Heterogeneity in Pancreatitis

Recognizing Heterogeneity and Its Role in the Management of Pancreatitis Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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Abstract: Both the clinical management and study of recurrent acute pancreatitis and chronic pancreatitis are complicated by significant heterogeneity in the etiology, mechanisms, symptoms, and complications of pancreatitis. The National Institutes of Diabetes and Digestive and Kidney Disease recently convened a workshop to address current knowledge and knowledge gaps in the field. Preclinical models that better replicate human disease are important for development of new therapies. Pain is often the most common and most difficult symptom to treat, as the causes are multifactorial and effective treatment may vary depending on whether pain is neuropathic or nociceptive in origin, and the placebo effect can complicate evaluation of the efficacy of medical and procedural interventions. Novel technologies like functional magnetic resonance imaging and virtual reality may offer novel means for assessing and treating pain, respectively. Clinical trial designs will need to consider best approaches to addressing the heterogeneity of chronic pancreatitis, including careful attention to designing eligibility criteria, and establishing accepted and validated core outcomes criteria for the field. The latter may be informed by consensus in pain research. Recruitment of participants into clinical trials has been challenging, often requiring multiple centers. Establishment of a clinical trials network would facilitate greater opportunities for therapeutic trials in pancreatitis.

Key Words: pancreas, pancreatitis, therapies, trials, pain, drug, diabetes

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The clinical management and study of recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) are complicated by significant heterogeneity in the etiology, mechanisms, symptoms, and complications of pancreatitis. Developing strategies for monitoring disease activity and therapies to prevent or halt the progression of the disease has therefore been challenging. The National Institutes of Diabetes and Digestive and Kidney Disease convened a workshop in Cincinnati, OH on July 24, 2024 focusing on "Heterogeneity in pancreatitis: recognizing heterogeneity and its role in the management of pancreatitis." Experts in different aspects of the disease and in conducting clinical trials participated and shared their expertise and current status of the field. This manuscript summarizes the presentations and discussions at the workshop and the knowledge gaps and research opportunities identified. Keynote addresses at the beginning of the workshop highlighted 2 patient speakers who shared their experiences with pancreatitis with the workshop attendees, highlighting the variable presentation, severity, clinical course, and impact pancreatitis had on them and their families. The first patient suffered intractable chronic pain from CP eventually requiring a total pancreatectomy with islet autotransplantation, whereas the second has had over 15 episodes of acute pancreatitis (AP) (some needing prolonged intensive care unit admissions) secondary to hypertriglyceridemia requiring hospitalizations over 20 years. Both participants discussed the burden of disease, as well as challenges encountered in medical knowledge and stigmatization when seeking care for acute pain episodes.

SESSION I—THE ROLE OF HETEROGENEITY OF PANCREATITIS IN THE MANAGEMENT OF THE DISEASE AND ITS COMPLICATIONS

Pancreatitis describes inflammation of the pancreas. Two clinically defined terms define injury-driven inflammation—AP and CP. AP is sudden onset of inflammation driven by premature intrapancreatic trypsinogen activation to trypsin, causing cell and tissue autodigestion and an innate immune response that is far greater than predicted by tissue injury alone. CP is defined mechanistically as a pathologic fibro-inflammatory syndrome in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.[1] This defines CP as a progressive condition linked to the injury-inflammation-resolution-regeneration pathway. At least 30 different risk factors and combinations (see TIGAR-O Version 2) contribute to the variable clinical characteristics of pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, and dysplasia.[2]

The mechanistic definition of CP proposed 5 stages of disease that correspond to the continuum from AP and RAP to CP.[1] Although this staging system has limitations—including the variable and unpredictable course from AP to CP, the fact that only about 50%–70% of patients with CP have a history of preceding clinical AP/RAP, the lack of a definition for early CP, and that ~10% of patients present with primary painless CP—it is the most widely used model for clinical and research purposes.[3–6] There have been recent efforts to clinically define early CP, with 3 or more episodes of AP associated with the highest risk for CP in clinical cohorts (supported by laboratory tests and imaging) and in experimental models.[7,8] Although histopathologic evidence of pancreatic fibrosis is considered the gold standard for diagnosing CP, fibrosis alone cannot diagnose CP, as fibrosis may occur in asymptomatic conditions such as diabetes, and histologic findings vary across etiologies.[9,10]

