Advancing Treatment for Pancreatitis: A Prospective Observational Study of TPIAT (POST)

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A multicenter collaborative prospective study in TPIAT for chronic pancreatitis and recurrent acute pancreatitis

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Protocol Synopsis

Study Title	Advancing Treatment for Pancreatitis: A Prospective Observational Study of TPIAT (POST)
Study Design	Multi-center, prospective, observational cohort study
Study Duration	5 years
Accrual Objective	450 patients (total for all sites)
Study Objectives	Aim 1: To determine (1a) whether patient and disease characteristics are associated with favorable pain and health-related quality-of-life outcomes (HRQOL) after TPIAT; (1b) the optimal timing of the TPIAT intervention to resolve pain and improve HRQOL; and (1c) in a subset of patients, the impact of central sensitization on pain resolution. Aim 2: To determine (2a) whether patient and disease characteristics are associated with favorable glycemic outcomes from the IAT procedure; and (2b) the optimal timing of TPIAT to obtain post-surgical insulin independence. Aim 3: To determine the cost-effectiveness of TPIAT.
Study Outcomes	Study outcomes are observational measures after TPIAT, collected from a combination of patient-obtained history at study visits, standardized questionnaires, and medical records abstraction. Key outcomes include: 1. Pain Resolution: a. Primary: VAS pain score b. Secondary: opioid use (on/off and morphine equivalents); pain interference score 2. Health Related Quality of Life: a. Primary: SF-12 version 2 physical and mental component summary scores b. Secondary: SF-12 subscores; hospitalizations; functional status (disability) 3. Diabetes: a. Primary: Insulin independence b. Secondary: Insulin dose; islet graft function, fasting C-peptide, HbA1c level; severe hypoglycemia
Inclusion Criteria	1. Any patient with chronic or recurrent acute pancreatitis undergoing total or completion pancreatectomy with islet autotransplantation at a participating center.
Exclusion Criteria	1. Patient undergoing partial pancreatectomy 2. TPIAT performed for a diagnosis other than chronic or recurrent acute pancreatitis (for example benign or malignant pancreatic tumor)
Study Procedures	Informed consent and baseline history will be obtained prior to TPIAT procedure. Follow up visits performed face-to-face or by remote (telephone) follow up at 6 months, 1 year, and then yearly post-transplant until completion of the study (1-4 years follow up per participant), to assess predefined study out-

	comes (endpoints). In addition, medical records abstraction will be performed for key details on surgical history, pancreatitis, and hospitalization events. Because this is an observational study, collection of study-related adverse events is limited to AEs directly attributed to research measures.
Study Oversight	Study monitoring: Annual site monitoring for protocol compliance and data accuracy will be performed by a member of the DCC Study oversight: The steering committee (made up of a PI from each clinical center and the DCC PI) will review study AEs and unanticipated events on a semi-annual basis.

1. INTRODUCTION AND AIMS OF THE CURRENT STUDY

Total pancreatectomy with islet autotransplantation (TPIAT) is a promising emerging therapy for intractable chronic pancreatitis. The rationale for TPIAT is to treat the severe, disabling pain of chronic pancreatitis. With this procedure, the pancreas is completely resected, the pancreatic islets are isolated through enzymatic and mechanical digestion of the pancreas, and the islets are infused back into the recipient's liver to reduce the risk of post-pancreatectomy diabetes (1, 2). More than 15 centers in the U.S. now offer this specialized procedure. However, fundamental questions remain regarding the selection of candidates, outcomes, and timing of intervention. With increasing utilization of TPIAT, it is critical that the major centers performing this procedure collaborate to better define the patient population and post-procedural outcomes, particularly for pain resolution and associated functional measures, and use this information to develop predictive models to aid in selection of candidates for and timing of intervention. This has been recognized as a priority area for research funding by experts convening at a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored workshop to define research priorities in TPIAT in July 2014 (3, 4).

This multi-center consortium will conduct a multi-center prospective observational cohort study of TPIAT with a focus on patient selection and timing of intervention as they affect the chance of a successful outcome. This first-of-its-kind multicenter collaborative effort will directly address critical research gaps, including determining what factors predict successful resolution of debilitating pain after TPIAT, what factors predict successful remission of diabetes, appropriate timing for intervention with TPIAT, and cost-effectiveness of the procedure.

AIM 1: The *primary aim* of this study is to determine (1a) whether patient and disease characteristics are associated with favorable pain and health-related quality-of-life outcomes (HRQOL) after TPIAT; (1b) the optimal timing of the TPIAT intervention to resolve pain and improve HRQOL; and (1c) in a subset of patients, the impact of central sensitization on pain resolution. To address this aim, using a multi-center prospective approach enrolling 450 participants, we will collect key patient characteristics including (but not limited to): diagnostic studies used to establish diagnosis of pancreatitis; purported cause of disease; other risk factors including cigarette smoking and drinking; medical comorbidities (particularly prior surgical interventions, ERCP, and other GI disease such as dysmotility); and psychological comorbidities. A subset of 75 patients at a single site will undergo quantitative sensory testing. We will also collect key outcome markers at 6 months, 1 year, then yearly after TPIAT including: narcotic use and morphine equivalents dose, visual analog pain scale, HRQOL, hospitalizations or ED visits, and disability. In addition, we will maintain a biorepository of histopathology, serum, and urine from TPIAT recipients, to be stored for later ancillary studies of biochemical markers in this population.

AIM 2: To determine (2a) whether patient and disease characteristics are associated with favorable glycemic outcomes from the IAT procedure; and (2b) the optimal timing of TPIAT to obtain post-surgical insulin independence. For this aim, we will collect key outcome markers at 6 months, 1 year, and yearly for diabetes outcomes, including insulin requirements, hemoglobin A1c, and C-peptide level.

