PAtient-CenTric Chronic Pancreatitis Registry (PACT-CP)

PROTOCOL

Protocol ID:	NES-EPI-100	Study Type:	Non-Interventional
Version Number:	3.0	Sponsor:	Nestlé Health Science USA
Version Date:	13 April 2021		

PROTOCOL SYNOPSIS

Protocol ID	NES-EPI-100	**Sponsor**	Nestlé Health Science USA
Study Title	PACT-CP		

Study Objective & Specific Aims

The main objective of this study is to generate real-world evidence reflecting the experience of individuals with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP). Efforts will be directed toward understanding the unmet need and therapeutic burden to identify the most critical factors that influence treatment choices/prescribing patterns, quality of life, and healthcare utilization outcomes in standard of care for individuals with EPI due to CP. This study has the following specific aims:

1. Create a cohort of well-characterized patients with EPI due to CP for participation in retrospective and prospective research
2. Collect clinical data to characterize both the EPI due to CP disease history and disease progression through a combination of retrospective and prospective collection of medical history, comorbidities, and treatment approaches aimed at increasing the level of understanding of a heterogeneous condition such as EPI
3. Collect data on the differing clinical care practices for patients with EPI to better understand the impact of those patterns on outcomes (including quality of life, comorbidities, and treatments)
4. Collect data on treatment compliance that may impact the EPI due to CP disease experience and/or outcome
5. Collect baseline and longitudinal participant-reported outcome (PRO) data on abdominal pain, gastrointestinal (GI) symptoms, dietary habits, health-related quality of life, depression/anxiety, and PERT use and treatment satisfaction to evaluate the impact of EPI on individuals' health and daily life
6. Gather data on healthcare utilization to be combined with clinical data to generate evidence for the impact and burden of EPI due to CP in this cohort on the healthcare system.

Study Design

This is a prospective, non-interventional research study for individuals diagnosed with EPI due to CP under the care of a gastroenterologist. Target enrollment is approximately 400 individuals, to be recruited over a period of 24 months. The study duration from enrollment to closeout will be five (5) years. Approximately 20 clinical gastroenterology practices in the United States will be contracted to participate.

Eligibility Criteria

To be eligible for the study, study participants must meet all the inclusion criteria and none of the exclusion criteria at the time of enrollment.

Inclusion criteria

To be eligible for enrollment, a study participant must meet the inclusion criteria below:

1. At least 18 years of age (or age of majority)
2. Willing to provide consent to participate
3. Meet ONE (1) of the following at the time of enrollment:
    a. Diagnosis of chronic pancreatitis (CP)
    b. Diagnosis of recurrent acute pancreatitis (RAP)

4. Suspected or confirmed diagnosis of EPI made by a healthcare provider
5. On pancreatic enzyme replacement therapy (PERT), either prior to the Enrollment Visit or newly prescribed at the time of the Enrollment Visit.

Exclusion criteria

To be eligible for enrollment into the registry, a study participant must not meet any of the criteria below:

1. Currently participating in or planning to participate in a double-blind randomized trial and/or open-label Phase 3b/4 on CP or EPI
2. Diagnosed with any of the following conditions at the time of enrollment:
    a. Cystic fibrosis
    b. Fibrosing colonopathy
    c. A history of or current diagnosis of pancreatic cancer, main duct papillary mucinous neoplasms (IPMNs), and other pancreatic malignancies
    d. Allergy to pork or other porcine pancreatic enzyme products (PEPs)
    e. Any condition that would, in the investigator's opinion, limit the individual's ability to complete the study.

Study Procedures

Study data will be collected from Investigators at the time of routine clinical encounters, as well as from study participants remotely in between routine visits.

Enrollment

Study participants will be enrolled in the study if they meet eligibility criteria and after they have provided consent to participate. During the Enrollment Visit, the Investigator will confirm eligibility and will provide information on suspected/confirmed EPI diagnosis (date of diagnosis, date of onset of symptoms indicative of EPI, method of EPI diagnosis, if applicable), CP etiology, clinical manifestations of EPI (i.e., GI and nutritional manifestations), medical history (comorbidities, surgical and radiological procedures, endoscopic procedures, and laboratory abnormalities), and current treatment(s). Information collected from the study participant includes demographics, current work status, current insurance coverage, family disease history, weight/height, current over the counter (OTC) herbal/nutritional supplements, healthcare utilization, and participant-reported outcome assessments on abdominal pain, GI symptoms, health-related quality of life, depression/anxiety, and PERT use and treatment satisfaction.

Follow-Up

Follow-up data will be collected from the study participants remotely via electronic data capture (EDC) portal. Every 3 months, study participants will complete assessments on current work status, current insurance coverage, current weight, current OTC herbal/nutritional supplements, and abdominal pain, GI symptoms, and PERT use and treatment satisfaction. Every 6 months, in addition to the assessments completed every 3 months, study participants will also complete assessments on health-related quality of life, depression/anxiety, and healthcare utilization.

The Investigator will provide updates during routine clinical encounters approximately every 6 months or at least 150 days from the last registry visits. Data will be collected on clinical manifestations of EPI, current treatment(s), and active assessment of adverse events/serious adverse events (AEs/SAEs) since last visit. "Early" follow-up visits will be conducted whenever a study participant is prescribed a new PERT product. The Investigator will not complete any assessments if the study participants do not return to the sites for their expected routine clinical encounter.

Study Participant Exit

Study participants exit the study upon withdrawal from the study, lost to follow-up (LTFU), transfer of care to a different gastroenterologist, death, or any other reason resulting in a study participant's exit. The Investigator will document the reason for the exit.

Data Collection

Study participants will be followed prospectively, and data from study participants will be collected at 3-month intervals via EDC portal. Investigators will complete assessments approximately every 6 months at the time of routine clinical encounters. AEs will be collected as part of the study data collection forms. SAEs are to be reported within 24 hours (1 business day) of awareness, whether or not the site learns of the event at the time of a registry follow-up visit.

Data Analysis

Analyses will be guided by the specific aims of the registry. Complete details of all analyses will be described in a standalone Statistical Analysis Plan (SAP) with accompanying mock Tables, Figures and Listings (TFLs). Briefly, all data will be summarized descriptively. Study disposition of all participants will be summarized including dropouts (with reasons presented for those who drop out), and for lost to follow-up (at what point they are lost, and if they return). Multivariate modeling will be employed to analyze clinical data on EPI disease history and disease progression by analyzing patterns of medical history, comorbidities, and treatment approaches. Clinical care practices will be explored with their potential impact on quality of life, comorbidities, and treatments using the same multivariate modeling. Treatment compliance will be examined for each of the models, knowing that biases are introduced with participant recall. Prescribing practices will be descriptively presented (to include type of PERT, dose at initiation and escalation, recommendation on how to take PERT, and reason for switching to another PERT, if applicable). If trends are identified in prescribing patterns, these trends may be further explored. Healthcare utilization data will be assessed with key variables from the clinical dataset.

Confounding will be assessed for predicting outcomes with the registry data. If any confounding is identified, statistical procedures may be employed as appropriate for that confounder and outcome. Given that groupings within a study population may exist, these potential grouping effects will be handled with use of ANOVA (analysis of variance) models. Data quality assessed in terms of missing data, out of range values, and completeness will be presented, as to allow for appropriate interpretation and extrapolation of the study results.

PROTOCOL SIGNATURE PAGE

Investigator Agreement

This agreement at the front of this document must be signed and dated by the Investigator. The original must be kept on file with the Investigator and a copy sent to HealthiVibe.

By my signature below, I acknowledge that I have read the protocol and agree that it contains all necessary details for carrying out the research described therein. Furthermore, I agree to conduct this research in compliance with said Protocol, all applicable research regulations, and in compliance with my contractual obligations to HealthiVibe, a division of CorEvitas, LLC.

_____
Investigator Full Name (print)

_____ _____
Investigator Signature Date Signed

HealthiVibe Site ID Number

ABBREVIATIONS

AE	Adverse event
AP	Acute pancreatitis
CP	Chronic pancreatitis
eCRF	Electronic case report form
EDC	Electronic data capture
EPI	Exocrine pancreatic insufficiency
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
HRQOL	Health-related quality of life
ICF	Informed consent form
IRB	Institutional review board
LTFU	Lost to follow-up
OTC	Over the counter
PERT	Pancreatic enzyme replacement therapy
PRO	Participant-reported outcome
RAP	Recurrent acute pancreatitis
RMP	Registry monitoring plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-12	12-item Short Form Survey
TSQM-9	Treatment Satisfaction Questionnaire for Medication – 9 items

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1. BACKGROUND

Exocrine pancreatic insufficiency (EPI) is a condition caused by reduced or inappropriate secretion or activity of pancreatic juice and its digestive enzymes, and pancreatic lipase in particular. EPI can result in clinical manifestations such as steatorrhea, weight loss, and biochemical alterations related to lipids and liposoluble micronutrients malabsorption and maldigestion (Perbtani & Forsmark, 2019). While overt maldigestion is associated with easily detectable symptoms and impact on quality of life (Johnson et al., 2017), long-term malnutrition can have significant detrimental consequences on overall health, as well as increased risk of mortality in patients with chronic pancreatitis (CP) due to cancer, infections, and cardiovascular events (de la Iglesia-Garcia et al., 2018). Thus, it is important that EPI is diagnosed early and treated appropriately to alleviate symptoms and reduce the risk of long-term complications associated with EPI; however, EPI symptoms and manifestations are not specific and are often shared with other common gastrointestinal (GI) conditions. This can lead to a lack of recognition in many individuals with EPI. Even in those who are correctly diagnosed, many are not treated with appropriate dosages of pancreatic enzyme replacement therapy.

The prevalence of EPI in the general population is unknown. It is most often associated with diseases of the exocrine pancreas, being a common late-stage manifestation of CP. CP is a disorder characterized by ongoing pathological pancreatic inflammation, leading to fibrosis and eventually to the loss of both endocrine and exocrine function. EPI typically develops after 5 – 10 years of CP, requiring approximately 90% of the endogenous pancreatic enzyme secretion to be lost (C. E. Forsmark, 2013). The risk of EPI varies with the underlying etiology of CP, with the highest risk population being those with chronic alcohol use (Ammann et al., 1987). Smoking has an independent effect on the development of CP, and the probability of EPI increases when tobacco exposure is combined with alcohol (Luaces-Regueira et al., 2014). In addition, EPI can also occur following severe acute pancreatitis (AP) as a result of loss of pancreatic parenchyma and functional capacity due to significant amounts of pancreatic necrosis (Hollemans et al., 2018), or recurrent acute pancreatitis without the overt presence of CP at the time of evaluation. Other causes for EPI are pancreatic malignancies (Sikkens et al., 2014) and resective pancreatic surgeries such as pancreatic duodenectomy (Goess et al., 2016) and distal pancreatectomy (Okano et al., 2016). EPI is also observed in other conditions, such as cystic fibrosis (Singh & Schwarzenberg, 2017), diabetes (Mohapatra et al., 2016), inflammatory bowel disease (Maconi et al., 2008), and GI surgeries (Antonini et al., 2018; Huddy et al., 2013; Straatman et al., 2017).

The diagnosis of EPI is best made by a combination of clinical history, ruling out other causes of malabsorption, cross sectional imaging of the pancreas, and diagnostic tests. The most practical approach involves diagnostic procedures that are noninvasive, inexpensive, and readily available. Such available lab tests are indirect measures of pancreatic function and include fecal elastase-1 (FE-1) test, fecal fat measurement, and fat-soluble vitamin measurements. These tests are generally less expensive and easier to perform compared to direct pancreatic functional tests.

Treatment of EPI relies on pancreatic enzyme replacement therapy (PERT). Pancrelipase formulations available in the United States are enteric coated (brand names: Creon®, Pancreaze®, Pertzye®, and Zenpep®) and non-enteric coated (brand name: Viokase®). Enteric coating prevents the enzymes from being denatured by gastric acid and the coating dissolves in the duodenum. All available formulations are derived from porcine origin. Finding the ideal dosing of PERT for a particular patient can be challenging because the response to treatment is variable from patient to patient. In general, enteric coated formulations are preferred because of gastric acid protection. Multiple studies have estimated that at least 30,000 IU (or about 90,000 USP units) of lipase delivered to the intestine with each meal should eliminate steatorrhea (Forsmark et al., 2002; Imrie et al., 2010; Keller & Layer, 2005). This amount represents approximately 10% of normal pancreatic secretion (Shandro et al., 2018). The goal is not to

replace 100% of estimated pancreatic function since steatorrhea only develops in severe disease. Therefore, starting doses should be between 30–40,000 IU with every meal and 15–20,000 IU with snacks (Imrie et al., 2010; Keller & Layer, 2005; Shandro et al., 2018). Patients should be instructed to take ½ the total dose with the first bite of the meal and other ½ either during the meal or at the end of the meal. In clinical practice, the choice of formulation will also be determined by cost and insurance coverage of the individual patient. In addition to PERT, lifestyle changes are paramount in the management of EPI. All patients should be counseled to stop smoking and drinking alcohol. Diet changes such as a healthy balanced diet and more frequent, smaller meals can also alleviate symptoms.

The benefits in treatment of EPI have led to practice guideline recommendations for the use of PERT in patients with CP, pancreatic cancer, and pancreatic surgery (Sabater et al., 2016). However, studies suggest that the majority of patients are either not treated or treated with inadequate dosages. In a European survey study of patients with EPI due to CP or pancreatic cancer, one-quarter of patients took three or fewer capsules a day and more than two-thirds of patients reported ongoing symptoms of steatorrhea (Sikkens et al., 2012b). Similarly, in a Dutch national survey of patients with CP and EPI, the median initiating daily dosage was suboptimal (four capsules daily, 25,000 USP units of lipase each), and a majority of patients reported ongoing gastrointestinal symptoms of EPI including steatorrhea and weight loss (Sikkens et al., 2012a). More recently, in a US population-based analysis, 6.5% of patients with CP received any testing for EPI, 30.4% received a prescription for PERT, and only 10% received a minimally effective dose (Forsmark et al., 2017a). Likewise, in a similar analysis of patients with pancreatic cancer, only 1.9% of patients had testing for EPI and 22% received a prescription for PERT, with only 5.5% receiving an adequate dose (Forsmark et al., 2017b). Ultimately, these studies highlight that diagnostic testing is rarely performed, treatment with PERT is infrequent, and, if utilized, the dosage amounts are generally inadequate.

In order to better study the disease journey and the effectiveness and safety of available therapies for EPI, databases and registries are needed. To date, however, there have only been a few observational studies conducted on EPI. These existing databases are limited as they lack measures that could advance the understanding of the disease, comorbidities, disease progression, risk and/or mitigating factors. In addition, these studies do not provide a comprehensive assessment of existing treatments. This observational study with geographical representation across the United States will be well positioned to address the above-mentioned issues by collecting a comprehensive set of real-world data around disease and treatment outcomes.

2. STUDY OBJECTIVES

The main objective of this study is to generate real-world evidence reflecting the experience of individuals with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP). Efforts will be directed toward understanding the unmet need and therapeutic burden to identify the most critical factors that influence treatment choices/prescribing patterns, quality of life, and healthcare utilization outcomes in standard of care for individuals with EPI due to CP. This study has the following specific aims:

1. Create a cohort of well-characterized patients with EPI due to CP for participation in retrospective and prospective research
2. Collect clinical data to characterize both the EPI due to CP disease history and disease progression through a combination of retrospective and prospective collection of medical history, comorbidities, and treatment approaches aimed at increasing the level of understanding of a heterogeneous condition such as EPI
3. Collect data on the differing clinical care practices for patients with EPI to better understand the impact of those patterns on outcomes (including quality of life, comorbidities, and treatments)

4. Collect data on treatment compliance that may impact the EPI due to CP disease experience and/or outcome
5. Collect baseline and longitudinal participant-reported outcome (PRO) data on abdominal pain, GI symptoms, dietary habits, health-related quality of life, depression/anxiety, and PERT use and treatment satisfaction to evaluate the impact of EPI on individuals' health and daily life
6. Gather data on healthcare utilization to be combined with clinical data to generate evidence for the impact and burden of EPI due to CP in this cohort on the healthcare system.

3. STUDY DESIGN

This is a prospective, non-interventional study for individuals with EPI due to CP who are under the care of a gastroenterologist. Longitudinal data will be collected from both study participants as well as from their clinical encounters with their treating gastroenterology providers using a structured and standardized data collection method. The scope of data collection (see Schedule of Assessments) from the study participants includes demographics, current work status, current insurance coverage, family disease history, weight/height, current over the counter (OTC) herbal/nutritional supplements, healthcare utilization, and PROs on abdominal pain, GI symptoms, dietary habits, health-related quality of life, depression/anxiety, and PERT use and treatment satisfaction. At the time of routine clinical encounters, Investigators complete assessments on medical history, information on suspected/confirmed EPI diagnosis, CP etiology, clinical manifestations of EPI (GI and nutritional manifestations), AEs, and current treatment(s).

3.1 Study Plan and Duration

Target enrollment is approximately 400 study participants with suspected or confirmed EPI. Approximately 20 clinical gastroenterology sites in the United States will be contracted to participate.

3.2 Study Duration

This is a 5-year study with an anticipated first enrollment date of 01 April 2021. The total enrollment period will be 24 months in length and data collection and study close-out will take place 3 months prior to the anticipated study end date. The study duration from enrollment to study end is five (5) years.

4. SITE SELECTION

4.1 Investigator Qualifications

Investigators will be selected after review of required qualifications and available resources. Investigators will be selected based on a number of criteria (e.g., practice setting, practice geographical location, number of EPI patients seen per month, type of IRB, etc.) to ensure that a representative sample of sites will be included in the study. A qualified Investigator is entitled to provide health care under the laws of the state where the registry site is located and for the purposes of this study must also be a licensed board eligible or board-certified gastroenterologist, or an advanced practice provider (i.e., certified nurse practitioner, physician assistant, gastroenterology resident or fellow) working at a gastroenterology practice and in good standing with a professional medical association. The Investigator is responsible for validating all information in the defined study schedule. If the study is conducted by a team of individuals at a site, the Investigator will need to complete a delegation of authority log for the registry. Each qualified physician at a site is assigned a unique ID to use when collecting and providing data for the registry. The Investigator will be asked to complete an assessment on provider demographics (e.g., age, gender, years in practice, number of EPI patients per month) and other site metrics (e.g., specialty, practice setting, practice type, and geographical location).

4.2 Study-Specific Training for Investigators and Support Staff

Study-specific training must be completed by Investigators, Sub-Investigators, and all support staff at each participating registry site prior to the initiation of study participant enrollment and data collection. Required training presentations and assessments (if applicable) are provided by HealthiVibe via teleconference and/or videoconference sessions prior to enrollment. The registry site training will be documented in a training log, which will capture the site staff that completed the trainings along with confirmation that the training content was understood.

5. STUDY POPULATION

5.1 Study Participant Selection Criteria

To be eligible for the registry, study participants must meet all inclusion criteria and none of the exclusion criteria below.

5.2 Inclusion Criteria

To be eligible for enrollment, a study participant must meet the inclusion criteria below:

1. At least 18 years of age (or age of majority)
2. Willing to provide consent to participate
3. Meet ONE (1) of the following at the time of enrollment:
    a. Diagnosis of chronic pancreatitis (CP)
    b. Diagnosis of recurrent acute pancreatitis (RAP)
4. Suspected or confirmed diagnosis of EPI made by a healthcare provider
5. On PERT, either prior to the Enrollment Visit or newly prescribed at the time of the Enrollment Visit.

5.3 Exclusion Criteria

To be eligible for enrollment into the registry, a study participant must not have any of the criteria below:

1. Currently participating in or planning to participate in a double-blind randomized trial and/or open-label Phase 3b/4 on CP or EPI
2. Diagnosed with any of the following conditions at the time of enrollment:
    a. Cystic fibrosis
    b. Fibrosing colonopathy
    c. A history of or current diagnosis of pancreatic cancer, main duct papillary mucinous neoplasms (IPMNs), and other pancreatic malignancies
    d. Allergy to pork or other porcine pancreatic enzyme products (PEPs)
    e. Any condition that would, in the investigator's opinion, limit the individual's ability to complete the study.

6. STUDY PROCEDURES

6.1 Schedule of Assessments

The registry activities are summarized in the schedule of assessments outlined in **Table 1**.

Table 1. Schedule of Assessments

	Enrollment Day 0	**Follow-up direct from study participant** ± 7 days		**Follow-up on-site (Clinical encounter)** Every 6 months*	**Study participant exit‡** May occur any time; max. data collection period is 5 years
		Every 3 months	**Every 6 months**		
Study Participant Provided Data§					
Informed consent	X				
Demographic information	X				
Family disease history	X				
Training for remote assessment completion	X				
Height	X				
Weight	X	X			
Current Insurance/work status	X	X			
Current OTC nutritional/herbal supplements	X	X			
Abdominal pain	X	X			
GI symptoms	X	X			
PERT use and treatment satisfaction	X	X			
Dietary habits	X		X		
Health-related quality of life	X		X		
Anxiety/depression	X		X		
Healthcare utilization	X		X		
Investigator Provided Data*					
Review/confirm participant eligibility	X				
EPI diagnosis	X				
CP etiology	X				
Medical history	X				
EPI clinical manifestations	X			X	
AEs•				X	
Current treatment(s)	X			X	
Reason for exit					X

§ Study participant provided data will be collected remotely via EDC portal.

* Investigator provided data will be provided during clinical encounters at the registry site. Every 180 days ±30 days with minimum 150 days between visits unless follow-up visit meets criteria for EARLY On-Site Follow-Up (see section 6.3.2)

‡ Occurs if data collection period has ended or if study participant exits the study due to death, is LTFU, transfers to another gastroenterologist, withdraws from the study or being terminated by the Investigator.

• The Investigator will provide information about the occurrence and seriousness of AEs at Follow-up. In the event that an AE is serious, the Investigator will complete an SAE form.

6.2 Enrollment

6.2.1 Informed Consent

Study participants will be enrolled when all of their questions about the study have been addressed, they have signed the informed consent form (ICF) and have met all of the inclusion criteria and none of the exclusion criteria (see Study Participant Selection Criteria). Informed consent will be obtained either via paper and/or electronic consent.

Once the participant's consent is obtained, a unique study participant identifier will be assigned that will be used to collect the participant's data throughout the study.

6.2.2 Clinical Data Points

During the Enrollment visit, the following information will be collected from the study participant:

- Demographics (i.e., age, gender, ethnicity, race, marital status, highest level of education, annual household income, residence setting, and zip code)
- Current insurance coverage and current work status
- Height/weight (current weight, highest weight ever, unintentional weight loss)
- Family history of pancreatic disease, pancreatic cancer, pancreatic resection, celiac disease, and diabetes
- Current OTC herbal/nutritional supplements
- Abdominal pain, GI symptoms, dietary habits, health-related quality of life, depression/anxiety, PERT use and treatment satisfaction, and healthcare utilization.

The following assessments will be collected during the clinical encounters with the Investigator:

- EPI-related information including EPI diagnosis, date of onset of symptoms indicative of EPI, method of confirmed/suspected EPI diagnosis (i.e., abnormal fecal elastase FE-1 test, clinical steatorrhea, vitamin deficiency, weight loss, pancreatic function testing, and/or other), CP etiology following the Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive (TIGAR-O) v2.0 classification (Whitcomb, 2019), and clinical manifestations of EPI (i.e., GI manifestations such as diarrhea/loose stool, steatorrhea, abdominal pain, bloating; nutritional manifestations such as unintentional weight loss/difficulty gaining weight, malnutrition, vitamin D and other vitamin/mineral deficiencies, and other)
- Medical history (history of comorbidities and surgical/endoscopic procedures, laboratory abnormalities)
- Current treatment(s) including medication (i.e., PERT and others) and other therapies, such as nutritional support, cognitive-behavioral therapy, as well as response to therapy.

6.3 Follow-Up

At Follow-Up, data will be collected from the study participant through remote data collection and by the Investigator at on-site clinical encounters. Study procedures for Follow-Up will be described in the sections below.

6.3.1 Direct From Study Participant Follow-Up

The study participant will complete assessments remotely via EDC portal, accessed via a mobile-friendly secure web URL every 3 months.

Autogenerated reminders via email or text (depending on study participant preference) will be sent weekly starting 3 weeks prior to the scheduled data collection date. If the study participant does not complete their assessments through the EDC portal within 7 days of the scheduled date, reminders will be sent to the study participant every other day. If the participant has not completed the assessments 21 days after the scheduled data collection date, the HealthiVibe Registry Manager will call the study participant to remind them to complete the assessments and/or find out about the reason for the delay.

6.3.2 On-Site Follow-Up Visit

Routine clinical encounters are performed approximately every 6 months or sooner if a study participant is prescribed another PERT (see Appendix A for eligible PERT). Each registry visit is anchored to the date of the previous on-site visit. There must be at least 150 days between each on-site visit unless the Early Follow-Up Visit criteria are met (see section EARLY Follow-Up Visit). Other routine clinical encounters may occur in between two registry visits, but the data collected in the Follow-Up forms should cover the time period since the last registry visit. If registry Follow-Up visits cannot occur approximately every 6 months, the site is encouraged to attempt to schedule a Follow-Up visit as soon as possible.

6.3.3 EARLY Follow-Up Visit

An EARLY Follow-up is considered any visit that occurs within fewer than 150 days from the previous visit. As stated above, an on-site visit does not qualify as Follow-Up visit if the visit occurs within fewer than 150 days since the last visit, unless the study participant is prescribed another PERT (see Appendix A for eligible PERT). When the EARLY Follow-Up criteria are met, the next follow-up visit will be calculated from the date of the Early Follow-Up visit.

6.3.4 Clinical Data Points

The following information will be collected from the study participants remotely via EDC portal every 3 months:

- Weight (current)
- Current insurance coverage and current work status
- Current OTC herbal/nutritional supplements
- Abdominal pain
- GI symptoms
- PERT use and treatment satisfaction

To limit burden on study participants, the following data will be collected from via EDC portal every 6 months:

- Dietary habits
- Health-related quality of life
- Anxiety/depression
- Healthcare utilization

The Investigator will provide the following information during the routine clinical encounters (approx. every 6 months):

- Clinical manifestations of EPI
- Current treatment(s) since last visit including medication (PERT and others) and other therapies such as nutritional support, and cognitive-behavioral therapy, as well as response to therapy
- Collection of AEs/SAEs occurring during the study (see Medical History and AEs and SAFETY REPORTING for more details).