With complex and heterogenous disorders such as AP and CP, disease etiology, mechanisms, and stage of disease all present opportunities to individualize therapies to meet the needs of each patient. Currently, a few treatments targeting etiology to reduce RAP include cholecystectomy for gallstones, triglyceride lowering agents for hypertriglyceridemia, alcohol and smoking cessation for toxic etiologies, and CFTR potentiators for CFTR-related RAP.[11,12] Gaps continue to exist in our ability to accurately diagnose complex genetic and overlapping etiologies and to develop targeted treatments for the dysfunctional processes related to AP severity and for mechanisms driving progression to CP and its complications.

When considering the mechanistic stage of the disease, primary and secondary prevention are the focus of management in the early stages of pancreatitis, whereas treatments are directed at the complications of end-stage CP. Pharmacologic prophylaxis consisting of rectal nonsteroidal anti-inflammatory drugs and intravenous fluids, and endoscopic prophylaxis consisting of pancreatic stent placement are used for primary prevention of post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Secondary prevention aims to modify disease risk in individuals who have already had 1 or more episodes of AP. Secondary prevention may also be directed by etiology, as noted above. The majority of medical and invasive treatments for end-stage CP are directed toward its primary complication of pain. Patients with late-onset idiopathic CP and those with genetic/hereditary CP are at a higher risk of pancreatic cancer over time and warrant close surveillance.

To continue progress in the field, human-relevant models are needed. Genetic, functional, and animal modeling studies can provide a mechanistic framework that will inform and facilitate preclinical drug testing. Hereditary pancreatitis provides 1 example of this approach. A mutation in p.R122H in the *PRSS1* gene encoding human cationic trypsinogen was identified in 1996 as the causative genetic lesion in hereditary pancreatitis.[13] Experiments using recombinant trypsinogen demonstrated that *PRSS1* mutations increase autoactivation of trypsinogen in a chymotrypsin C (CTRC)–dependent manner, either by blocking CTRC-mediated trypsinogen degradation or by enhancing CTRC-mediated stimulation of autoactivation. Three mouse models of hereditary pancreatitis were generated that harbor mutations in the activation peptide of mouse cationic trypsinogen (isoform T7), resulting in various degrees of acceleration of autoactivation of trypsinogen in mice, and clinical manifestations from inducible but nonspontaneous AP with subsequent progression to CP, to spontaneous AP with rapid progression to CP.[14] These mouse models can be used for preclinical testing of novel drug and genetic therapies that increase trypsin inhibitory capacity and/or enhance CTRC expression in the pancreas. Promising preclinical data suggest the anticoagulant dabigatran can ameliorate trypsin-dependent pancreatitis in mice and that adeno-associated viral expression of human SPINK1 can improve pancreatitis outcomes in mouse models.[15]

One complication of AP and CP is pancreatogenic diabetes. Pancreatogenic diabetes consists of a group of closely related forms of diabetes that occurs because of pancreatic disease or surgical resection.[16] Considerable heterogeneity can occur in this form of diabetes.[17] A common mechanism in this form of diabetes related to pancreatitis is insulin deficiency. However, heterogeneity occurs because of variable severity of pancreatic damage, with severe CP or pancreatic resections having more severe insulin deficiency, hyperglycemia, and insulin dependence than those with AP.[18–20] Concomitant development of exocrine pancreatic dysfunction may affect carbohydrate digestion, with consequences for nutrition and intestinal glucose absorption. Variability in insulin responsiveness may also be present as it has been suggested that insulin resistance may occur in some subtypes, albeit with inconsistent findings across studies.[18,21,22] Other factors that may

contribute variably to diabetes mechanisms and treatments include variable nutritional status (eg, obesity vs underweight) and the comorbidities of certain etiologies such as alcohol use disorder or hypertriglyceridemia.[17]