AIM 3: To determine the cost-effectiveness of TPIAT. For this, the history of medical care utilization during the 18 months prior to TPIAT for chronic pancreatitis management will be used to estimate the cost of chronic pancreatitis, compared to the cost of TPIAT (surgery and post-TPIAT care) over a 2 year interval as a marker of costs of TPIAT. Cost per Quality-Adjusted-Life-Year (QALY) will be computed and compared for non-TPIAT treatment (baseline, before TPIAT) vs TPIAT.

2. BACKGROUND AND SIGNIFICANCE

Chronic pancreatitis is a debilitating disease with few effective treatment options

Approximately one in every 2,500 persons in the United States is affected by chronic pancreatitis (5). The major symptom of this disease is severe, intractable abdominal pain. Over time, progressive fibrosis within the pancreatic parenchyma often results in exocrine insufficiency and/or diabetes. The cause of disease is complex; chronic pancreatitis can be triggered by a variety of inciting factors, alone or in combination, including obstructive disease, genetic risk factors, toxic exposures including alcohol and smoking, and recurrent episodes of acute pancreatitis, although often the cause remains unknown (6).

For affected patients, the disease burden is high. Children report frequent missed school days (7) and disability is common among adults, particularly when pain is constant or severe (8). The majority of patients have repeated hospital admissions and emergency room visits (7, 8), and frequently narcotic dependence results from the chronic pain. This results in not only a patient burden but an economic burden to the health system: patients with chronic pancreatitis disproportionately use a high volume of economic and health care resources (9), and admission for *acute* pancreatitis attacks (often a precursor to chronic pancreatitis) alone results in $2.6 billion per year of inpatient costs in the U.S. (10).

First-line therapies for recurrent acute or chronic pancreatitis include medical management and endoscopic interventions. Low-fat diet and pancreatic enzymes are administered to reduce pancreatic stimulation. Pain management approaches include non-pharmacologic and pharmacologic strategies (11, 12). Non-opioid and opioid analgesics are used for treatment of visceral pain, and gabapentin or pregabalin for non-visceral (neuropathic) pain (13-15). Anti-oxidants are occasionally tried (16). Endoscopic management with endoscopic retrograde cholangiography (ERCP) with sphincterotomy or stent placement is directed at relieving ductal obstruction (strictures) and removing ductal stones (17). Unfortunately, for many patients with chronic pancreatitis, these interventions fail to provide pain relief or pain recurs. For these individuals the only remaining options are to live with chronic pain or attempt surgical intervention.

Total pancreatectomy removes the source of the pain; the islet autotransplant reduces the subsequent risk for and severity of diabetes mellitus.

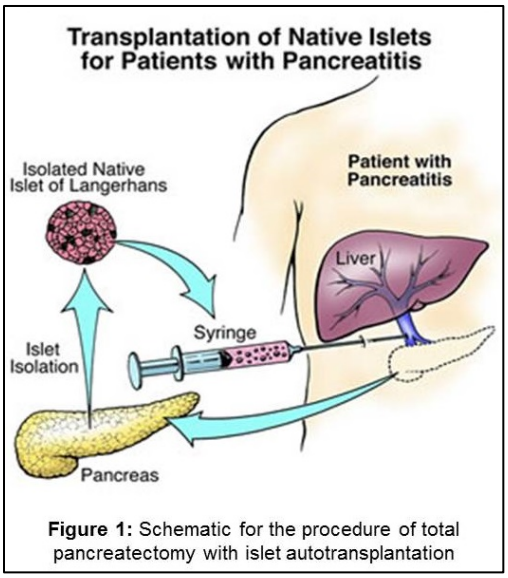


Figure 1: Schematic for the procedure of total pancreatectomy with islet autotransplantation

When medical and endoscopic therapies fail, surgical therapy including total pancreatectomy (TP) may relieve the root cause of pain. Although the primary goal of a TP is to *relieve the debilitating pain* of chronic pancreatitis, TP results in certain diabetes unless the islets are returned using autologous islet transplantation (IAT). In this procedure, the patient's pancreas is completely removed, mechanically and enzymatically digested with collagenase, and the islets are isolated and infused into the portal vein. The islets engraft and potentially survive long term in the liver, releasing insulin in response to glucose (18). IAT results in complete insulin independence in 1/3rd of patients, with another 1/3rd requiring only small doses of insulin (4).

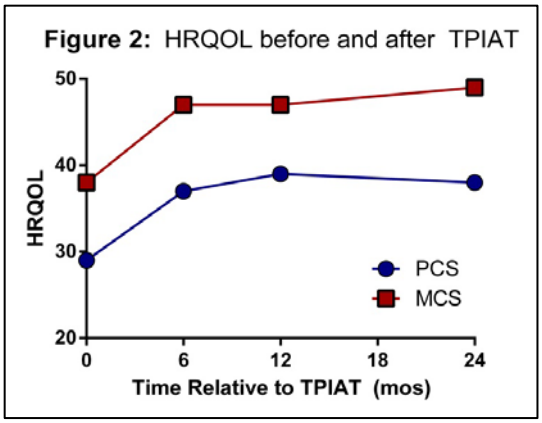
The field of TPIAT is growing, with increasing referral of patients for this procedure from the medical community. This is reflected in the growing number of centers performing the procedure and growing number

of procedures performed in the past decade (1, 19-26). However, medical providers still have some natural reluctance to refer patients for such a major surgical procedure. Some of this reluctance stems from the many remaining questions in this field: How are candidates chosen for the procedure? When is the appropriate time to intervene? How does this procedure affect visceral and non-visceral pain in chronic pancreatitis? Why do some patients fail to recover after surgery? With no medical therapies available to halt the progression of the disease, TPIAT is likely to remain one of the few treatment options for many patients, particularly those with debilitating small duct chronic pancreatitis. Thus it is critically important to advance the field of TPIAT by conducting multi-center research to understand which patients benefit most from this procedure, and when and how to intervene.