6.4 Study Participant Exit

A study participant exits the study for one of the following reasons:

- Death
- The study participant withdraws from the study
- The study participant is being terminated by the Investigator
- The study participant transfers to a different gastroenterologist who is not a participating registry site
- The study participant is lost to follow-up (LTFU)
- The data collection period of the registry has ended

A study participant is LTFU when, despite all reasonable efforts (phone calls, email, letters, etc.), contact with the study participant cannot be reestablished, if a study participant does not complete their assessments remotely for 2 consecutive timepoints. This effort must be clearly documented by the HealthiVibe Registry Manager and information about the study participant's vital status (living or deceased) should be documented when known.

The Investigator will document the reason for the study participant's exit using the Study Participant Exit form (see Appendix B). If the reason for exit is due to death, any associated AEs, and/or AEs occurring after the last follow-up visit should be recorded and reported to HealthiVibe (see SAFETY REPORTING). The Investigator should carefully choose the option that best reflects the reason for exit at the time; the form should be completed within 5 business days of site awareness of the study participant's exit from the study.

7. STUDY EVALUATIONS AND MEASUREMENTS

7.1 Diagnosis, Etiology, and Clinical Manifestations

The Investigator will confirm eligibility criteria and provide detailed information on the history of EPI, date of the confirmed/suspected EPI diagnosis, method of confirmed/suspected EPI diagnosis (i.e., abnormal fecal elastase FE-1 test, clinical steatorrhea, vitamin deficiency, weight loss, pancreatic function testing, and/or other), and the date of start of EPI symptoms that may precede a confirmed diagnosis of EPI.

The Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive (TIGAR-O) v2.0 classification (Whitcomb, 2019) classification will be used to define the CP etiology.

The Investigator will also report the clinical manifestations of EPI that have been observed in the study participant. These clinical manifestations include GI (i.e., diarrhea/loose stool, steatorrhea, abdominal pain, bloating, and flatulence) and nutritional manifestations (i.e., unintentional weight loss/difficulty gaining weight, malnutrition, vitamin/mineral deficiencies).

7.2 Medical History and AEs

At Enrollment, the Investigator will provide information on the study participant's medical history related to the following:

- GI disorders
- Cardiovascular disorders
- Infections/inflammatory diseases

- Metabolic, endocrine, and bone health
- Mental health
- Social history
- Malignancies
- Surgical, radiological, and endoscopic procedures
- Laboratory abnormalities, if available/ordered as part of routine clinical practice

At the Follow-Up Visits, Investigators will provide information on any AEs/SAEs that may have occurred since last visit. For every AE that is reported, the following information will be collected:

- Event term
- Onset date
- Relation to PERT
- Event seriousness
- Any other events meeting SAE definition
- Outcome of SAE.

For any reported SAE, the following information will be collected:

- SAE event term
- SAE onset date
- SAE outcome (i.e., hospitalization, immediately life-threatening, death, persistent/significant disability, congenital abnormality or birth defect, treatment with intravenous antibiotics or anti-infectives, otherwise serious in the option of the Investigator)
- SAE final outcome/status (i.e., resolved/fully recovered, recovered with sequalae, ongoing, death, condition worsening)
- Brief description of the study participant with no personal identifying information
- Intervention/treatment for the SAE (i.e., medication or nutritional supplement, device, surgery, behavioral/lifestyle, observation)
- Details on medications used for the disease under study (i.e., drug name, dose, frequency, route, start date, date of last dose, event relation to the drug, continuation/discontinuation/changes of the drug)
- List of any relevant tests, laboratory data/results, and history, including preexisting conditions
- Brief description/narrative of the SAE
- Status of the SAE report (i.e., confirmed event, SAE previously reported between registry visits/duplicate, not an event)

At each Follow-up, Investigators will also complete a COVID-19 reporting form, which will collect the following information:

- COVID-19 diagnosis

- COVID-19 symptoms (i.e., fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea)
- COVID-19 vaccination date(s) and manufacturer(s), if applicable
- COVID-19 vaccine side effects (i.e., tiredness, headache, muscle pain, chills, fever, nausea), if applicable.

7.3 Treatments

The Investigator will complete a questionnaire on treatments at Enrollment with focus on:

- Medical therapies (PERT, pain medication, neuromodulators, antidiarrheals, vitamins and antioxidants, and other medication such as antidiabetics, proton pump inhibitors, and H2 blockers)
- Dietician and other nutritional support
- Cognitive behavioral therapy.

At the On-Site Follow-Up Visits, the Investigator will provide any updates on treatment(s) since the last visit (5-point scale; major symptom improvement to major worsening in symptoms).

7.4 Study Participant Demographics and Other Study Metrics

At Enrollment, information collected on demographics includes age, gender, race/ethnicity, highest level of education, marital status, annual household income, and geographical location (zip code and residence setting). Other study metrics include height, current weight, and weight history (maximum weight ever, episodes of unintentional weight loss, difficulty gaining weight). Family history of pancreatic cancer, chronic pancreatitis, pancreatic surgery, cystic fibrosis, and diabetes (Type I, II, or IIIc) will also be collected. Additionally, current insurance coverage, current work status, current OTC herbal/nutritional supplements, and healthcare utilization metrics (i.e., number of healthcare provider/ER/tele health visits, hospitalizations and length of stay, and number of sick days, if employed in the past 6 months) will be documented at Enrollment and at Follow-Up.

7.5 Study Participant Assessments

Study participants will complete a number of participant-reported assessments at Enrollment and Follow-Up. The information collected comprises the following domains: abdominal pain, GI symptoms, dietary habits, HRQOL, anxiety/depression, and PERT use and treatment satisfaction. Each of these domains is described in more detail below.

7.5.1 Abdominal Pain

Multiple constructs will be measured for abdominal pain, which will be collected with single-item questions around the abdominal pain pattern (constant vs. episodic), episodic abdominal pain intensity (0 – 10 numerical rating scale), frequency (number of abdominal pain episodes last month), and episode duration over the past month. Additionally, the abdominal pain history (in months), abdominal pain triggers (high-fat meals, stress, alcohol, tobacco, activity, other), abdominal pain relief methods (bowel movement, OTC analgesic medication, rest, fasting/diet adjustment), and abdominal pain control over the past month will be collected. Study participants will also be asked whether the abdominal pain was severe enough to seek medical attention, and if so, when and what type of medical attention they received (primary care provider, specialist, emergency room, urgent care, hospitalization). In the event they were hospitalized, the length of stay will be collected as well.