Knowledge Gaps and Research Opportunities

- Using the Mechanistic Model framework, the field of pancreatology must move past *reactive-supportive care* and, like other disciplines, begin developing targeted treatment strategies based on the individual's risks and noninvasive biomarkers of disease linked to *probability and trajectory models*.
- Work on dynamic gene regulation and phenotypic responses within specialized cells that interact within relevant systems are needed to add precision to evolving mechanistic models.
- Genetic variant-informed mechanistic targets with clinical risks, biomarkers, and outcomes linked to the specific disease manifestation being studied need to be incorporated into pancreatitis research. Adoption of N-of-1 cases series or other nonclassical case-control study frameworks may facilitate this.
- Efforts to develop new drugs or repurpose existing drugs for future studies are needed.
- Studies are needed to inform the development of physician friendly clinical decision support tools to inform clinicians in real time of best treatments based on the patient's genotype, phenotype (including biomarkers), disease stage, and trajectory.
- Preclinical models of specific subtypes of pancreatitis, such as PRSS1 hereditary pancreatitis, are needed to facilitate effective preclinical testing of therapies directed at the underlying etiology and mechanisms in AP and CP.
- More rigorous research is needed to define the contributions of insulin resistance, exocrine pancreas dysfunction, nutritional status, etiologies, and other comorbidities to the development, progression, and treatment of disease, which will inform treatment decisions in diabetes related to pancreatitis.

SESSION II—HETEROGENEITY OF PAIN, THE PRINCIPAL SYMPTOM OF PANCREATITIS

Pain is the most frequent (85%–90%), and often the most vexing symptom of CP for patients who seek medical care. Painful CP is associated with significant disability and contributes to the decline of quality of life (QOL) and mental health for patients.[23,24]

Our understanding of the effectiveness and durability of therapies for managing painful CP remains limited, due to several challenges faced by investigators who study painful CP. Pain in the setting of CP is protean. The pain experience not only varies from patient to patient but can evolve over time within an individual patient. This creates moving targets for therapies.[25] The pathophysiologic mechanisms for pain in CP are multiple, for example: (1) pancreatic duct obstruction with increased intraglandular pressure, (2) inflammation and damage of the peripheral nerves with ectopic neural activity, (3) sprouting and hypertrophy of the sensory afferent fibers and sympathetic neurons, and (4) structural changes in the brain and impairment of the descending inhibitory pathways. It is difficult to determine which of these factors is the main driving force at any 1 point in time in CP in individual patients. Moreover, cross-sectional imaging findings of the pancreas fail to correlate with the pain experience, complicating patient selection for therapies based on structural abnormalities.[26]

Available therapies to improve CP pain may target a number of these mechanisms. However, current therapies are based on studies with significant limitations. Studies are hindered by retrospective or observational designs, lack sham or placebo arms, incomplete phenotyping of study populations, and rudimentary definitions, as well as a lack of standardized and comprehensive outcomes.

Recent, rigorously designed randomized controlled trials have made significant contributions to our understanding of therapies for painful CP.[27–30] These studies have design strengths evaluating medical management against placebo, endoscopic interventions against sham procedures, and endoscopic versus surgical interventions. However, they also highlight the ongoing challenges and offer important lessons, informing how we can more effectively design future CP trials. For example, we should select subjects for research carefully based on the timing of disease onset. The timing of interventions (conservative or invasive) can influence the effectiveness of therapies. Specifically, pancreatic pain may respond differently (favorably) to early interventions. The placebo effect is also substantial (up to 60%) and longer lasting in patients with painful CP.[31] CP pain intervention trials should be designed with longer-term follow-up, as treatment is often overestimated when only assessed at short intervals.

