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Statistical Analysis Plan (SAP)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	Term or Definition
AE	Adverse event
AP	Acute pancreatitis
BSFS	Bristol Stool Form Scale
CP	Chronic pancreatitis
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of Study
EPI	Exocrine pancreatic insufficiency
ER	Emergency room
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
N/A	Not applicable
OTC	Over the counter

Abbreviations	Term or Definition
PACT-CP	PAtient-CenTric Chronic Pancreatitis Registry
PERT	Pancreatic enzyme replacement therapy
PRO	Participant-reported outcome
PT	Preferred Term
RAP	Recurrent acute pancreatitis
RMP	Registry monitoring plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SF-12	12-item Short Form Survey
TFL(s)	Tables, Figures and Listings
TSQM-9	Treatment Satisfaction Questionnaire for Medication – 9 items

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1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays for study protocol NES-EPI-100 "PAtient-CenTric Chronic Pancreatitis Registry" version 3.0 (13APR2021). The table of contents and templates for the Tables, Figures and Listings (TFLs) will be produced in a separate document.

All data analyses and generation of TFLs will be performed using SAS® version 9.4 or higher. The SAP will be finalized and signed off prior to locking the database.

2 STUDY OBJECTIVES

2.1 Main Objective

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

3.1 Overall 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 Table 1) 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).

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.

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.

3.2 Schedule of Assessments

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

3.3 Sample Size

Sample size is determined by the investigators' judgment. 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.

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		

	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		
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.

4 STUDY POPULATION

4.1 Screened Population

The screened population will consist of enrolled patients who fill the informed consent form.

4.2 Enrolled Population

The enrolled population will consist of enrolled patients who both fill the informed consent form and meet eligibility criteria.

5 STATISTICAL CONSIDERATIONS AND ANALYSES

5.1 General Considerations

All statistical procedures will be completed using SAS® version 9.4 or higher.

Continuous variables will be summarized using descriptive statistics, including the number of patients with non-missing value (n), mean, median, standard deviation (SD), minimum and maximum. “n” will be presented without a decimal point, minimum and maximum values will be presented with the same precision as in the database, mean and median will be presented with one more decimal place than the minimum and maximum, and SD will be presented with one more decimal place than the mean and median.

For categorical variables, summaries will include counts of patients (frequencies) and percentages. Percentages will be rounded to one decimal place. Descriptive summaries of change from baseline in categorical variables will be provided using shift tables, if applicable.

Day 0 is defined as the date when patients sign ICF.

No data imputation for any missing data will be done in this study.

5.2 Patient Dispositions

The number (%) of participants in enrolled population will be summarized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Participants who completed the study period as per protocol.
    - EOS is the date collected on “Study Participant Exit Form”.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation (“Death”, “The study participant withdraws from the study”, “The study participant is being terminated by the investigator”, “The study participant transfers

to another gastroenterologist", "The study participant is lost to follow-up", "Other reasons").

5.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be collected during the enrollment visits (See Table 1). Descriptive summaries of demographics and other baseline characteristics in the following categories will be presented for all enrolled population.

- Age
- Gender ("Woman", "Man", "Other", "Prefer not to say")
- Ethnicity ("Hispanic or Latino", "Not Hispanic or Latino")
- Race ("American Indian or Alaska Native", "Native Hawaiian or Other Pacific Islander", "Asian", "Black or African American", "White", "Other")
- Marital status ("Single", "Married/Partnered", "Divorced/Separated", "Windowed")
- Highest level of education ("High school, not completed", "High school, completed", "University, no degree", "Associate or equivalent", "Bachelor's or equivalent", "Master's or equivalent", "PhD or equivalent")
- Annual household income
- Residence setting ("Rural", "Suburban", "Urban")
- Current insurance coverage ("Insurance through a current or former employer or union", "Insurance purchased directly from an insurance company", "Medicare", "Medicaid", "TRICARE or other military healthcare", "VA", "Indian Health Service", "Other type of insurance or health coverage plan", "No insurance")
- Current work status ("Full-time employed", "Part-time employed", "Retired", "Unemployed, looking for work", "Unemployed, unable to work", "Student")
- 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

- The patient's chronic pancreatic etiology ("Toxic-Metabolic", "Metabolic", "Idiopathic", "Genetic", "Autoimmune", "Recurrent and severe acute pancreatitis", Obstructive, "Other")
- Evidence of suspected/confirmed EPI diagnosis ("Abnormal fecal elastase -1 test", "Clinical steatorrhea", "Vitamin deficiency", "Weight loss", "Pancreatic function testing", "Other")
- Clinical manifestations of EPI ("Diarrhea/loose stool", "Steatorrhea", "Abdominal pain", "Bloating", "Flatulence", "Unintentional weight loss/difficulty gaining weight", "Malnutrition", "Vitamin D deficiency", "Other vitamin/mineral deficiencies")

The baseline characteristics of abdominal pain, GI symptoms, dietary habits, health-related quality of life, depression/anxiety, PERT use and treatment satisfaction, and healthcare utilization will also be collected. Please see their individual sections below for detailed analysis.