Data collected individually from multiple centers suggest that patients referred for TPIAT have greatly impaired health-related quality of life before surgery, and that HRQOL improves significantly after surgery.

Chronic pancreatitis is a debilitating disease in general, with poor physical and mental quality of life scores, compared to the general U.S. population, using multiple measures, most commonly the Short Form (SF) 12 or 36 (8, 27-29). However, because the sickest, most debilitated patients are often the ones referred for surgery, this subset seen for TPIAT may represent the more highly impaired end of the spectrum. This is supported by data from multiple institutions including the University of Minnesota and the Medical University of South Carolina (1, 23). On the SF-36 and -12, before surgery, patients undergoing TPIAT had physical component summary scores more than 2 standard deviations below the population mean (29 and 27 respectively, vs population mean 50±10) and mental component summary scores more than one standard deviation below the population mean (38 and 38, vs population mean 50 ±10).

After TPIAT, HRQOL scores based on the SF-12 and -36 improved significantly, as measured by the Physical Component Summary score (PCS) and Mental Component Summary Score (MCS) and by the 8 subscales that comprise these instruments. Among patients at the University of Minnesota undergoing surgery from 2007-2012, the PCS improved from 29 at baseline (n=160) to 39 at 12 months (n=70); the MCS improved from 38 at baseline to 47 at 1 year, with stable measures at 2 years. In this measure, a score of 50 represents the normal population mean, and each 10 points is 1 standard deviation (higher score indicates better status). Thus, this represents a ~1 standard deviation improvement in PCS and MCS (Figure 2). Other institutions have documented similar improvements using the SF-12 or -36 measures. However, about 15% of patients report that their general health is no better after surgery. Certain populations of patients may have less benefit; for example, in some cohorts, patients with alcohol-related pancreatitis show less improvement in HRQOL (30). More research is needed to establish risk modelling to identify patients who benefit least from TPIAT, so that other more appropriate treatment modalities may be employed for these patients.



Measured quality of life is an important component of assessing TPIAT's quality-of-life adjusted cost-effectiveness. In one small series of 46 patients with non-calcific chronic pancreatitis, TPIAT was found to be less expensive with better quality of life than continued medical management ($153,575/14.9 Quality-adjusted life years (QALYs) vs $196,042/11.5 QALYs) in just a one year interval (31). Data from the United Kingdom similarly document benefits in health and survival

(with TPIAT vs TP), although because of the up-front cost of TPIAT, more than one decade was needed for equalization of costs compared to medical management (32).

Notably, such prospective assessments are largely conducted in the absence of any specific funding (at least in our center at the University of Minnesota), which limits staffing to contact patients who do not return for assessments. This results in missing patient data, a confounder and a major critique of the field of TPIAT (although also a limitation in evaluating other treatments for chronic pancreatitis).

Use of opioid analgesics is nearly universal before TPIAT. However, some patients struggle to discontinue opioids after TPIAT, possibly because of central sensitization and opioid-induced hyperalgesia from years of chronic pain. This is an important barrier to success in need of study.

Visual analog pain scores and pancreatitis-like pain are reduced after TPIAT (1, 33-35). However, withdrawal from opioid analgesics is often slow. In several large series, about half of patients are off opioids by 1 year; long-term follow up suggests that three-quarters will be off by 5 years (36). Some patients continue to experience chronic pain despite TPIAT. Preliminary data from the University of Minnesota indicates that ~15% of patients report, at 1-3 years after surgery, that pain is about the same or worse compared to before TPIAT (1).

Increasingly, pain in chronic pancreatitis is now recognized to be a particularly complex interplay between visceral and non-visceral pain. Chronic pancreatitis is not a simple plumbing and mechanical structure problem; it is also a (central nervous system) wiring problem. Recurrent episodes of nociceptive pain may lead to irreversible changes in pain processing pathways in the central nervous system (37-39). Both peripheral and central sensitization are believed to contribute to hyperalgesia and a chronic pain syndrome. The impact of this is well-documented in emerging data from the Dutch Pancreatitis Study Group: patients undergoing other surgical treatments (partial resections and drainage procedures), who have measurable central sensitization before surgery by quantitative sensory testing (QST), recover poorly after surgery (40). The impact of central sensitization on TPIAT success has not been previously studied, but is likely to contribute to residual pain. Also, prolonged use of narcotic therapy, in and of itself, can cause an opioid-induced hyperalgesia state (41-43). Prolonged disease duration, recurrent interventions, and long narcotic use may all contribute to development of neuropathic pain, which may respond poorly to TPIAT and require ancillary or alternative treatments, but this remains largely unexplored.

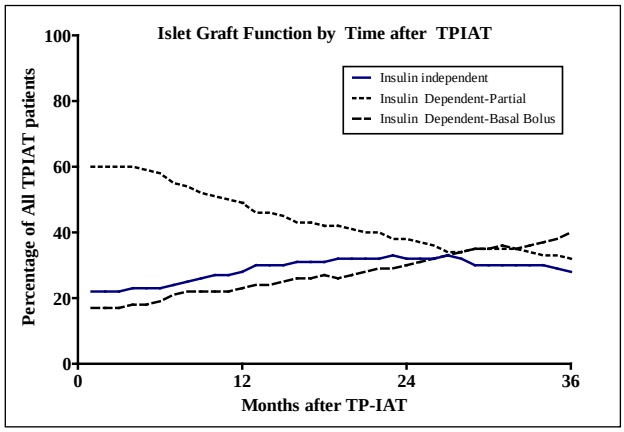
Medical comorbidities such as gastroparesis and psychological distress may complicate surgical recovery.

Chronic pancreatitis does not exist in isolation. Many patients have comorbidities that may affect the trajectory of response to treatment with TPIAT. Gastroparesis has been reported as more frequent in patients with chronic pancreatitis (44). Gastroparesis mimics many symptoms of chronic pancreatitis (pain with eating, nausea) and is difficult to measure accurately when patients require daily narcotics. However, gastroparesis and other bowel motility issues may contribute to residual pain after TPIAT. Psychological comorbidities are also frequent in this population (45, 46). The recurrent trauma of illness, pain, and disability may lead to high rates of depression and anxiety. This impact on emotional health is reflected in the HRQOL measures. The mental/emotional measures of HRQOL are substantially impaired (1, 23). This may affect both physical symptoms (somatization of pain) and ability to engage in a post-surgical rehabilitation program necessary to achieve optimal outcomes. We need to better understand the extent and impact of these comorbidities in the TPIAT population.

While TPIAT can prevent post-operative diabetes mellitus, patients with a compromised islet mass are unlikely to achieve insulin-free status. Thus, timing of intervention needs

Fig. 3:

to balance too-early use of major surgery versus preserving enough beta cell mass to allow diabetes remission.



About one-third of TPIAT patients are insulin independent in the first 3 years post-transplant (Figure 3), but the majority have functioning islets which benefits glycemic control. Many patients maintain hemoglobin A1c level <7% (1), the goal recommended by the American Diabetes Association and shown by the Diabetes Control and Complications Trial to reduce risk of microvascular complications of diabetes (47). The major hurdle to successful islet transplant is the number of islets available; the transplanted islet mass is an important predictor of subsequent diabetes risk (1, 2, 48, 49). About 70% of IAT recipients with >5000 islet equivalents (IEQ)/ kilogram body weight transplanted achieve insulin independence, compared to only 10% of those patients with a very low islet mass (<2500 IEQ/kg) (1).

In summary, data from multiple institutions and several hundred patients with chronic pancreatitis who have undergone TPIAT indicate a largely improved quality of life and reduced pain. However, a subset of patients continue to struggle after the procedure, and more than half will have some degree of diabetes. Constructing risk models that adequately describe the contributions of patient and disease-specific characteristics to resolution of debilitating pain (AIM 1, primary) and to resolution of diabetes (AIM 2), and determining the cost-effectiveness of TPIAT (AIM 3) are the most immediate needs in advancing the application of TPIAT to patients with intractable pancreatitis. The primary objective of this study is to evaluate those factors that impede successful resolution of pain and restored HRQOL, as TPIAT is performed specifically to treat the pain of chronic pancreatitis. However, because this surgery involves a substantial risk of diabetes mellitus, and incurs costly medical expenditures, it is critically important to simultaneously study the diabetes outcomes and cost effectiveness of the procedure.

3. MULTICENTER CONSORTIUM STRUCTURE

C.1. Organization for the Consortium for the Study of TPIAT

The study consortium will include multiple U.S. centers performing TPIAT and a Data and Coordinating Center (DCC). The primary center will be located at the University of Minnesota (including the University of Minnesota Medical Center and Masonic Children's Hospital). Each center will have a site P.I. who is the primary person responsible for overseeing the center's data collection and submission, and communication with grant PI Dr Bellin and the DCC.

One investigator from each site will comprise the steering committee, along with the DCC director and the DCC staff performing the day-to-day data management. The steering committee will hold monthly teleconference meetings to assess recruitment, retention, and completeness of data elements, as well as planning for presentations and publications. All proposals for data analyses, presentations, and publications for multicenter data will be reviewed by the steering committee, as well as proposals for use of stored specimens for ancillary studies.

4. STUDY DESIGN OVERVIEW

A total of 450 participants will be recruited across all participating centers. Patients of all ages, races, ethnicities, and genders undergoing TPIAT will be recruited equally for participation.

4a. Inclusion/Exclusion Criteria

Inclusion criteria**:** Patients of any age undergoing TPIAT (including completion pancreatectomy with IAT) for a primary diagnosis of chronic pancreatitis or recurrent acute pancreatitis, as determined by each individual site, will be included.

Exclusion criteria**:** Patients undergoing TPIAT for a diagnosis other than pancreatitis and patients who undergo a partial pancreatectomy only with IAT will be excluded.

By design, this study will not provide criteria for defining chronic pancreatitis or recurrent acute pancreatitis for study entry. The rationale is that we need to assess the cohort representing *all* patients currently selected for this procedure in the U.S. As described below, we will collect information about the studies supporting the diagnosis of chronic pancreatitis or recurrent acute pancreatitis (enzyme elevations, imaging evidence, pancreatic function tests) and in this way we can determine which patients are most likely to benefit from the procedure. Recruitment and informed consent will take place before TPIAT surgery, at which point baseline assessments will be collected.

Patients with chronic pancreatitis are referred for consideration of TPIAT at various stages in the disease process, with variable opioid use, extent of disability, and duration of disease, and with varying durations of chronic opioid therapy. Because such variables may impact pain relief after surgery (54), we intend to enroll this full spectrum of patients undergoing TPIAT.

Inclusion/exclusion of potential vulnerable populations: children are an important subcohort of patients undergoing this procedure and are included in this minimal risk study. For children under the age of 18 years, informed parental consent and patient assent will be obtained (children age 8-17 years). We expect that all or nearly all adults will be able to provide informed consent, as psychiatric disease significant enough to interfere with consent would also be a contraindication to the procedure. Only adults who can provide informed consent on their own behalf will be included in the study.

4b. Study Visit Schedule

Patients will be seen before TPIAT for the informed consent process and to obtain key baseline history, outlined in section 5. This history will be collected through face-to-face visits with the patient and abstraction of medical history from the medical records. Subsequently, after surgery, additional details on the surgical approach and surgical complications will be collected.

Follow up visits assessments post-TPIAT will occur at:

- 6 months after TPIAT
- 1 year after TPIAT
- 2 years after TPIAT
- 3 years after TPIAT
- 4 years after TPIAT

Follow up visits will be conducted by the coordinator either (1) on site (for patients following up at the study center, estimated to be 70% overall) or (2) remotely by telephone interview, mailed questionnaires, and abstracted from the medical history from local follow up for items such as weight, BMI, and local laboratory results. All participants will be followed to the end of the project period, i.e., at least 1 year and up to 4 years, depending on time of study entry.

5. DATA ELEMENTS AND ENDPOINTS

5a. Baseline Data

Collection of comprehensive yet focused patient and surgical baseline characteristics is essential to accurate assessment of factors that affect the likelihood of favorable response to TPIAT and optimal timing for TPIAT. Before TPIAT surgery, after consent is obtained, the following data elements will be collected by abstraction from medical records (for hospitalizations, surgery details), by patient history obtained by patient visit with the investigator/coordinator, and from questionnaires completed by the participants.

PATIENT CHARACTERISTICS/ MEDICAL HISTORY	
Demographics	Age, Sex, Race, Ethnicity, and additional social history (including employment /school attendance, financial/insurance status, marital status, history of smoking or alcohol consumption).
Anthropometric measures	Weight, height, BMI
Medical Comorbidities	Medical history (pre-existing diagnoses); with gastroparesis or bowel dysmotility diagnosis specifically assessed as present or absent; fatty liver disease; liver biopsy results (if done pre or at time of TPIAT for clinical purposes)
Prior Surgery	Including pancreas specific surgeries: lateral pancreaticojejunostomy and variants, Whipple, distal pancreatectomy, open sphincterotomy
Psychological Comorbidities	Diagnosis of depression, bipolar disorder, anxiety, PTSD, alcoholism; patient symptom report by NIH PROMIS depression-8 and anxiety-8 inventory
Health related quality of life	Baseline HRQOL assessed by SF-12; and EQ-5D (for cost-effectiveness analysis)
Visual analog pain scale (VAS)	Documented at baseline for comparison to later outcomes assessment.
PANCREATITIS HISTORY	
Etiology of Disease	Classified by components of the TIGAR-O criteria: toxic/metabolic (including alcohol), idiopathic, genetic (genes specified), autoimmune, recurrent acute pancreatitis, obstructive (including pancreas divisum and sphincter of Oddi dysfunction)
Tests used to establish the diagnosis of pancreatitis	Normal, abnormal, or not done, and specific findings/results for: pancreatic enzyme elevation; endoscopic ultrasound; MRCP; CT scan; pancreatic function tests; previous histopathology; ERCP; and any vascular complications of pancreatitis on imaging
Duration of disease	Date of onset abdominal pain; date of pancreatitis diagnosis
ERCP history	Previously done (Y/N), number of procedures, stents, sphincterotomy
Celiac plexus block	Previously done (Y/N) and number of procedures
Hospitalization and other procedure history	Number of hospitalizations and length of stay, for pancreatitis or pain; and other procedures related to

	pancreatitis management (central line, feeding tube, imaging, endoscopic interventions as noted above) and whether inpatient or outpatient
Analgesic use, including opioid therapy	Medication names, doses, and frequency per day, to calculate average daily dose for all narcotic therapy
Pre-Existing Diabetes Mellitus	Diagnosis of diabetes mellitus, autoantibody status (if known), and treatment (insulin, oral medications, or both)
Pancreatic Exocrine Insufficiency	Stool elastase level; pancreatic enzyme therapy (Y/N, dose, and rationale)
TPIAT SURGICAL HISTORY (collected after TPIAT)	
Date of TP; Date of IAT	Date of both TP and IAT will be recorded (rarely the IAT is done as a second procedure the next day)
Islet processing location	On site, or remote facility used and site; and details on approach to isolation including COBE purification (Y/N)
Islet number	IEQ, IEQ/kg, and tissue volume
Islet infusion site(s)	Intraportal; other
Islet culture	Pancreas preservation solution culture positive or negative; islet product culture positive or negative
Enteral tubes	Gastrojejunostomy placed (Y/N); jejunostomy placed (Y/N); gastrostomy tube (Y/N); nasojejunal tube (Y/N)
Surgical approach details	Including open or laprscopic (larpscopic assisted) or robotic approach; splenectomy (Y/N), pancreatectomy in continuity or split; type of biliary reconstruction
Pylorus sparing approach	Yes/No
Type of GI reconstruction	Duodenoduodenostomy; duodenojejunostomy; gastrojejunostomy; Roux-en-Y
Complications of surgery	Specifically assessed for: Infection requiring re-operation or interventional radiology; wound infection requiring intervention; bleeding requiring reoperation; blood transfusions; biliary duct obstruction or leak; portal vein thrombosis; severe hypoglycemia causing seizure or loss of consciousness in hospital; chylous leak; DVT, PE; >24h mechanical ventilation; >24h vasopressor support
Hospital length of stay	Days in hospital after TP date
Readmission within 30 days of TPIAT	Y/N; number of readmissions and reason

In addition, for Aim 1c, in a subset of 75 patients at the University of Minnesota site, **quantitative sensory testing (QST) will be performed within 30 days prior to surgery**. The purpose of this test is to measure central sensitization. One possible explanation for poor pain relief in some patients after TPIAT is that *altered central pain processing* occurs in those patients with a long duration of exposure to chronic pain (40). QST assesses altered cental pain processing. This test will be performed by a trained technologist using a Pathway device, in the clinical lab of co-investigator David Walk, M.D. Thermal perception thresholds (warm, cool, and heat-pain) and suprathreshold heat/cold-pain rating will be determined in limb sites remote from the abdomen as well as over the abdominal wall and compared with values from a control cohort. Next, conditioned pain modulation (CPM), a measure of pain sensitization, will be assessed using a heat-pain

conditioning stimulus (55). Pressure thresholds for pain will be determined in the same distribution using a pressure pain algometer. **For this assessment (QST) only, because it will occur in only 75 patients at one site, a separate informed consent will be obtained (relevant to the University of Minnesota site only), and testing will be limited to patients ages 16 years and older**, an age where central sensitization may be more likely to complicate resolution of pain after TPIAT.