Accurately phenotyping patients for CP pain trials are also paramount. We must not only standardize how we characterize disease-specific features, sequelae, and complications of CP, but also utilize reliable, reproducible assessments of the pain experience. Validated instruments to assess a patient's pain, QOL, and mental health are available and offer reliable methods for tracking outcomes for future trials.[32] Use of core outcome sets (COSs) will harmonize the collection of comprehensive and validated outcomes in CP. The Patient Reported Outcome Measurement Information System and Chronic Pancreatitis Assessment Tool are examples of such important tools.[32–36]

Phenotyping the pattern of pain processing will also facilitate appropriate selection of patients for clinical trials. CP patients with central sensitization are thought to manifest with symptoms of widespread hyperalgesia and hypersensitivity of nerves throughout the peripheral and central nervous systems, resulting in lack of anticipated response to invasive therapies for treatment of pain. Phillips et al[36] have developed and refined a bedside testing algorithm for pancreatic quantitative sensory testing that can identify patterns of nociception in patients with CP suggestive of central sensitization. This technique may accurately phenotype painful CP patients as having normal pain processing, segmental or central sensitization. Patients with widespread hyperalgesia suggestive of central sensitization have been shown in pilot data to have lower rates of response to technically successful endoscopic or surgical therapies intended to relieve their pain.[37] A larger appropriately powered clinical trial is ongoing to determine the ability of pancreatic quantitative sensory testing to predict the likelihood of response to pancreatic ductal decompression therapies (NCT04996628).[38] The identification of specific biomarkers that associate with various pain patterns seems not only feasible, but may provide targets for future therapies and mechanism-based approaches to treatment of painful CP. [39,40] Pancreatic quantitative sensory testing and biomarkers that associate with pain phenotypes are avenues of investigation that may enhance our understanding of painful CP, optimize patient selection for therapeutic trials, and identify new targets for interventions.

Functional magnetic resonance imaging (fMRI) is also a promising field of investigation to understand brain systems involved in processing and regulating pain. Examining region-to-region correlations in fluctuations of spontaneous blood oxygenation level dependent signal in the absence of a task (noxious stimuli) may be linked to various aspects of chronic pain conditions. Examination of functional connectivity (FC) of the amygdala has expanded our understanding of chronic pain conditions other than CP, such as pediatric migraine and functional abdominal pain. FC of the amygdala in these populations seems to differ from that of healthy control participants, with increased connectivity in the posterior cingulate/precuneus and portions of the frontal

cortex.[41,42] Dynamic changes are also seen in connectivity between the amygdala with such regions as the prefrontal cortex, anterior cingulate, and insular cortex with symptom provocation and after cognitive behavior therapy (CBT).[43] For the individuals with migraine who had the greatest change in headache frequency, the FC of the amygdala decreased the most in portions of the anterior cingulate cortex. Finally, FC of the amygdala at baseline can predict responsiveness to therapies such as treatment with CBT.[44] Arterial spin labeling represents a promising alternative to blood oxygenation level dependent for designs that examine activation during brain states that last longer than 4 minutes. With arterial spin labeling, blood is tagged magnetically and used as a tracer. This allows cerebral blood flow to be fully quantified and may strengthen the ability to perform serial scanning sessions pretreatment versus posttreatment. Further study of fMRI as a tool for mapping brain systems involved in pain processing may expand our capabilities to characterize and quantify the pain experience in CP patients.

Virtual reality (VR) technology is a novel therapeutic tool that transcends traditional boundaries in medical treatment and psychological intervention and represents a potential modality to reduce pain burden in RAP and CP. VR has utility in the management of patients with chronic pain in a variety of ways. By creating immersive environments, VR facilitates mental and emotional escape. Through engagement, VR can also replicate a "flow state" associated with meditation and intense focus activities, instrumental in psychological healing and resilience. VR therapy harnesses the brain's attention resources. Through this mechanism of neural suppression, VR minimizes external stimuli associated with the ambient hospital environment and physical discomfort, focusing the patient's attention on alternate stimuli. This is demonstrated as VR users often report altered time perception, underestimating the duration of painful or uncomfortable procedures.[45]

VR software facilitates education and rehabilitation of patients, offering CBT exercises and educational content about gastrointestinal health. The addition of artificial intelligence to VR technologies may further enhance its therapeutic capabilities. Artificial intelligence may help mimic the techniques of CBT by adapting in real time to the user's emotional and cognitive responses. This ensures that each patient's unique mental health needs are met with greater precision and sensitivity.

Knowledge Gaps and Research Opportunities

- Pancreatic pain is a dynamic process. Patient selection for trials should incorporate clear and careful procedures for phenotyping subjects based on their natural history of and how they experience pain.
- Although pancreatic pain is a subjective outcome, validated multidimensional assessment tools should be incorporated into trial designs as they can reliably characterize a subjects' pain experience and may delineate patterns of nociception.
- Placebo response may account for up to 60% of treatment effect. Consequently, control arms are an indispensable design element for rigorous medical and endoscopic trials.
- Treatment effects for pancreatic pain may be overestimated in the short term. Therefore, adequate (intermediate and longer) duration of follow-up is needed for interventional trials.
- Future trials should prioritize the characterization of and development of therapeutic interventions that target central sensitization.
- The study and development of biomarkers that reliably phenotype nociception in CP should be prioritized.
- Although there are significant gaps in our understanding of brain systems involved in the CP pain experience, fMRI offers promise and should be explored as a tool to characterize patterns at baseline and in response to interventions for painful CP.
- VR is promising technology to deliver interventions and education for painful CP patients. VR platforms should be evaluated in future trials to address knowledge gaps of its efficacy in CP and understand the optimal deployment of this technology.

SESSION III—TREATMENT TRIALS FOR PANCREATITIS: CURRENT AND FUTURE CONSIDERATIONS

Heterogeneity in pancreatitis etiology, pathophysiology, and disease course complicates the design of clinical trials focusing on treatments. The timing of intervention may influence treatment response, and factors like pathophysiology (immunology of disease, for example) may influence treatment success. In designing inclusion criteria, and selecting trial endpoints, factors like disease cause, stage of disease, and symptoms or disease complications being assessed need to be considered.

Pain is the most disabling and disruptive symptom of CP. Both endoscopic therapy (performed at ERCP) and surgery may play a role to mitigate or eliminate pancreatic pain. Although both treatments have demonstrated reasonable efficacy, failures and complications do occur, and the appropriate timing of these interventions remains unclear. Many case series have compared the effectiveness of ERCP and surgery, but few randomized controlled trials have evaluated the impact of timing upon outcomes when comparing ERCP versus surgery first.[27,46,47] Ahmed et al[47] identified high-dose daily opioids, greater than 5 ERCPs, and duration of pain >3 years as independent clinical predictors of surgical failure. In the ESCAPE trial, the early surgery approach resulted in significantly less pain over 18 months compared with the endoscopy first arm.[27] Furthermore, when crossover from endoscopy to surgery occurred, failure of endoscopy did not predict surgical failure, nor did it negatively impact potential success of surgery provided that crossover occurred within 2 years of the development of pain. These data support the concept that earlier intervention may result in superior outcomes by preventing or mitigating the development of a hyperalgesia syndrome.[48] However, data are overall sparse regarding the timing or sequence of endoscopic and surgical interventions for painful pancreatitis. Long-term data regarding durability of pain relief and the impact of invasive interventions upon endocrine or exocrine progressive dysfunction are also lacking. An improved understanding of the natural history of progression of this disease and hyperalgesia syndromes hints at the notion that earlier intervention may result in superior outcomes for mitigation of pain.

