study enrollment will continue throughout the safety run-in, and enrollment will be halted if recommended by the DSMC after completion of the run-in. If 2 or more of the first 6 participants enrolled experience delay in planned surgery ≥ 14 days (due to significant GI hemorrhage, perforation, or adverse reaction to BTX) or pancreatitis requiring hospitalization, then the study will be halted for safety. If 2 or more of the first 6 participants experience delay in planned surgery ≥ 14 days (due to significant GI hemorrhage, perforation, or adverse reaction to BTX) or pancreatitis requiring hospitalization, the study will be halted for safety. An analysis of adverse events will be performed, and if an alteration in the intervention technique or other prophylactic treatment cannot be identified the study will be terminated. If an alteration or prophylactic treatment can be found, the study will resume with an additional 6 patient safety run-in with identical stopping rules.

A futility analysis will be conducted based on the stopping rule of Simon's two-stage design after 25 Stage I participants have met the eligibility criteria for the efficacy evaluable population (defined in 11.3.2). All participants enrolled on stage 1 (n=25) will need to complete the study intervention, distal pancreas resection, and 30 days of follow up for postoperative pancreatic fistula before the interim analysis can be completed. Recruitment will be paused until interim analysis is completed. The trial will be terminated if there are 2 or more crPOPF among these 25 participants. If there are less than 2 crCOPF among these Stage I participants, the trial will continue and enroll 25 additional participants in Stage II. The treatment will be considered promising and deserving of further investigation if there are less than 3 crCOPF among the total of evaluable 50 participants.

11.5 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially. No missing value imputation will be performed.

12. CLINICAL MONITORING

12.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

All clinical trials at the Knight are required to have Data and Safety Monitoring Plan (DSMP). This study is under the oversight of the Knight Cancer Institute's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data, and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate, risk-based oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

The Knight DSMC reviews and monitors study progress, toxicity, safety, and other data for this study. The DSMC will address any issue that raises questions about data integrity or trial participant safety with the Investigator and study team. Should any major concern arise, the Knight DSMC may recommend corrective action, and determine whether to suspend or terminate the study.

12.2 CLINICAL DATA & SAFETY MONITORING

As part of the Quality Assurance plan and in full agreement with NIH policy (NIH Guide, NIH Policy for Data and Safety Monitoring, June 10, 1998) that states all clinical trials require monitoring to ensure the safety of study participants and the validity and integrity of the data, monitoring will be a continuous, ongoing and multifaceted process. This includes external review by the DSMC and IRB(s), as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities.
The OHSU Investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all sub-sites, and final analysis of study data.

In the absence of a formal monitoring plan, the Investigator may work with his/her study team to conduct and document internal monitoring of the study to verify protection of human participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If at any time Investigator noncompliance is discovered at OHSU or any sub-site, the Investigator shall promptly either secure compliance or end the Investigator's participation in the study.

Independent audits will be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

12.3 QUALITY ASSURANCE & QUALITY CONTROL

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

All clinical trials at the Knight Cancer Institute are required to have a Data and Safety Monitoring Plan (DSMP). All clinical work conducted under this protocol is subject to ICH GCP guidelines. This includes inspection of study-related records by the lead site, Sponsor, its designee, or health authority representatives at any time.

QA audit activities will occur as detailed in the Knight's institutional DSMP. All discrepancies, queries, deviations, observations, and findings of non-compliance will be compiled into a final audit report. The PI must review and assess each finding, and generate a response to the audit report that incorporates Corrective and Preventative Action (CAPA). A CAPA must approach analyzes root cause(s) of noncompliance in order to identify and determine changes to correct and resolve issues, and prevent recurrence.

Quality Control (QC) activities will occur to monitor and ensure the safety of study participants and the validity and integrity of data. Monitoring will be a continuous, ongoing and multifaceted process. This includes review by the Knight DSMC and applicable IRB(s), as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities.

The Sponsor-Investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate CRFs, electronic (e)CRFs and relevant electronic data capture (EDC) system (if applicable), and all relevant source documentation.

13.1.1 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the site Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, or after the appropriate period of record retention stated in Section 13.1.3, all study databases will be de-identified and archived within the Knight Cancer Institute.

13.1.2 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical research information system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system that is approved by OHSU's office of Information Privacy and Security. To preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Where applicable, data from correlative studies may be entered into the EDC system by study personnel. All other electronic data extracts will be stored only on local study site computers and restricted drives, which are limited to only study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 12.3, Quality Assurance & Quality Control

13.1.2.1 *National Surgical Quality Improvement Project (NSQIP) & Efficacy Data Collection*

NSQIP is an international initiative sponsored by the American College of Surgeons that records patient demographics, treatment regarding surgical interventions, and captures 30-day postoperative complications data.[35] "Procedure-targeting" allows institutions to capture 100% of certain surgical procedures along with an expanded set of procedure-specific datapoints (e.g., data on POPF and crPOPF for pancreatectomies). OHSU has been procedure-targeting pancreatectomies since 2013.

Data collection for 30-day postoperative complications, including POPF and crPOPF, will be performed by a trained NSQIP surgical clinical reviewer. Due to the workflow of NSQIP reviewers, a lag period between surgery is anticipated equaling up to 3-months. For the purposes of the interim efficacy analysis, subject charts may be reviewed for information relevant to the primary endpoint by individuals other than the NSQIP reviewer. Data obtained from the NSQIP reviewer relating to primary or secondary endpoints will be separately reviewed by a member of the study team and any conflicts or discrepancies resolved. Finalized data will be entered into the EDC system and used for final analysis.

13.1.3 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years. If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

13.2 MULTI-SITE GUIDELINES

Each sub-site is expected to maintain appropriate medical and research records in compliance with ICH GCP and regulatory and institutional requirements for the protection and confidentiality of participants.

OHSU Coordinating Center will provide a manual of procedures and/or data management plan to sub-sites to describe required data and document submission requirements and timelines.

OHSU Coordinating Center will communicate with sub-site(s) on a routine basis and will retain essential documents in accordance with ICH GCP and regulatory and institutional requirements.

13.3 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the PI.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

13.4 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. Conflicts of interest, for all study group members, should be disclosed and managed according to OHSU's established policies and procedures.

Refer to link: https://o2.ohsu.edu/integrity-department/conflict-of-interest/index.cfm

14. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

14.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312, and/or the ICH E6.

14.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

14.3 INFORMED CONSENT

All sites must have IRB approval of informed consent form by the IRB of record before consenting any participants.

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. If a participant's signature cannot be obtained, the Investigator must ensure that the informed consent is signed by the participant's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

14.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study. All sites must have IRB approval of protocol by the IRB of record before consenting any participants.

14.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB (and sponsor/FDA if under an IND/IDE) within 5 business days after the implementation.

A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with §56.104(c) (21 CFR 312.30(b)(2)(ii)).

Sub-sites must submit proposed protocol changes to the OHSU Coordinating Center for review and endorsement before sub-site may implement changes.

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