5b. Biorepository: Serum, urine, genetic specimens, and tissue

Included in the informed consent process and documentation will be an 'opt in/out' for collection of biospecimens. From consenting subjects, the following baseline specimens will be collected to support future ancillary research studies in this population:

- Serum: Obtained from two – 10mL tiger top tubes and processed, aliquoted and frozen at -80 Celsius.
- Clean catch urine.
- Plasma: Obtained from two – 10mL purple top (EDTA) tubes, aliquoted and frozen at -80 Celsius.
- DNA (buffy coat): Obtained from the buffy coat of the same two – 10 mL purple top (EDTA) collection tubes, separated for the buffy coat and plasma (see above). The buffy coat is aliquoted into two – 15mL conical tubes, stored at -80 Celsius.
- DNA (saliva): Saliva is collected into a prepared container and stored at room temperature until analysis. Intended for pancreatitis genotype panel (known pancreatitis risk genes and potential disease modifiers).
- 1-2 small pancreatic biopsies (region of pancreas is noted at collection as head, uncinate, neck body, or tail), collected in a manner that will not compromise the islet isolation process or result, with maximum recommend tissue volume of 300-400 mcg per biopsy (1x1x0.4 cm biopsy).
- Gene expression (biopsy): 1 small pancreas biopsy (maximum recommend tissue volume of 300-400 mcg per biopsy) split into small tissue pieces and placed into RNA-later for preservation of tissue RNA for later analysis.

5c. Key outcomes measured at follow up visits

TPIAT is a complex procedure with the potential to alleviate pain and to improve functional status emotional health, nutritional status, and HRQOL. We will focus on the following **KEY OUTCOMES at each visit**:

1) **Pain resolution:**
   a. PRIMARY outcome: pain VAS (0-10, 10 being the worst pain imaginable).
   b. SECONDARY outcomes: Opioid use (yes/no), daily opioid dose in morphine equivalents, and pain interference with daily function (measured by NIH PROMIS instrument).
2) **Health-related quality of life:**
   a. PRIMARY outcome: Physical component summary score (PCS) and mental component summary score (MCS), both standardized scores obtained from the SF-12 version 2.
   b. SECONDARY outcomes: Subscale scores from the SF-12, number of Hospitalizations/year, number of emergency department visits/year, and *functional* status as measured by disability (from work/school).
3) **Diabetes** outcomes are defined *a priori* as:
   a. PRIMARY outcome: Insulin independence (defined as no insulin past 14 days and HbA1c $\leq$6.5%).
   b. SECONDARY outcomes: Insulin dose (unit/kg/day based on patient self-report of total daily dose); fasting C-peptide; hemoglobin A1c level; islet graft function defined based on

fasting C-peptide level ≥0.3 ng/mL; and severe hypoglycemia (defined by an episode causing loss of consciousness or seizure).

4) Other measures will include **nutritional outcomes** including weight, body mass index, pancreatic enzyme therapy (type/dose), presence of steatorrhea from patient report, and fat soluble vitamin deficiencies, and **pre-specified comorbidities and medical events of interest** including hospitalization events with rationale for admission, abdominal surgery, and diagnosis of specific gastrointestinal complications including small bowel obstruction and dysmotility/gastroparesis. **Repeat serum, plasma, and urine samples** will be obtained at 1 year for the biorepository, as feasible [may not be obtainable for some patients who are completing remote follow up at 1 year].

Laboratory assessments are designed to be in accordance with recommended routine care, as previously published (50). At 6 months and annually after TPIAT the following will be collected for clinical purposes and included in the dataset: hemoglobin A1c, fasting glucose and C-peptide, vitamin A, D, and E levels. Weight will be obtained and BMI calculated at the clinic visit. In addition, some participating sites collect meal stimulated glucose and C-peptide (from a mixed meal tolerance test) as part of their center's clinical routine. Because this is not uniform across participating sites, the stimulated glucose and C-peptide are not included as a secondary endpoint, but may be reviewed later where available for site-specific sub-analyses of islet graft function.

5d. Data collection for the cost-effectiveness analysis (Aim 3)

To address the cost-effectiveness of TPIAT, we will compare costs of TPIAT with those of continued medical (non-TPIAT) care using the patient's baseline costs in the 18 months before surgery to estimate the cost of continued medical care. To do so, we will assume that patients would continue in the same state of impaired health if not treated with TPIAT. This is likely a conservative estimate, as these are chronically ill patients, many of whom have escalating disease burden and progressive increase in risk of complications (like diabetes) as disease goes untreated; however, the medical literature in chronic pancreatitis supports that, on average, patients who follow standard medical management maintain a poor but stable quality of life (27). Procedures, hospitalizations, and basic medication utilization will be included, with Medicare estimates applied for unit cost to quantify costs for comparison.

The following data elements will be collected for the purpose of the cost-benefit analysis:

1) Baseline status: Baseline costs will be determined by the healthcare utilization experience related to pancreatitis abstracted from the patient's electronic medical record during the 18 months prior to TPIAT, converted to dollars based on Medicare unit costs. Relation to pancreatitis will be determined first by the site PI, and then verified by an event adjudication panel consisting of 3 study investigators, from 3 sites, who will review the data on a every 6 month basis. Most events are expected to be straightforward, and thus summary of event and relation to pancreatitis (yes/no) will be presented to committee and questionable cases reviewed in detail. Utilization includes medication use (opioid use, pancreatic enzyme use, and diabetes medications), inpatient procedures (DRGs, or number and length of stay), emergency department use, office visits, diagnostic tests, and outpatient procedures (ERCP, celiac plexus block, feeding tube or central line placement, imaging and non-TPIAT surgery). These items will be collected by history obtained at baseline visit, with hospitalizations, emergency department visits, and procedures verified by medical records (reviewed for procedure/admission date, date of discharge, and reason for admission).