AP is an inflammatory disorder with an immunological-based pathogenesis once instigated with acinar cell injury. Acinar cell injury produces and recruits proinflammatory mediators through several different mechanisms that include neutrophil and macrophage recruitment, release of extracellular substrates including DNA histones and other critical proteins such as HMGB1 called damage-associated molecular patterns, and release of pathogen-associated molecular patterns.[49] In CP, T-cells and macrophages predominate within the pancreas tissue, with a shift in macrophage polarization (M2), which in turn activates a profibrogenic environment via pancreatic stellate cells.[50] In sum, the immune mechanisms currently elicited are multiple, creating a complex, heterogeneous, and overlapping system, which has implications for treatment trials that target immune mechanisms.

Empirical work of defining circulating immune markers in various stages of human pancreatitis has correlated with preclinical observations of progressive increased activation of proinflammatory signaling with disease progression from AP to CP.[51,52] These studies also showed how environmental factors including smoking, alcohol, and diabetes appear to correlate with unique

immune markers contributing to additional complexity and heterogeneity to interpretation of immune profiles in pancreatitis. Immune-targeted treatment trials have been pursued with mixed results. Pentoxifylline showed early promise in a human pilot study, but a subsequent validation study did not confirm efficacy.[53,54] Studies of infliximab (RAPID-1) for AP and tocilizumab for CP (TOPAC) are underway. Other studies are focused on understanding the natural history of detectable circulating cytokines and chemokines in the first 72 hours of pancreatitis, which is being pursued by the MoSAIC study (NCT05878236).

The eligibility for clinical trials for RAP and CP needs to consider multiple factors, including the pathogenesis of disease and the symptom being treated. Two clinical trials were presented as examples, both double-blind, placebo-controlled pilot trials, using paricalcitol (NCT05664880) and simvastatin (NCT05771675), respectively. In CP, activated stellate cells mediate the fibroinflammatory response. Tumor growth factor-β and Smad3 signaling mediate pain signaling in pancreatitis.[55] In animal models, the vitamin D analogue, paricalcitol, inhibited the effect of tumor growth factor-β and Smad3 signaling of activated pancreatic stellate cells and attenuated pancreatitis responses.[56,57] Additionally, the HMG CoA reductase inhibitor, simvastatin, inhibited the activated state of the pancreatic stellate cell in preclinical models[58] and decreased pain and use of narcotic medications in a pilot clinical trial.[59] The paricalcitol and simvastatin trials are both enrolling and evaluating adult patients with RAP and CP with moderate pain intensity. The primary outcome measure for both trials is patient-reported pain. Secondary outcomes include QOL measures. Blood proteomic and imaging studies are included to determine if there are associations between responses and biomarkers measured, which may provide eligibility information for future studies.

Clinical trials will evolve with improved understanding of the molecular mechanisms underlying disease pathogenesis, including genetic targets when applicable. The stage of disease also needs to be considered in designing eligibility criteria, as advanced CP with significant fibrosis may not respond to agents that address early steps in pathogenesis. Alternatively, there is the opportunity to use agents that are effective in treating CP resulting from AP episodes.[60] Eligibility criteria for clinical trials for RAP and CP currently are broad and include subsets of different disease geno-phenotypes. Eligibility criteria for drug trials need to be tailored to individual subtypes and target specific pathways.

When designing clinical trials, COSs, which represent the minimum set of domains and specific measures to be included and reported for a given health area, are instrumental to increasing data harmonization and comparison in research. Establishing a COS and identifying relevant outcome measures that aligns with patient priorities will contribute significantly to the advancement of effective treatment strategies for RAP and CP.

Pain is the main symptom being targeted in most RAP and CP trials. Various initiatives have been focused on creating COS for chronic pain. The Innovative Medicines Initiative–National Institutes of Health Transatlantic Emphasis Group on Research and Translation-to-Care Efforts for Pain consortium focused on developing COS for different types of pain in adults.[61] In pediatrics, the Core Outcomes in Pediatric Persistent Pain work group has recently updated a COS for pediatric chronic pain clinical trials.[62,63] However, these efforts have not included RAP/CP.