5.4 Protocol 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 the sponsor.

Important protocol deviations, if applicable, will be identified prior to database lock. The number of patients with identified important protocol deviations will be summarized. Details on important protocol deviations will be provided in a listing.

5.5 PERT and other supplement/medication/therapies

Patients are considered as compliant if they are kept on PERT during the study. The eligible PERTs are listed in Appendix A. If any patient answers "No" to the question "Do you take your

enzymes everyday?" two times for two consecutive timepoints, , the patient is considered as noncompliant.

Descriptive summaries of the following categories will be presented, if applicable:

- Type of PERT (Creon®, Pancreaze®, Pertzye®, Viokase®, Zenpep®, Other)
- PERT Dose at initiation
- PERT Dose escalation ("Yes", "Not Applicable")
- PERT Dosing frequency per day
- Number of pills of PERT taken per day
- Habit when taking PERT ("With my meals only", "With my snacks only", "With my meals and snacks", "Outside of my meals/snacks", "Other")
- PERT Route of administration ("Oral", "Enteral feeding tube", "Other")
- Recommendation on how to take PERT ("Entire dose at the beginning of meal", "Half before the meal and the other half during the meal", "Entire dose 20 minutes before the meal", "PERT should be taken with meals only", "PERT should be taken with meals and snacks", "Other")
- Reason for switching to another PERT ("Efficacy", "Dosing", "Insurance coverage", "Patient preference", "Physician preference", "Other")
- How have enzymes been impacting the symptoms ("Greatly improved symptoms", "Somewhat improved symptoms", "Symptoms are unchanged", "Somewhat worsened my symptoms", "Greatly worsened my symptoms")
- Type of vitamins and antioxidants ("Fat soluble vitamin supplement or repletion", "Vitamin B 12 supplement", "Zinc", "Calcium", "Probiotics", "Other")
- Type of pain medications ("Opioids", "Simple analgesics", "Tramadol", "Non-steroidal anti-inflammatory drugs", "Gabapentin", "Cannabinoid", "Other")
- Type of neuromodulators ("Selective Serotonin Reuptake Inhibitors", "Serotonin and Norepinephrine Reuptake Inhibitors", "Tricyclic Antidepressants", "Monoamine Oxidase Inhibitors", "Atypical Antidepressants", "Other")

- Type of Antidiarrheals ("Lomotil", "Imodium", "Other")
- Type of other medication ("Insulin", "Metformin", "Other antidiabetic medications", "Proton pump inhibitors", "H2 blockers", "Other")
- Type of other therapies ("Dietician consultation", "Other nutritional support/management", "Cognitive behavioural therapy", "Other")

5.5.1 Treatment Satisfaction

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 [1]. 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) * 3 items = 18 for the effectiveness and convenience, and 14 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.

Table 2 Algorithm for Transforming TSQM-9 Composite Score **[3]**

Subscale	Algorithm	Handle missing score
Global Satisfaction	([Sum(Item 7 to Item 9) – 3] divided by 14) * 100	If either Item 7 or 8 is missing ([(Sum(the two completed items)) – 2] divided by 10) * 100; If Item 9 is missing ([(Sum(Item7 and Item8)) – 2] divided by 8) * 100
Effectiveness	([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100	If one item is missing ([(Sum(the two completed

		items – 2] divided by 12) * 100
Convenience	([Sum(Item 4 to Item 6) – 3] divided by 18) * 100	If one item is missing ([(Sum(the two completed items)) – 2] divided by 12) * 100

Descriptive statistics per subscale will be provided to summarize treatment satisfaction. Patients' treatment satisfaction score will also be listed.

5.6 Medical and Surgical History

The study participant's medical history related to the following will be collected at enrollment visits:

- 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

The frequencies and percentages of patients with reported medical and surgical history will be presented by term alphabetically. Medical and surgical history will also be listed.