2) Follow up interval: The same utilization data outlined in item 1 will be collected at each protocol visit. Because participants will have variable durations of follow up depending on time of enrollment, for the purpose of this analyses, we will include patients with at least 2

years of follow-up (n=375). To hold constant the time period, the costs will be rolled up and converted to expenditures per month, adjusted for inflation by the medical care portion of the Consumer Price Index, and discounted at a 3% rate.

3) QALY assessment is performed using the 5-question EQ-5D at baseline and at each follow-up data collection point. Although cost data extend 18 months prior to TPIAT, only the baseline EQ-5D weight is available to characterize the control (pre-TPIAT) period. The literature (27) supports our assumption that the HRQOL weights over the previous 18 month period are characterized by this level and can be used to construct counterfactual QALYs. EQ-5D responses will be converted to quality of life (QOL) weights according to the American calibration (45) and QALYs for the intervention period will be constructed by a linear interpolation between EQ-5D collection points. Validation of the EQ-5D QOL weights will be performed by comparison with the SF-12 scores. QALY scores will also be discounted.

6. STATISTICAL ANALYSES AND POWER CALCLUATIONS

6a. Power calculation and statistical plan for SA 1 (predictors of pain relief and improved HRQOL)

For each of the primary outcomes for HRQOL and pain we will devise a likely-to-benefit score, computed from patient and disease characteristics including timing, and allowing the effect of other characteristics to depend on timing (i.e., including timing-by-X interactions) so that a higher score indicates that the patient is more likely to benefit. For each primary outcome measure, regression (linear or logistic, as appropriate) will be performed to model how the primary outcome is related to the predictors.

Based on an initial sample size of 450 patients, and allowing for loss to follow up, with at least 400 patients completing 1 year follow up, for the primary analyses with up to 10 predictors, we will have a 80% power to detect a R^2 of 0.04 (equivalent to Pearson's r =0.20) and 90% power to detect a R^2 of 0.05 (equivalent to a Pearson's r=0.22). In univariate models for individual predictors, for binary outcomes (for example, using or not using opioid analgesics), we will have 80% power to detect an odds ratio of 0.74-0.77 (equivalently 1.30-1.35) depending on the overall rate of the dependent variable event, and 90% power to detect an OR of 0.71-0.74 (or 1.35-1.40). For continuous outcomes modelled for an individual predictor, for a one standard deviation (SD) difference in the predictor, we will have 80% power to detect a difference of 0.14 SD in the dependent variable and 90% power to detect a 0.16 SD difference.

To characterize predictive ability of the likely-to-benefit score(s), particularly regarding timing of TPIAT, secondary analyses will produce ROC curves showing true positive [benefited] and false positive [did not benefit] rates after 1, 2, 3, and 4 years, with diminishing amounts of data for longer follow up periods. To evaluate whether altered central processing plays a role in pain outcomes, we will compare (1) patients using vs not using opioid analgesics at 1 year post surgery; and (2) patients with and without a 50% reduction in mean pain VAS, using linear regression to adjust for confounders. The outcome measures (dependent variables) of thermal pain thresholds and central pain modulation will be measured in the 75 participants undergoing QST.

6b. Statistical plan for SA 2 (predictors of diabetes remission)

For the primary outcome measure of insulin independence, logistic regression analysis will be performed to model the primary outcome as a function of predictors. As in Aim 1, we will devise a likely-to-benefit score, computed from patient and disease characteristics including timing, and allowing the effect of other characteristics to depend on timing (i.e., including timing-by-X

interactions) so that a higher score indicates that the patient is more likely to benefit; secondary analyses will characterize predictive ability of the likely-to-benefit score using ROC curves. Power calculations for linear and logistic regression analyses are as for Aim 1.

6c. Statistical Plan for SA 3 (Cost-effectiveness analysis)

Incremental cost effectiveness ratios (ICERs) will be constructed using the baseline costs and QOL weights to represent the counterfactual natural history of the disease for those without the intervention during the 2 year follow-up period. This is a conservative assumption because we believe that cost levels would have likely have increased over this period without intervention, as aging interacts with the disease. To measure the effect of intervention, the QOL weights will be determined by the average QOL over the 2 years of follow up. Sensitivity analysis (one-way, threshold and probabilistic) will be conducted and cost-effectiveness acceptability curves will be calculated. Because no data on indirect (e.g., travel, productivity) costs in the pre-period were collected, the analysis will be done from the perspective of the payer, rather than society. Note that if this intervention is effective and reduces healthcare utilization during the follow-up period, the omission of these indirect cost savings would impart a conservative bias to the ICER.

Finally, if the intervention is successful, our follow-up period of 2 years will not accurately capture the true cost per QALY gain because the cost of the initial intervention is not allocated over all the years for which there will be a QALY gain. To remedy this, and as part of our sensitivity analysis, we will conduct a Markov model expansion of the data over a 5-year follow-up period, adding in data from the subsets of patients followed for 3 ($n \approx 250$) and 4 years ($n \approx 100$) to obtain event probabilities and alternative estimates of costs and QALY gains. The Markov model will use both deterministic and Monte Carlo approaches, and the latter will generate estimates used in probabilistic sensitivity analysis and construction of cost-effectiveness acceptability curves.

7. STRUCTURE OF THE DATA AND COORDINATING CENTER AND DATABASE

The University of Minnesota DCC will include a biostatistician, part-time study manager, part-time database manager and possibly other staff. These individuals collectively will be responsible for: (1) creating and maintaining the electronic database structure for data entry; (2) designing case report forms (electronic and paper versions); (3) designing and maintaining a manual of procedures for patient recruitment/consent, data collection, and data entry; (4) providing day-to-day telephone support for site coordinators for technical issues or questions; (5) conducting weekly meetings internally and weekly coordinator meetings, and monthly teleconferences for all investigators (with frequency of all of the aforementioned adjusted depending on study need); (6) providing initial training sessions for all investigators and coordinators; and (7) conducting annual site visits for monitoring and trouble-shooting.

Study data maintained at the DCC will be de-identified per HIPAA. Nonetheless, data confidentiality will be strongly protected: data transmission between the clinical sites and the DCC is encrypted and the study website is secured by individual usernames and strong passwords. Further information on protection of privacy and data security is included in the Protection of Human Subjects plan.

Study case-report forms will be paper forms available for download from the study website. Data entry screens (web pages) that are visually similar to the paper forms will be created for entering each form. An initial training session will be provided by the DCC for all study coordinators, and training will be maintained through regular conference and individual calls. Data quality control will include ensuring completion of all required forms/fields and detecting and correcting errors in keyed forms. For each participant, the study's database will identify which forms should be

entered and will send automatic reminder e-mails to each site's study coordinator for overdue forms. Regular reports of interest to PIs will describe enrollment, retention, and data completeness. Additional regular reports will be as determined by the study steering committee and DCC.

A **biorepository** will be maintained in the lab of the P.I. at the University of Minnesota. This will include **serum, plasma,** and **urine** samples from the baseline (pre-operative) and 1 year visits; saliva and the buffy coats from plasma for **DNA analysis**; and pancreas biopsies for **histopathology** and **gene expression**. Blood and urine samples from consenting participants will be collected at the study site using supplies (collection tubes) provided by the University of Minnesota (primary center), processed within 2 hours of collection, aliquoted into 500 microL tubes, stored at -80C and shipped from the study center to the repository at least quarterly on dry ice. Genetic material obtained from the buffy coat of plasma will be transferred to a conical tube and stored at -80C. Patients may have 1-3 small pancreatic core biopsies obtained at the time of TPIAT: patients may consent to 1-2 small pancreatic core biopsies for histopathology and/or 1 pancreatic core biopsy for gene expression. The biopsy samples for histopathology will be placed in formaldehyde for 48-72 hours and then transferred to 70% alcohol for long-term storage, and will be shipped to the biorepository for storage. The biopsy samples for genetic analysis will be split into small tissue pieces and placed into RNAlater for preservation of tissue RNA for later analysis. Within the biorepository, each specimen will be labelled with a study ID number, date and time of collection, material source, and aliquot tube #.

8. SUBJECT SAFETY

The intent of the current study is to carefully and consistently track key baseline characteristics, surgical approach, and long-term outcomes in a large well-defined cohort of patients undergoing TPIAT at various centers across the U.S. Importantly, all data collected for this study—apart from the biorepository samples and patient questionnaires—are a component of the patients' routine care, and will not be different whether or not the patient is participating in this protocol. Thus, we expect overall risk to be minimal.

Risks of study participation include:
(1) up to 80mL of extra blood for stored serum and DNA, collectively across the first 1 year of study; this is an amount the body can safely replace;
(2) risk of privacy violation; however, only deidentified data will be provided to the DCC;
(3) risk of modest discomfort with quantitative sensory testing (applies to only the 75 subjects in sub-study at University of Minnesota site and all will be separately consented for this additional study).

8a. Reporting of Adverse Events

Adverse events will be reported when an AE is considered directly related to a study protocol-driven procedure, for example in the case of AE associated with extra blood draw for stored specimens, or with QST. However, events resulting from the TPIAT procedure itself and routine clinical care will not be collected for the study, unless it is a data element of interest (i.e., specific surgical complications).

An AE will be considered a serious AE (SAE) only if it meets above criteria AND results in hospitalization, life-threatening medical event, death, or other significant medical event in the opinion of the investigator.

8b. Compensation for study participation

To compensate patients for time dedicated to the study and maintain high rates of retention, subjects will receive a nominal $25 gift card for each follow up visit completed.

9. HANDLING SUBJECT WITHDRAWLS, PROTOCOL DEVIATIONS, AND OTHER STUDY OVERSIGHT

9a. Subject Withdrawals and Lost to Follow Up

Although every effort will be made to maintain subjects in the study cohort, subjects may withdraw participation at any time. Whenever feasible, the study center should determine the reason underlying participant withdrawal. Participant withdrawal will be recorded in the database, along with rationale where available. Because the burden of follow up is minimal, we expect this to be rare. Data up to the point of subject withdrawal will be maintained in the study database.

A more common confounder in follow up of this population is loss to follow up. A study gift card is provided to participants for each follow up assessment to encourage high rate of adherence to follow up assessments. In the event that a study center cannot reach a participant at the last known phone number or address, the participant's emergency contact or primary doctor's may be contacted to determine current contact information.

9b. Protocol Deviations

Protocol deviations will be tracked by the DCC. Queries for missing and overdue data will be sent to the study centers by the DCC.

9c. Study Monitoring and Oversight:

The DCC will monitor each site on an approximately once yearly basis, assessing for protocol adherence and data accuracy. The safety risk of the study is considered to be minimal, as this is an observational study (no intervention). Thus, the steering committee will review AEs and protocol adherence/safety concerns on a semi-annual basis.

10. APPENDICES

Attached appendices are completed by patients for baseline and/or follow up assessments:

- Pain assessment with visual analog scale (VAS)
- SF-12 v2: Baseline and follow up
- EQ-5D: Baseline and follow up
- PROMIS (NIH) pain interference: baseline and follow up [adult]
- PROMIS (NIH) Anxiety-8: baseline [adult]
- PROMIS (NIH) Depression-8: baseline [adult]
- PROMIS (NIH) pain interference: baseline and follow up [pediatric, age <18y]
- PROMIS (NIH) Anxiety-8: baseline [pediatric, age <18y]
- PROMIS (NIH) Depression-8: baseline [pediatric, age <18y]

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