7.5.2 Gastrointestinal Symptoms

Single-item questions will be used to evaluate the severity of bloating (none to very severe), flatulence (none to very severe), and nausea (none to very severe) over the past week. Stool frequency will be captured with the average number of stools per day over the past week. Stool urgency will be measured with the number of urgency episodes over the past week (none to multiple times per day). Steatorrhea will be measured with a single-item question on the stool appearance (i.e., stool that is oily, bad smelling, and/or floats/difficult to flush; never to all the time). The stool consistency over the past week will be defined using the Bristol Stool Form Scale (BSFS). The BSFS is used for classifying the form of stool into 7 categories scored from 1 to 7; (1) Separate hard lumps like nuts (difficult to pass); (2) Sausage-shaped but lumpy; (3) Like a sausage but with cracks on its surface; (4) Like a sausage or snake, smooth and soft; (5) Soft blobs with clear-cut edges (passed easily); (6) Fluffy pieces with ragged edges, a mushy stool; (7) Watery, no solid pieces, entirely liquid. Study participants choose one of the BSFS scores which has a nearest analog form with their stools at every defecation.

7.5.3 Dietary Habits

Questions on dietary habits include the type of diet (vegetarian, mostly vegetarian, meat/poultry a few times/week or daily, vegan, gluten-free, low FODMAP, diabetic, other), number of meals/snacks per day, fat diet (high fat diet, average fat diet, low fat diet) and sweets intake (never to a few times per day). Study participants will also be asked if they have any dietary restrictions to avoid symptoms such as bloating, flatulence, abdominal pain, etc. (never to all the time).

7.5.4 Health-Related Quality of Life

HRQOL will be measured using the 12-item Short Form Survey (SF-12). The SF-12 is a survey designed for use with individuals with chronic conditions. This 12-item scale can be used to assess the physical and mental health of respondents. 10 of the 12 questions are answered on a 5-point Likert scale and 2 are answered on a 3-point Likert scale. The questions are then scored and weighted into 2 subscales, physical health and mental health. Respondents can have a score that ranges from 0 – 100 with 100 being the best score and indicating high physical or mental health. A 3-point change in SF-12 score reflects a meaningful difference.

7.5.5 Anxiety/Depression

Anxiety and depression levels will be measured with the Hospital Anxiety and Depression Scale (HADS). The HADS consists of 14 items divided into two 7-item subscales: Anxiety (HADS-A) and depression (HADS-D). Respondents rate each item on a 4-point scale from 0 (absence) to 3 (extreme presence). The total score is 42 (21 per subscale). Scores are derived by summing responses for each of the two subscales or for the scale as a whole. Higher scores indicate greater levels of anxiety and depression.

7.5.6 PERT Use and Treatment Satisfaction

Study participants will be asked whether PERTs have an impact on their symptoms (greatly improved symptoms to greatly worsened symptoms) and how they are taking the PERTs on a typical day (i.e., frequency, number of pills, and with/without meals and snacks). Treatment satisfaction related to PERTs will be measured with the Treatment Satisfaction Questionnaire for Medication – 9 items (TSQM-9). The TSQM-9 is a global satisfaction scale used to assess the overall level of participant's satisfaction or dissatisfaction with their medications. It comprises 9 items on 3 subscales: effectiveness, convenience and global satisfaction. The scores are computed by adding items for each domain, i.e., items 1 – 3 for effectiveness, items 4 – 6 for convenience and items 7 – 9 for global satisfaction (Bharmal et al., 2009). The lowest possible score (1 for each item and 3 for all 3 subscales) is subtracted from the composite score and divided by the greatest possible score range. The greatest range is (7-1) X 3 items = 18 for the effectiveness and convenience, and (5-1) x 3 items = 12 for global satisfaction. This provides a transformed score

between 0 and 1 that is then multiplied by 100; scores for the domains range from 0 (extremely dissatisfied) to 100 (extremely satisfied), with higher scores indicating greater satisfaction.

8. DATA COLLECTION AND MANAGEMENT

8.1 Electronic Data Capture System

Data collected in this registry will be entered into a 21 CFR Part 11-ready web-based EDC system at the specified data collection timepoints.

8.2 Investigator Forms

The Investigator or trained study site personnel will enter the data required by the registry directly into the EDC system. Instructions for proper completion of the electronic case report forms (eCRFs) and on how to use the EDC system will be provided to the site. An access code with login password will be provided to the Investigator following training. Any additional persons authorized to enter data into the eCRFs will be provided with a personal access code following training. The Investigator is responsible for ensuring that all sections of the eCRF are complete and correct and those entries can be verified against source data. At study closeout, the Investigator will be required to sign off on all eCRF before closure of the registry database.

8.3 Study Participant Forms

The study participant will complete their assessments at the site during Enrollment and remotely via EDC portal, accessed via a mobile-friendly secure web URL for Follow-Up.

Study personnel are prohibited from completing any part of the Study Participant forms on behalf of the study participant. However, study personnel are allowed to assist the study participant in the event of issues with the electronic device and can show the study participant where the data should be entered. If a study participant requests assistance during the visit, study personnel are permitted to facilitate completion of the form by transcribing the study participant's verbal responses to the Study Participant Form. At Enrollment, study participants will undergo a training on how to complete their assessments remotely via EDC portal for Follow-Up.

Site personnel are expected to review the study participants' responses for completeness, and to follow-up on any information captured in the forms. Details regarding any AEs occurring in the study participant and reported in the Study Participant Form must also be transcribed to the Investigator Form.

8.4 Study Participant Identification and Privacy

A registry study participant ID number (a unique, 6-character standard ID number) will be assigned to each study participant. To keep study participants' information confidential, this ID number will be used for data collection throughout the study. The site is responsible for assigning study participant IDs according to study-specific numbering requirements.

Each study participant's data collected in the registry will be stored under the registry participant ID number. The collection of protected health information (PHI) will be kept to the minimum that is required for the conduct of the study. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing study participant data. Study participants will be informed accordingly and will be asked to give their consent on data-handling procedures in accordance with national regulations.

8.5 Source Documents/Source Data

Source documents are original documents, data, and records (or certified copies of original records) of clinical findings and observations. Source documents are the records where clinical observations are first recorded (i.e., part of the medical record and the first point of entry). Some examples include hospital records, medical charts, and laboratory reports.

Source documents can exist in a paper or electronic format and they contain the raw data that are required to reconstruct, evaluate, and validate the integrity of a research study.

8.6 Corrections to Source Documents

Any corrections or changes made to source documents must be clearly attributable to the individual making the change and the date the change was made. An explanation should also accompany the change if it is not self-evident. If paper source documents are used, any modifications to the record must not obscure the original entry.

8.7 Case Report Forms (eCRFs)

eCRFs are forms designed to capture all required information for each registry participant. CRF data entry is done using the electronic EDC which constitutes the submission of registry data to HealthiVibe.

Data in the eCRFs that are first recorded/captured elsewhere (such as on paper or in an electronic database) should always be consistent with and substantiated by the source documents. When data for the registry are first recorded in an electronic CRF, the CRF is also a source document. Each registry site will document which data are being transcribed to the EDC and which data are considered source. This information will be kept in their registry binder.

8.8 Record Retention

To enable evaluations and/or audits from regulatory authorities or HealthiVibe, the Investigator agrees to keep all required study records in compliance with HealthiVibe's record retention policy. This includes but is not limited to the identity of all registry study participants, all source documents, and IRB approvals, as well as documentation of relevant study correspondence and change notifications (e.g., memos-to-file, reports, deviation forms, etc.). Study records can be stored electronically or converted to an electronic format as certified copies of the original paper documents.

All study records and source data should be retained by the Investigator throughout the entire duration of his or her study participation and in compliance with local laws. Upon Sponsor termination of the registry or Investigator termination of their participation, all source data should be retained according to state laws for the minimum medical record retention periods for records held by medical doctors and hospitals.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), HealthiVibe should be prospectively notified. The study records must be transferred to a designee acceptable to HealthiVibe, such as another Investigator, another institution, or to an independent third party arranged by HealthiVibe.

9. SAFETY REPORTING

9.1 Adverse Events

An AE is defined as any untoward medical occurrence in a study participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. AE data collection

begins *after* a study participant has completed an Enrollment Visit. During the Follow-Up on-site visits, the Investigator and/or designee is required to question the study participant regarding the occurrence of AEs since the previous registry visit. Pertinent details regarding any reported AEs are to be captured using the pertinent sections in the Investigator Follow-Up forms.

Any AEs that are reported by the study participant, discovered as a result of general questioning by the Investigator, should be recorded in the Investigator Follow-Up Form at the next scheduled registry visit following the onset of the event.

9.2 Serious Adverse Events

SAEs are defined as adverse events that result in any of the following outcomes:

- Hospitalization (new or prolongation)
- Death
- Immediately life threatening (urgent intervention required to prevent outcome of death)
- Persistent/significant disability or incapacity
- Congenital abnormality or birth defect
- Otherwise serious (important medical event) in the opinion of the Investigator (i.e., event that may jeopardize the study participant and require medical or surgical intervention/treatment to prevent one of the other outcomes listed above).

SAEs are to be reported by sites in accordance with registry AE Reporting Guidelines as soon as possible after the site learns of the event (within 1 business day), via the electronic data capture system or approved backup mechanism (per the AE Reporting Guidelines). These events should also be captured by the Investigator at the next registry visit following the onset date of the event. Sites are required to request supporting documents (e.g., hospital records, laboratory results, etc.) for each SAE. These records should be submitted as soon as they become available to the site (between registry visits). The Investigator or qualified designee must remove all of the study participant's personal identifiers from the supporting documents prior to submission to HealthiVibe.

10. STUDY PARTICIPANT WITHDRAWAL

Study participants have the right to withdraw their consent for participation in the registry at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled. They may withdraw by notifying the Investigator in writing, in person, or by telephone. When a study participant withdraws from the registry, the Investigator or the designee completes a Study Participant Exit Form and cites the reason(s) for withdrawal.

If a study participant also withdraws their consent for the use of their personal information either partially or completely, the Investigator or designee must notify HealthiVibe. If the participant withdraws from the registry, and also withdraws consent for disclosure of future information, no further evaluations are performed, and no additional data are collected.

Date of revocation is the date the study participant requested removal of contact info or withdrawal of consent. Because it is documented in the EDC system, it is of critical importance that registry personnel enter a study participant's decision to revoke use of their personal information immediately upon awareness to ensure there is no lag between when a study participant communicates their request for withdrawal and when HealthiVibe receives that request.

11. DATA ANALYSIS

Statistical analyses will be guided by the specific aims of the registry. Complete details of all analyses will be described in a standalone Statistical Analysis Plan (SAP) with accompanying mock Tables, Figures and Listings (TFLs).

All data will be summarized descriptively. Continuous variables will be described through reporting of the mean (± standard deviation), median and range, while categorical data will be described through reporting of frequency and percent. The participant population will be characterized by demographics and baseline attributes. From this characterization, important subgroups of interest may be identified if sample sizes are sufficiently robust for additional exploratory analyses. All pre-planned, clinically important subgroups for analyses will be identified in the SAP.

Study disposition of all participants will be summarized including dropouts (with reasons presented for those who drop out), and for lost to follow-up (at what point they are lost, and if they return).

Multivariate modeling will be employed to study both the EPI due to CP disease history and disease progression by analyzing patterns of medical history, comorbidities, and treatment approaches. Variables in the modeling will also include clinical care practices and their impact on the modeling.

Clinical care practices will be further explored with their potential impact on quality of life, comorbidities, and treatments using the same multivariate modeling. Treatment compliance will be examined for each of the models, knowing that biases are introduced with participant recall. Prescribing practices will be descriptively presented (to include type of PERT, dose at initiation and escalation, recommendation on how to take PERT, and reason for switching to another PERT, if applicable). If trends are identified in prescribing patterns, these trends may be further explored.

Healthcare utilization data will be assessed with key variables from the clinical dataset. Impact and burden of EPI due to CP will be assessed for impact on the healthcare system (the number of ER visits, healthcare provider visits, number of hospitalizations, length of hospital stay, and number of sick days taken). Associations will be presented descriptively, and if the data are robust, inferential statistics will be presented using rates and 95% confidence intervals.

Confounding will be assessed for predicting outcomes with the registry data. For example, selective prescribing (confounding by indication) will be reviewed to verify if those with more severe disease or those who have failed other treatments are more likely to receive experimental or newer treatments than those with less severe disease or less access to new treatments due to socioeconomic, geographic locations, or other identified factors collected in the registry. Other potential confounders of the data may be identified and will be further outlined in the SAP.

If any confounding is identified, statistical procedures such as stratified analysis, multivariable analysis, and/or sensitivity analysis may be employed as appropriate for that confounder and outcome. Given that groupings within a study population may exist (e.g., patients seen by a single site/practice/physician may themselves predict health outcomes of interest, these potential grouping effects will be handled with use of ANOVA (analysis of variance) models.

Data quality assessed in terms of missing data, out of range values, and completeness will be presented, as to allow for appropriate interpretation and extrapolation of the study results.

All analyses will be conducted in SAS version 9.1.3 or higher.

12. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, HealthiVibe will monitor and audit registry data and investigative sites to ensure the protocol, data collection requirements, and applicable research regulations are complied with. The monitors may review source documents to confirm that the data in the registry database are accurate and verifiable. The Investigator must allow HealthiVibe monitors and appropriate regulatory authorities direct access to source documents to perform this verification. These personnel, bound by study participant privacy laws, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

The study site may also be subject to review by the IRB, and/or to quality assurance audits performed by HealthiVibe, or companies working with or on behalf of HealthiVibe and/or to inspection by appropriate regulatory authorities.

12.1 Study Monitoring

12.1.1 Responsibilities of the Investigator

The Investigator is required to ensure compliance with all procedures required by this protocol and with all data collection requirements defined by the Sponsor. The Investigator agrees to participate in a site initiation visit and to participate in the required training. The Investigator also agrees to provide reliable data and all information requested by the registry protocol via the most current data collection requirements and any resulting requests for data clarifications in an accurate and timely manner in compliance with the procedures defined by HealthiVibe. The Investigator will also need to provide appropriate training to study participants on how to use the EDC portal for remote data collection at Follow-Up.

The Investigator must also ensure that authorized HealthiVibe representatives are given direct access upon request and sufficient notice to examine, analyze, and verify any source documents that are important to the evaluation and integrity of the registry study.

12.1.2 Responsibilities of the Sponsor

On behalf of the Sponsor, HealthiVibe is responsible for taking all reasonable steps to ensure the proper conduct of the registry protocol with regards to research ethics, compliance, and the standardization, integrity, and validity of the data collected. Thus, the main duty of the monitoring team and other authorized HealthiVibe representatives is to help the Investigator and Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the registry in accordance with data collection and quality assurance standards for non-interventional, observational registries.

At regular intervals as defined by the registry monitoring plan (RMP), Investigative sites are contacted by HealthiVibe representatives to participate in monitoring visits. These visits are primarily carried out remotely via email, phone, or a virtual meeting space, but may occur on location at a registry site.

Representatives may request to discuss study progress and performance, review compliance with registry evaluation and data collection requirements, verify registry data via source document verification, as well as investigate any emergent data quality issues detected from an aggregate review of data quality indicators.

12.2 Protocol Deviations

Because HealthiVibe registries support human research, HealthiVibe must have written procedures for sites that ensure prompt reporting of deviations. Protocol deviations for non-interventional, observational research are defined as those that may affect the rights or privacy of human subjects or the scientific integrity of the registry's objectives. If a protocol deviation occurs which meets this definition, the registry site will need to complete a protocol deviation form which will be sent to HealthiVibe.

13. ETHICAL AND REGULATORY STANDARDS

13.1 Ethical Principles

HealthiVibe is responsible for ensuring that the study will be conducted in accordance with applicable legal and regulatory requirements, as well as the Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), the Declaration of Helsinki (World Medical Association 2008), and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), where applicable.

The Investigator is responsible for ensuring that the registry is conducted in accordance with the protocol and all applicable local, state, and federal laws and regulations and is responsible for protecting the rights, privacy, and welfare of study participants participating in the registry under his or her care.

In compliance with HealthiVibe public disclosure commitments, this non-interventional study will be recorded in the public registry website clinicaltrials.gov. The registry will contain basic information about the study sufficient to inform interested study participants (and their healthcare practitioners) on how to enroll in the registry.

13.2 Informed Consent

The Investigator or designee must ensure that each study participant is fully informed about the nature and objectives of the registry and possible risks associated with participation, in language and terms the study participant is able to understand. The Investigator or designee will obtain documentation of informed consent from each study participant before any registry evaluation is performed.

The Investigator will retain the original of each study participant's signed ICF. If the study participant is legally blind and/or illiterate, an impartial witness must be present for the consent process and this individual must also sign and personally date the informed consent form.

13.3 Institutional Review Board

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, study participant data collection forms, and other relevant documents (e.g., recruitment advertisements, assessment completion reminders) from the Institutional Review Board (IRB). All correspondence with the IRB should be retained in the site regulatory file. Copies of local IRB approvals should be forwarded to HealthiVibe. Amendments to any documents may not be initiated prior to Sponsor, HealthiVibe, and IRB approval.

14. ADMINISTRATIVE EXPECTATIONS

14.1 Confidentiality

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the registry, including, but not limited to, the registry protocol, the data collection forms, and informed consent, is confidential. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this registry protocol and other necessary documentation to the IRB is expressly permitted, the IRB members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Investigator and Sub-Investigators of the confidential nature of the registry.

Furthermore, all Investigators and HealthiVibe agree to adhere to the principles of personal data confidentiality in relation to the study participants, Investigators, and all other collaborators involved in the study.

14.2 Data Protection

The study participant's personal information shall be treated in compliance with all applicable health information privacy laws and regulations. When archiving or processing study participant personal information, HealthiVibe shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The same privacy laws and regulations apply to the study participant's clinical data identified by a study participant ID that are stored in the EDC. HealthiVibe shall take all the appropriate measures to ensure that this database is protected and secured from unauthorized disclosure during processing or archiving of clinical database records.

In accordance with applicable research and health information privacy laws, clinical data and personal information collected for this registry are maintained in separate databases for an undefined time period.

HealthiVibe also collects demographic data on Investigators and any person involved in the registry which may be included in a database. Again, HealthiVibe shall take all the appropriate privacy measures to ensure that this information is protected and secured from unauthorized or inadvertent disclosure.

14.3 Study Results

At least thirty (30) days prior to submission for Publication, Investigator shall submit to Nestlé for review and comment any proposed oral or written Publication ("Review Period"). Investigator will consider any such comments in good faith but is under no obligation to incorporate Nestlé's suggestions. The Review Period for abstracts or poster presentations shall be thirty (30) days. If during the Review Period, Nestlé notifies Investigator in writing that: (i) it desires patent applications to be filed on any inventions disclosed or contained in the disclosures, Investigator will defer Publication for a period not to exceed sixty (60) days, to permit Nestlé to file any desired patent applications; and (ii) if the Publication contains Confidential Information as defined in Section 14.1 and Nestlé requests Investigator in writing to delete such Confidential Information, the Investigator agrees to delete such Confidential Information only to the extent such deletion does not preclude the complete and accurate presentation and interpretation of the Study results. Upon request by Nestlé, Investigator shall include an appropriate reference to Nestlé and the Study.

14.4 Registry Termination or Completion

The Sponsor reserves the right to terminate the registry at any time. Both the Sponsor and HealthiVibe have the right to terminate the Investigator's participation in the study according to the registry study agreements.

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16. Appendices

Appendix A – Eligible PERT

Drug Type	Non-Proprietary Name	Brand Name
Pancreatic Enzyme Replacement Therapy	Pancrelipase	Zenpep®
	Pancrelipase	Creon®
	Pancrelipase	Pancreaze®
	Pancrelipase	Pertzye®
	Pancrelipase	Viokase®

Appendix B – Study Participant Exit Form

What is the reason for the study participant's exit?

- ☐ Study participant withdrew from the study
- ☐ Study participant was terminated by the Investigator
  - ☐ Please specify reason: **[ADD FREE TEXT]**
- ☐ Study participant is lost to follow up
- ☐ Study participant transferred care to another gastroenterologist
- ☐ Data collection period of the registry has ended