Mission Cure, a nonprofit organization whose mission is centered on identifying curative therapies for CP, initiated a study aimed at identifying a COS aligned with patient and provider priorities for RAP and CP. Leveraging the Outcomes Measures in Rheumatology framework, a 2-round Delphi poll was conducted among 3 stakeholder groups: adult patients, parents and pediatric patients, and adult and pediatric health care providers. Steering committee consensus further refined the core outcome domains, categorizing them as mandatory, important but optional, or research agenda domains. Pain severity, ability to participate in social roles, pancreatitis-related hospitalization/ER visits, and AP flare-ups were recommended as mandatory domains in all trials.[64] The second phase of work to identify validated measures for each domain is ongoing. Moving forward, clinical trials in RAP/CP should begin using the new COS to obtain further validation data and ensure consistency among studies.

Knowledge Gaps and Research Opportunities

- Clinical trials that address timing of surgery and endoscopic therapy, including endpoints of durability of pain relief, endocrine and exocrine function, and QOL with long-term follow-up, are needed.
- Defining the natural history of the immune process in AP and CP will aid in developing potential treatments and trials.
- There is a need to identify opportunities to repurpose drugs like infliximab, pentoxifylline, and tocilizumab, either individually or in combination, which may expedite the identification of promising treatments.
- Clinical trial eligibility criteria need to be defined to account for subtypes of CP, mechanistic pathways, and specific geno-phenotypes that will be important to advancing clinical trials.
- Clinical trials in RAP/CP should begin using agreed-upon COSs to ensure consistency among studies. Ideally, these outcomes would be consistent among both pediatric and adult studies.

SESSION IV—A PANCREATITIS CLINICAL TRIALS NETWORK: CONSIDERATIONS AND RECOMMENDATIONS

Although substantial progress has been made in understanding the pathobiological mechanisms underlying pancreatitis using experimental animal models, limited progress has been made in translating these findings into effective treatment for patients with AP or CP. An exception is progress in evaluating endoscopic interventions[65,66]; these trials have required extensive planning, resources, and collaboration.

Multiple challenges exist when considering expanding these efforts to therapeutic trials in pancreatitis. These include heterogeneity of the disease, lack of well-defined clinically meaningful endpoints, as well as the broad range of medical specialties involved. Beyond disease-specific concerns, typical challenges associated with large-scale trials such as regulatory oversight, administrative requirements, and quality assurance are essential aspects of trial conduct. Two recently completed industry-sponsored phase 2 clinical trials illustrate the challenges of conducting therapeutic trials in patients with pancreatitis. The TACTIC study,[28] a double-blind placebo-controlled study of a protease inhibitor (camostat mesylate) for pain in CP, required 48 sites across the United States, Ukraine, and Russia to enroll 264 participants with CP and chronic pain, whereas the CARPO study (NCT04681066) of calcium release-activated calcium channel inhibitor for treatment of AP required 37 sites across the United States and India to enroll 214 patients with AP and systemic inflammatory response syndrome (personal communication by Behien Wu). Based on the high number of sites needed to achieve these modest accrual numbers, sufficiently powered studies to evaluate clinical efficacy in patients with pancreatitis are only possible with even greater collaborative and organized effort.

A multicenter trials network in pancreatitis would bring together established nodes of collective expertise to facilitate conduct of clinical trials that can rapidly accelerate development of efficacious treatments for patients across the spectrum of disease.

Examples exist with respect to trial networks that incorporate disparate diseases such as the Strategies to Innovate Emergency Care Clinical Trials Network that seeks to "improve the outcomes of patients with neurologic, cardiac respiratory, and hematologic emergencies by identifying effective treatments given in the earliest stages of care."[67] Several key elements of a successful trials network such as a well-defined governance and access rules, organizational structure, and clearly defined data-sharing structure within the network are established within existing National Institutes of Diabetes and Digestive and Kidney Disease consortia such as the consortium for the study of CP, diabetes, and pancreatic cancer (CPDPC, U01), as well as the type 1 diabetes in AP (T1DAPC, U01) consortium.