Laboratory abnormalities include but not limit to

- Fecal elastase-1 test <200 mcg/g
- Iron deficiency anemia <12 ng/mL
- Megaloblastic anemia: hemoglobin <13 g/dl in men and <12 g/dl in women

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- Pancytopenia: Red blood cell: <4.2 million cells/cc in women / <4.7 million cells/cc in men and White blood cell: <4,000 cells/cc and Platelet: <150,000 cells/cc
- Pre-albumin <16 mg/dL
- Albumin <35 g/L or >52 g/L
- AST > 3x NL
- ALT > 3x NL
- Total bilirubin > 1.2 mg/dL
- ALP > 3x NL
- Triglycerides >300 mg/dL fasting, or >500 mg/dL non-fasting
- Elevated lipase
- Elevated amylase
- Serum lipids >200 mg/dL
- Total calcium >12.0 mg/dL
- Vitamin B12 ,160 pg/ml (118 pmol/L)
- Vitamin A <28 µg/dL
- 25-Hydroxyvitamin D <20 ng/ml
- Vitamin E <4 mg/L
- Elevated INR
- Selenium <40 ng/mL
- Zinc <70 µg/dL
- Folate <2 ng/mL
- Iron <60 µg/dL in men and <35 µg/dL in menstruating women
- Hydrogen breath test/duodenal aspirates >100,000 cfu/mL
- Elevated high-sensitivity C-reactive protein (hs-CRP) >3.0 mg/dL
- Oral glucose tolerance test (OGTT) >200 mg/dL
- Serum lipids and triglycerides >500 mg/dL or above (5.7 mmol/L or above)
- Other laboratory abnormality

The age started at alcohol, tobacco, cannabis, opioids or substance abuse, and frequencies, if any, will be descriptively summarized.

5.7 Adverse Events/Serious 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.

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

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

- Hospitalization (new or prolongation)
- Death

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- 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)

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)

Severity and causality of all AEs are determined by the Investigators.

An overall summary of the incidence of AEs/SAEs (number of patients with any events and number of events, if applicable) will include the following:

- All AEs
- All SAEs
- PERT- suspected to be related AEs
- SAEs leading to study discontinuation
- SAEs leading to dose interrupted
- AEs leading to death

AEs (number of patients with any events and the number of patients with specific AEs/SAEs arranged alphabetically by term will be tabulated for the following:

- AEs
- SAEs
- PERT- suspected to be related AEs
- SAEs leading to study discontinuation
- SAEs leading to dose interrupted
- AEs leading to death

When a patient has the same adverse event reported multiple times, the patient will only be counted once in adverse event frequency tables.

All AEs, SAEs and deaths will be listed.

5.8 Abdominal Pain

Descriptive summaries of the following categories will be presented, if applicable:

- Abdominal pain pattern (“No pain”, “Episodes of mild/moderate pain-but no constant pain”, “Constant mild/moderate pain-but no episodes”, “Episodes of severe pain-but no constant pain”, “Constant mild/moderate pain plus episodes of more severe pain”, “Constant severe pain”)

- Average episodic abdominal pain intensity (0 – 10 numerical rating scale)
- Worst episodic abdominal pain intensity (0 – 10 numerical rating scale)
- Frequency of episodes of abdominal pain (number of abdominal pain episodes last month)
- Episode typical duration ("A few hours", "More or less a day", "Several days", "More than a week")
- Abdominal pain triggers ("High-fat meals", "Stress", "Alcohol", "Tobacco", "Physical activity", "Other")
- Abdomianl pain lasting period before enrolment ("Less than 3 months", "between 3 and 6 months", "longer than 6 months")
- Abdominal pain relief methods ("OTC pain medication", "Rest", "Fasting and/or adjusting diet", "Bowel movement", "Other")
- Abdominal pain control ("Yes", "No")
- Abdominal pain severe enough to seek medical attention ("Primary healthcare provider", "Specialist", "Emergency room", "Urgent care", "Hospital")
- Hospitalization due to abdominal pain ("Less than 24 hrs", "A few days", "A week", "More than a week")

5.9 Gastrointestinal Symptoms

Descriptive summaries of the following categories will be presented, if applicable:

- Level of bloating over the past week ("None", "Mild", "Moderate", "Severe", "Very Severe")
- Level of flatulence over the past week ("None", "Mild", "Moderate", "Severe", "Very Severe")
- Level of nausea over the past week ("None", "Mild", "Moderate", "Severe", "Very Severe")
- Number of bowel movement per day over the past week

- Number of urgency episodes over the past week ("Never", "One time", "A few times", "Once per day", "Multiple times per day")
- Steatorrhea (stool look oily, smelled really bad, and/or floated/was difficult to flush) over the past week ("Never", "Rarely", "Some of the time", "Often", "All the time")
- Stool consistency over the past week (Type 1 – 7)

5.9.1 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

5.10 Dietary Habits

Descriptive summaries of the following categories will be presented, if applicable:

- Type of diet ("Vegetarian", "Mostly vegetarian with occasional meat", "Meat/poultry a few times/week", "Daily poultry/meat", "Vegan", "Gluten-free", "Low FODMAP", "Diabetic", "Other")
- Number of meals/snacks per day
- Amount of fat in diet per day ("High in fat", "Average fat", "Low in fat")
- Frequency of sweets intake ("Never", "Once a week", "A few times per week", "Once a day", "A few times a day")
- Frequency of dietary restrictions to avoid symptoms ("Never", "Rarely", "Some of the time", "Often", "All the time")

5.11 Health-Related Quality of Life

HRQOL will be measured using the 12-item Short Form Survey (SF-12). 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. The methodology used to transform raw scores to 100 scale is based on [2].