One very successful clinical research network is the Cystic Fibrosis Therapeutics Development Network (TDN) formed to facilitate the clinical study of new and existing therapies to cure and control cystic fibrosis (CF). This mission driven network has 2 key mandates: (1) to partner with industry to bring new therapies to CF and (2) to design and conduct investigator-led studies (ILSs).[68] These ILSs include studies of existing therapies to improve access and optimize treatment for people with CF and to develop outcome measures that can be used for early proof of concept studies. The TDN is funded by the Cystic Fibrosis Foundation through academic grants and consists of 3 key components: national resource centers (laboratories and overreading centers for the development of outcome measures), therapeutic development centers (the clinical research sites), and a coordinating center. The coordinating center has primary responsibility for interactions with industry sponsors, network oversight, and functions as both a clinical and data coordinating center for the ILS. Over time, the TDN has expanded from 8 centers in 1998 to over 90 in 2022 to facilitate clinical study of more than 82 potential therapeutic agents.[69–71] Some of these agents are now available to people with CF, and clinical outcomes (including survival) have dramatically improved.

The primary reason for the improvements in the health of people with CF was the partnership that was established among the CF Foundation, the TDN, and Vertex Pharmaceuticals to develop a suite of CFTR modulator therapies.[72,73] Although industry partnerships have brought multiple new treatments to CF, academic initiatives and investigator led studies conducted in the TDN also support the mission. Development of new outcome measures is still ongoing, with a focus on identifying early proof of concept outcomes for nucleic acid–based therapies.[74] Additionally, the 286,000 biospecimens collected during multiple ILS over the last 25 years are linked to clinical data and are available for use by academic investigators for translational research.[69]

The success of the TDN is due to its ample funding, focused mission, visionary leadership, long-standing culture of research within the CF community, standardized clinical care models, and long-term collection of clinical data through the CF Patient Registry. An additional aspect of the network's success has been its recognition of the important role research coordinators play in effective recruitment and skillful execution of clinical studies.[75]

A Pancreatitis Clinical Trial Network (PCTN) will need a plan for funding and commercialization strategies to sustain it. This could be a combination of academic institutions, pharmaceutical companies, government agencies, philanthropy, and advocacy organizations. Both venture philanthropy and impact investing have emerged as powerful funding strategies that go beyond traditional philanthropy and investment methods. These investment vehicles aim to create social or health-related benefits, while also seeking financial returns for the organization or impact investors.

Key features of the PCTN include collaboration and coordination, protocol standardization, patient recruitment and retention, promotion of innovation and translational research, and financial and operational efficiency. Creating a unified platform for groundbreaking clinical trials and accelerating the translation of research into effective therapies for pancreatitis are needed to attract sufficient and appropriate funding throughout the life cycle of the network.

The PCTN must strive to become a sustainable, revenue-generating entity while maintaining its primary mission of advancing medical research and improving patient outcomes. Key steps include (a) identifying the value proposition, including PCTN's unique strengths and fit to market need; (b) developing a business model that identifies potential revenue streams such as service contracts, subscription fees, consulting services, or grant funding; (c) developing a robust infrastructure to include data management systems, IT infrastructure for efficient trial management, data collection and analysis, and robust data security; (d) establishing a strong brand and marketing strategy; (e) secure funding and investment; (f) ensure regulatory compliance and finally; and (g) measure and demonstrate impact.

Knowledge Gaps and Research Opportunities

- A PCTN would provide an efficient mechanism for conducting large-scale clinical trials that are urgently needed to transform care for patients suffering from pancreatitis.
- A clear mission and focus are key to develop a PCTN, as well as a dedicated group of investigators.
- Clinically informative and widely accepted outcome measures are needed for success of PCTN-supported trials.

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