Descriptive statistics per subscale will be provided to summarize health-related quality of life. Patients' response will also be listed.

5.12 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.

Descriptive statistics per subscale will be provided to summarize patients' anxiety/depression level. Patients' response will also be listed.

5.13 Healthcare utilization

Healthcare utilization data will be assessed in terms of the impact and burden of EPI due to CP on the healthcare system.

Descriptive summaries of the following categories will be presented, if applicable:

- Number of healthcare provider
- Number of ER

- Number of telephone/health visits
- Hospitalizations and length of stay
- Number of sick days, if employed in the past 6 months

5.14 COVID-19 information

Descriptive summaries of the following categories will be presented, if applicable:

- If the patient is diagnosed with COVID-19
- COVID-19 Symptoms ("Fever or chills", "Cough", "Shortness of breath or difficulty breathing", "Fatigue", "Muscle or body aches", "New loss of taste or smell", "Sore throat", "Congestion or runny nose", "Nausea or vomiting", "Diarrhea", "N/A")
- If the patient is vaccinated
- COVID-19 vaccine-associated side effects ("Tiredness", "Headache", "Muscle Pain", "Chills", "Fever", "Nausea", "N/A")

5.15 Exploratory Analysis

Multivariate modeling will be employed to study both the EPI due to CP disease history and disease progression. The coefficients across the different models will be provided. P-value of exact F statistics test comparing the coefficients among different variables may also be provided.

Potential dependent variables are:

- Clinical manifestations of EPI ("Diarrhea/loose stool", "Steatorrhea", "Abdominal pain", "Bloating", "Flatulence", "Unintentional weight loss/difficulty gaining weight", "Malnutrition", "Vitamin D deficiency", "Other vitamin/mineral deficiencies")
- How have enzymes been impacting the symptoms ("Greatly improved symptoms", "Somewhat improved symptoms", "Symptoms are unchanged", "Somewhat worsened my symptoms", "Greatly worsened my symptoms")

- The patient's chronic pancreatic etiology ("Toxic-Metabolic", "Metabolic", "Idiopathic", "Genetic", "Autoimmune", "Recurrent and severe acute pancreatitis", Obstructive, "Other")
- Evidence of suspected/confirmed EPI diagnosis ("Abnormal fecal elastase -1 test", "Clinical steatorrhea", "Vitamin deficiency", "Weight loss", "Pancreatic function testing", "Other")
- Abdominal pain pattern ("No pain", "Episodes of mild/moderate pain", "Constant mild/moderate pain", "Episodes of severe pain", "Constant mild/moderate pain plus episodes of more severe pain", "Constant severe pain")
- Health-Related Quality of Life
- Treatment compliance

Potential independent variables are:

- Type of PERT (Creon®, Pancreaze®, Pertzye®, Viokase®, Zenpep®, Other)
- Medical History
- Comorbidities (simultaneous presence of two or more diseases or medical conditions)
- PERT Dose at initiation
- PERT Dose escalation
- Recommendation on how to take PERT ("Entire dose at the beginning of meal", "Half before the meal and the other half during the meal", "Entire dose 20 minutes before the meal", "PERT should be taken with meals only", "PERT should be taken within meals and snacks", "Other")
- Reason for switching to another PERT ("Efficacy", "Dosing", "Insurance coverage", "Patient preference", "Physician preference", "Other")

Healthcare utilization rate may be calculated based on

- Number of healthcare providers
- Number of ER visits

- Number of tele health visits
- Hospitalizations and length of stay
- Number of sick days, if employed in the past 6 months

Potential confounders will be explored for predicting outcomes with the registry data. 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.

6 APPENDICES

6.1 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®

7 REFERENCES

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2. Ware, J. E. (1998, January). *(PDF) sf-12: How to score the SF-12 physical and mental Health SUMMARY Scales*. ResearchGate. https://www.researchgate.net/publication/242636950_SF-12_How_to_Score_the_SF-12_Physical_and_Mental_Health_Summary_Scales.
3. IQVIA™ (2021, January). User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM).