

# Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis

## Summary of the Working Group on Drug Development and Trials in Chronic Pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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**Abstract:** The lack of effective therapeutic agents specifically tailored for chronic pancreatitis (CP) has hampered clinical care and negatively impacted patients' lives. New mechanistic insights now point to novel therapies, which involve both recently developed and/or repurposed agents. This working group focused on 2 main outcomes for CP: pain and progression of disease. The goal is to frame the essential aspects of trial design including patient-centered outcomes, proposed methods to measure the outcomes of pain and progression, and study design considerations for future trials to facilitate rapid drug development for patients with CP.

**Key Words:** chronic pancreatitis, clinical trial design, natural history of chronic pancreatitis, pain in chronic pancreatitis

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The worldwide incidence of chronic pancreatitis (CP) shows wide variation, with increasing prevalence reported from several countries.<sup>1–3</sup> Mortality from CP is reported to be 12.8% to 19.8%, over a mean observation period of 6.3 to 9.8 years.<sup>4,5</sup>

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One-third of patients suffering from CP are no longer able to pursue their profession.<sup>5,6</sup>

There are limited effective therapeutic options for CP. Therapy does exist for pancreatic exocrine insufficiency (ie, pancreatic enzyme replacement therapy), although this therapy is vastly underutilized, and complications of exocrine insufficiency such as osteoporosis and fragility fractures are common in CP. Similarly, therapy for pancreatic endocrine insufficiency is available, but type 3c diabetes may be quite brittle and difficult to manage. Unfortunately, abdominal pain, the most frequent and most deleterious clinical consequence of CP, has no consistently effective therapy and greatly impairs patients' quality of life (QOL). Similarly, no therapy has been demonstrated to consistently alter the progression of CP.

The effectiveness of therapeutic agents has been difficult to determine, as most previous studies utilized variable definitions, metrics and instruments, duration of treatment, and end points and lacked sham or placebo controls. In addition, very few studies utilized patient-focused or patient-reported outcomes, and none has reached the threshold of US Food and Drug Administration (FDA) approval for CP pain. In addition to pain, therapies that might impact progression, with perhaps the exception of alcohol and smoking cessation, have rarely been studied. This working group chose to focus on 4 main topics to help frame and harmonize future studies, with a view to facilitating FDA consideration and approval of these therapies. These include (1) a review of the need to incorporate patient experience and outcomes into future trials and examples of how to achieve this; (2) a review of existing research and knowledge on 2 main outcomes: abdominal pain (and its impact) and progression of CP; (3) best practices for future trials of pain associated with CP, with examples from other conditions that would facilitate FDA approval; and (4) proposals for future trial designs to test potential agents to prevent disease progression. Further, we sought to identify major gaps in knowledge that prevent progress in identifying and demonstrating the effectiveness of therapies for both pain and progression of CP (Table 1).

### PATIENT-FOCUSED DRUG DEVELOPMENT FOR CP: INCORPORATING PATIENT INPUT IN DEVELOPING TREATMENTS

The ultimate goal of drug development is to improve the way that patients feel, function, and survive. The medical community has recognized that patient perspectives might differ significantly from what is anticipated by researchers, drug developers, and providers, and what patients care most about may not always be factored into clinical trials or approved labeling.<sup>7</sup> This is

**TABLE 1.** Research Gaps and Opportunities**A. PFDD for CP: Incorporating Patient Input in Developing Treatments**

- Comprehensively characterize the burden of disease, symptoms of most concern to patients, and patients' perspectives on current treatment options.
- Identify subgroups that have different symptoms or different needs (including pediatric patients).
- Identify the clinical improvements that patients value most and the relative importance of different improvements.
- Determine how patients evaluate the trade-offs between potential benefits and risks of specific types of treatments.
- Determine the challenges of participating in clinical trials, especially reasons for dropout; gathering patient suggestions on how clinical trials process and design can be improved.

**B. Outcome Selection for CP-Related Pain**

- Improve understanding of pain mechanisms and identify biomarkers (eg, in biological fluids, such as serum, pancreas fluid, urine) unique to pain phenotype (eg, inflammatory or neuropathic) in individual patients, to allow appropriate patient selection for targeted intervention and identification of novel therapies.
- Develop clinical algorithms for patient selection for clinical trials. For example, account for patient selection based on evidence of pancreatic ductal anatomy, duration and character of pain, use of prior therapies, or presumed pain mechanism for selecting and stratifying patients for future trials.
- Determine best instruments and end points for pain trials in CP. In particular, develop CP-specific QOL instruments, patient-focused end points, and recommended core measures for consistency in future pain trials. Develop consensus primary and secondary outcomes and patient-reported outcomes. Define appropriate duration of randomized pain therapy trials.

**C. Outcome Selection for CP Progression–Related Outcomes**

- Compare fibrosis in disease states to identify similarities and differences between fibrosis affecting different organs (eg, pancreas, liver, lungs).
- Develop new approaches to current imaging and novel imaging techniques to characterize different stages and progression of pancreatic structure and function.
- Develop consensus clinical scoring systems, with patient input, as surrogate markers of disease progression.
- Define primary, secondary, and surrogate outcomes and end points for intervention trials.

**D. Considerations for Pain-Centered Outcome Trials**

- Facilitate incorporation of best practices of chronic pain trials into studies of CP pain.
- Develop consensus criteria on metrics and instruments for pain studies in CP.
- Inform regulatory agencies of best measures of pain outcome for CP.

**E. Considerations for Natural History–Centered Outcome Trials**

- Develop consensus criteria for inclusion and exclusion, patient-centered outcomes, disease-related manifestations, and disease progression that can be used in randomized clinical trials for treatment of CP.
- Define accurate estimates of the frequency and determinants of progression in CP and of patient-centered and individual disease-related events observed during the natural course of CP.
- Develop single or composite outcome measures for use in short-, intermediate-, and long-term studies focusing on progression of CP (phases 2 and 3 studies).
- Develop surrogate panel consisting of biofluid markers to test biologic effect of an intervention for use in short-, intermediate-, and long-term efficacy trials.
- Develop analytical methods for the joint analysis of multivariate survival and longitudinal data of mixed data types, for the exploration of the disease progression heterogeneity, and for the validation of multivariate surrogate end points for CP progression.

especially the case for rare, chronic, and often stigmatized diseases such as CP.

Patients with CP often suffer from debilitating pain, nausea, and fatigue, which has a major impact on their ability to work, attend school, tend to family responsibilities, and generally conduct their activities of daily living.<sup>8</sup> Yet, there is a paucity of research about patient experiences and perspectives, in a way that might guide researchers and drug developers. Patients' needs are largely unmet, and patients and caregivers often feel misunderstood and unsupported. For example, pain intensity has been a main target of treatment trials. When it comes to evaluation of pain management, however, a reduction in pain intensity is often less important to patients than an improvement in overall function and daily activity.<sup>9</sup> To adequately inform both drug development and evaluation, a more comprehensive understanding of what patients truly seek from treatment is necessary.

The pancreatic research community has recently begun to bridge this knowledge gap. In a recent report, the Dutch Pancreatitis Study Group surveyed 252 patients with acute pancreatitis (AP) or CP regarding their symptoms, experience participating in clinical

research, and suggestions for future clinical research topics.<sup>10</sup> The authors argue that the predominant patient-reported clinical symptoms (eg, pain, fatigue) and future research topics suggested by patients (eg, nutrition) contrast with those focused on by most current studies, and therefore, a better understanding of patient opinions and experiences should be a priority of future research. Much more needs to be done to develop consistent measures and instruments for clinical research in these patients.

## Patient-Focused Drug Development

In 2012, pursuant to a congressional mandate, the FDA established the Patient-Focused Drug Development (PFDD) initiative, with the goal of ensuring that “patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.”<sup>11</sup> This new focus on patients in the drug development process was legally required under the Prescription Drug User Fee Act V (2012), the 21st Century Cures Act Section 3002 (2016), and Prescription Drug User Fee Act VI (2017). The FDA has made significant progress in advancing PFDD,

including conducting 26 condition-specific PFDD meetings to gather patient perspectives about their conditions and available therapies,<sup>12</sup> and developing a series of 4 methodological guidance documents for collecting and submitting patient experience data.<sup>13</sup>

Armed with this new roadmap provided by the FDA, several patient organizations have conducted pioneering work in collecting, analyzing, and utilizing patient experience data to facilitate drug development and regulatory decision making. The Duchenne Muscular Dystrophy (DMD) community, for example, launched a rigorous patient preference study to quantify patient benefit-risk assessment, expanded the scope of acceptable end points to include those that patients care most about, and submitted a community-led draft industry guidance to the FDA. These efforts have led to collaborations with the pharmaceutical industry to develop drugs that directly address unmet needs for patients with DMD (Fig. 1).<sup>14</sup>

## Applying PFDD to CP

With congressional support for PFDD, FDA guidance,<sup>15</sup> and successful case examples from other patient groups, the CP community should apply the emerging paradigm of PFDD to its own practice. The first step is to collect and analyze patient experience data. With the newly published FDA guidance, "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input,"<sup>15</sup> stakeholders should work collaboratively to collect information on patient experiences and needs, about what improvements patients and caregivers would most like to see, and about the level of risk they are willing to tolerate. Patient-focused groups, including Mission: Cure, a new nonprofit organization dedicated to dramatically improving outcomes for CP patients, and the National Pancreas Foundation, are able to work with the wider pancreas community and the FDA in this effort. The collected patient experience data will be a crucial step to guide drug discovery, inform end point selection, and facilitate regulatory decision making.

## OUTCOME SELECTION FOR CLINICAL TRIALS

### CP and Pain

Previous cohort studies have documented that abdominal pain is frequent (>75%) in patients with CP, that certain etiologies

may be more commonly associated with pain (eg, alcohol > idiopathic), that different pain patterns occur (eg, constant vs intermittent), and that pain may evolve (or even burn out) over prolonged follow-up.<sup>4,8,16–19</sup> In patients with intermittent pain, which is more common in the early stages of CP, there may be long periods of freedom from pain. Pain is the most common reason for intervention or hospitalization, and most detracts from QOL. Chronic or continuous pain in particular has the most negative impact on QOL in these patients.<sup>18</sup> In the United States, approximately half of all patients with CP are on opioid therapy,<sup>20</sup> and this is far more common than in many other countries. Many patients are on adjunctive agents (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, and gabapentoids) as well. Although they are recommended in guidelines,<sup>21,22</sup> the impact and effectiveness of these agents are not known. Endoscopic and surgical intervention is possible in certain individuals with appropriate pancreatic ductal anatomy, generally a dilated pancreatic duct, or an inflammatory mass in the head of the pancreas. The effectiveness of these therapies on pain and the predictors of pain improvement with these therapies are not clearly defined.<sup>21–24</sup> Current therapies are often ineffective, and chronic pain remains a dominant symptom for many patients.

Approximately 80% of children with CP report abdominal pain (approximately half have some form of constant pain), and pain is the major driver of cost in the INSPPIRE population.<sup>25</sup> Children with constant pain experience more emergency room visits, miss more school, and require more hospitalizations compared with those without chronic pain.<sup>25,26</sup> Forty-one percent of children with CP in INSPPIRE cohort use an opioid to control pain.<sup>27</sup>

Predicting patient response to a particular therapy for pain is currently not possible. One confusing feature of this disease is that the amount of damage to the pancreas (eg, that which is visible on computed tomography [CT] scanning) does not correlate with the severity or even presence of pain.<sup>28</sup> Even therapies that appear to work in a similar fashion (eg, endoscopic stenting or surgical decompression of a dilated pancreatic duct) may not have the same effect in individual patients pointing out our lack of understanding of the etiologies of symptoms in CP. The mechanisms of pain in CP are complex, variable, and poorly understood. Some mechanisms of pain include pancreatic inflammation and ischemia, intrapancreatic nerve injury, altered nociception with sensitization, altered central

## PFDD in Practice – the Duchenne Example

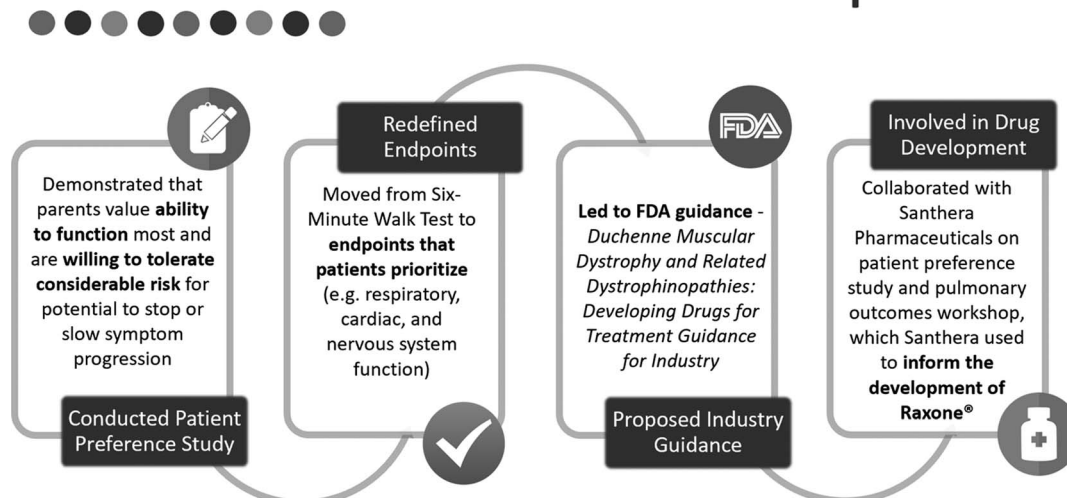


FIGURE 1. Efforts made by the DMD community to bring patient input to facilitate drug development.

pain processing, complications of CP (eg, pseudocyst), adverse effects of therapy (eg, narcotic bowel), and others.<sup>22,29</sup> It is usually difficult to identify the dominant pain mechanism in individual patients, and thus, therapy becomes a matter of trial and error.

Underlying the problem in the study of pain in CP is the natural variability of the symptoms and the diseases over time. Previous studies of pain therapies in CP have used a variety of medical, endoscopic, and surgical therapies, but few placebo-controlled trials exist. Most trials are retrospective or prospective cohort studies, with a small number of randomized (non-placebo controlled) trials. When a placebo-treated group is used, a response of approximately 20% is found in studies of CP pain.<sup>30</sup> Most studies are cohort studies without a control group. An additional source of variability can be ascribed to the instrument utilized to measure pain and pain improvement. A few CP-specific pain assessment tools used in previous studies have utilized measures of pain severity and impact on QOL (eg, Izicki score).<sup>31</sup> Others measure only the character and temporal nature of the pain (such as the A-E, Ammann, or Group 1–3 systems).<sup>31</sup> In most randomized trials of therapy for pain in CP, unidimensional studies of pain intensity, frequency, or pattern have been used. In very limited studies, multidimensional pain scores (eg, McGill Pain Questionnaire, Pain Detect Questionnaire) and/or pain impact instruments (QOL scores, Brief Pain Inventory, Pain Disability Index) have been utilized.<sup>31</sup> Several expert consensus guidelines have recommended different pain assessment tools for future studies.<sup>22,32–35</sup> These recommendations include visual analog scale pain tools, as well as some measures of QOL using generic (Short Form 12, Patient-reported Outcomes Measurement Information System, European Organization for Research and Treatment Cancer Quality of Life Questionnaire C30) or CP-specific instruments (European Organization for Research and Treatment Cancer Quality of Life Questionnaire Pancreatic Modification). Three CP-specific QOL instruments are available: European Organization for Research and Treatment Cancer Quality of Life Questionnaire Pancreatic Modification, Pancreatitis Quality of Life Instrument (now partially validated),<sup>36</sup> and Comprehensive Pain Assessment Tool for Chronic Pancreatitis (not yet validated).<sup>37</sup> The recommendations from various guidelines do not specify the core measures recommended for chronic pain trials.<sup>9</sup>

## CP and Progression

There is often a progression in patients, from AP to recurrent AP to CP as a continuum over time. The pooled estimate of the frequency of progression from AP to CP is 10% (95% confidence interval, 6%–15%), with smoking and alcohol abuse in male subjects being the strongest risk factors.<sup>38</sup> Of note, many of these studies did not analyze genetic predispositions, which are likely to be additional predictors of progression to CP.

Imaging is a cornerstone of diagnosis and staging of CP, and multiple imaging modalities have been assessed that focus on the pancreatic ductal anatomy or pancreatic parenchyma.<sup>39</sup> A well-recognized challenge in diagnosis is that changes visible on these imaging modalities develop over time and may be absent early in the clinical course. A recent systematic review and meta-analysis<sup>40</sup> noted similar diagnostic accuracy for endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and CT in the initial diagnosis of CP. However, none have been shown to have a strong relationship with the symptoms patients report.

Endoscopic ultrasound-elastography and MRI-elastography have the capability to qualitatively or quantitatively assess pancreatic stiffness as a marker of fibrosis.<sup>41–43</sup> This method might enable staging and a platform to identify disease progression, although no long-term follow-up of these techniques in individual

patients is available. Endoscopic ultrasound-elastography using “mean of reflection” is able to grade pancreatic fibrosis through a quantitative analysis into mild, marked or higher-grade fibrosis, and severe fibrosis with areas under the receiver operating characteristic curve of 0.90, 0.90, and 0.90, respectively.<sup>44</sup> In a total of 115 patients, EUS-guided elastography allowed quantification of the probability of exocrine insufficiency with an accuracy of 87.5%.<sup>45</sup> Magnetic resonance imaging with secretin infusion, or quantitative measures of MRI signal, may indicate the extent or stage of CP,<sup>46,47</sup> but MRI changes were only weakly correlated with other staging criteria, such as the M-ANNHEIM classification. Gland volume was negatively correlated to the duration of CP ( $r = -0.39$ ,  $P < 0.001$ ) and baseline apparent diffusion coefficient measured by MRI ( $r = -0.35$ ,  $P = 0.027$ ). When stratified by clinical stage (M-ANNHEIM), the pancreatic gland volume was significantly decreased in the severe stages of CP ( $P = 0.001$ ).<sup>48</sup> Studies of EUS and MRI suggest some potential for usefulness in clinical studies but require more research to define the best techniques.

Parenchymal calcifications are considered a hallmark finding of advanced CP, but these are not consistently linked to clinical presentation and symptoms, and other morphological features such as atrophy, fibrosis, and ductal changes. In a recent publication,<sup>49</sup> number and size of parenchymal calcifications and any of the other morphological CT and MRI parameters were not correlated (all  $P > 0.05$ ), with the exception of larger size of calcifications in those with higher number of calcifications. The number of parenchymal calcifications was negatively correlated with body mass index ( $r = -0.35$ ,  $P = 0.0088$ ) but not with any other clinical parameter such as CP etiology or duration, M-ANNHEIM clinical stage, tobacco or alcohol use, pain score, or QOL.<sup>49</sup> This analysis reinforces the concept that calcification alone is a poor metric for measuring progression. Interestingly, parenchymal calcifications are not a common feature of pediatric CP.<sup>26</sup>

The progression to exocrine and endocrine insufficiency appears to vary by etiology and particularly due to differences in the natural history of alcoholic and idiopathic (nonalcoholic) CP.<sup>17</sup> The development of exocrine or endocrine insufficiency usually occurs after more than 5 years. The progression to exocrine insufficiency (86%–100%) and calcification (80%–91%) lasts 2- to 5-fold longer in idiopathic and some genetic types of CP if compared with other forms of CP. The common early stage of CP, characterized by recurrent pancreatitis, lasts up to 5-fold longer in idiopathic CP if compared with CP due to alcohol.<sup>17,47,48,50</sup> Endocrine insufficiency is diagnosed in 8% of CP patients at the onset of disease and in 78% at 10 years into the disease.<sup>17,51</sup> As deterioration of endocrine and exocrine function depends on the etiology of the disease and occurs over many years, pancreatic function alone may not be suitable as an end point for clinical trials.

Several scoring systems to evaluate the severity of CP exist. The Cambridge classification for severity grading using endoscopic retrograde cholangiopancreatography,<sup>52</sup> and its adaptation for other types of imaging,<sup>21,53,54</sup> is still used for diagnosing and scoring of CP in adults. The ABC system uses a classification consisting of 3 stages, which combine clinical criteria (pain, recurrent attacks of pancreatitis, local complications, steatorrhea, and diabetes mellitus) with imaging (ductal or parenchymal changes).<sup>55</sup> The Rosemont classification provides diagnosis and stages CP using “major” and “minor” endoscopic ultrasonography criteria.<sup>56</sup> The number of observed abnormalities correlates with the histologic severity of the disease, but not with other clinical markers of CP. The M-ANNHEIM classification is more comprehensive and attempts to characterize patients according to etiology, clinical stage, and severity.<sup>57</sup> The severity of the inflammatory reaction is evaluated using clinical symptoms and therapeutic interventions, resulting in a rather complex classification criteria involving a

point system describing severity of CP. The CP Prognostic Score predicts individual short-term (12-month) prognosis using C-reactive protein levels, thrombocyte count, glycosylated hemoglobin levels, body mass index, and pain severity.<sup>58</sup> This scoring system correlated with the need for hospital admission and length of hospital stay, but not with Cambridge grading. Similar to radiographic imaging, these scoring systems may not have a strong correlation with patients' symptoms.

## CONSIDERATIONS FOR PAIN-CENTERED OUTCOME TRIALS

Consistent with the findings in CP, our expanded knowledge of pain in other chronic conditions has shown that the correlation between objective findings and symptoms is not strong. In part this is due to multiple etiologies and mechanisms for pain including injury to nerve tissue, which can perpetuate pain even after the original stimulus resolves. In treating many conditions, it is often useful to use a disease-specific measure that combines the important components of the disease into a single score. However, in considering the treatment of persistent symptoms (ie, pain) that continue despite improvement in the underlying disease, there is evidence that combining symptoms may be inappropriate<sup>59</sup> when testing therapeutic interventions. When this is the case, as it is in CP, different treatment approaches are needed to relieve symptoms, and studies of pain-specific treatments for CP can be modeled after other chronic pain conditions.

Over the past 20 years, there has been significant progress made in understanding how to design, conduct, analyze, and interpret pain studies. The 2 public-private partnerships of IMMPACT and ACTION have published more than 50 articles summarizing this work (see IMMPACT.org and ACTION.org). Studies of pain therapeutics are required to have a measure of pain as the primary outcome, and the 0- to 10-point numerical rating scale (NRS) of average pain over the last 24-hour or 1-week period is the most commonly used measure. Some studies use worst pain as a primary outcome, but recent work has demonstrated that both worst and average pain measures perform similarly, leaving the choice to be based on the likely effect of the treatment.<sup>60,61</sup> Worst, least, and average pain, as well as pain interference questions, are part of the Brief Pain Inventory,<sup>62</sup> which is one of the most widely used pain outcome scales. Measurement frequency is widely discussed, but many pain studies now collect the pain measure once daily (often at bedtime to be consistent across time and easier to remember) and average at least 4 to 5/7 days to achieve a stable weekly average.<sup>63,64</sup>

The growth in our understanding of the complexity of the brain processes involved in the perception of pain has provided important information relevant to the design of pain-focused clinical trials. Nociceptive input is only 1 component leading to a patient's report of pain. It is important to measure other aspects of a patient's condition to understand the effect of the treatment being studied. The primary categories of such characteristics have been published from the consensus meetings of experts at IMMPACT. These include (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events, and (6) participant disposition.<sup>65</sup> An initial set of measures was defined in 2005,<sup>66</sup> but variations and updates<sup>3</sup> have been explored for specific diseases.

A basis for all clinical trials is the assumption that subjects will remain relatively stable in all other factors related to their medical condition during the period of the study, such that we may reasonably conclude that any changes observed during the study period are attributable to the treatment being studied. This is no less true for studies of pain and has important implications for the design of such studies. First, many patients enrolled in pain

studies are also on other treatments that may influence their perception of pain, such as antidepressants, antianxiety, and nonpharmacologic or local therapies. In general, as long as they remain on stable doses over the period of the study, these should not directly affect the outcome attributable to the study treatment. Because it can be difficult to ask subjects to stop such medications, they often maintain their current levels rather than discontinue. Second, although it is difficult to interpret whether a 0- to 10-point NRS pain score reported by 1 patient is better or worse than a similar pain score reported by another patient, if both patients report improved scores with treatment, we can conclude that their pain improved. The 0- to 10-point NRS has significant benefits over verbal descriptor or diagrammatic scales in its ease of use across many different platforms (verbal, device, telephone, etc) and ease of translation into almost any language. In addition to pain, it is important to include measures of other outcomes that can reasonably be assumed to be affected by the treatment as secondary outcomes, which will support findings in the primary pain outcome.<sup>67</sup>

As with all symptomatic treatments, the brain-mediated mind-body connection is an important consideration coupled to patient expectation and the placebo response. This has included methods to reduce the placebo group response on trial outcome. However, it is important that a substantial amount of the response noted in the placebo-treated group is due to the natural history of disease and regression to the mean, which applies to all subjects in the study. Some of the response is related to the mind-body neurotransmitter-mediated process of the descending inhibition of pain. Various run-in period processes have been tried, but exclusion of "placebo responders" is generally discouraged because a majority of these subjects are not true placebo responders,<sup>68</sup> and evidence from depression studies indicates it can be counterproductive.<sup>69</sup> Factors that may improve clinical trial assay sensitivity have been suggested,<sup>70–72</sup> but to date, only 1 feature has been demonstrated to help—excluding patients with extremely variable pain pattern during the baseline phase.<sup>73</sup> Other features that are thought to improve the conduct of clinical trials include (1) careful phenotyping of patients enrolled<sup>74</sup>; (2) comprehensive assessment of patient characteristics to allow evaluation of subgroups; (3) limited publication and communication of complete study inclusion/exclusion criteria to avoid manipulation; (4) standardization of the consent process and study personnel behavior to limit patient expectation; (5) central decision making about inclusion of patients and randomization; (6) run-in periods to test patient commitment to full participation; (7) measurement strategies to minimize missing data by convenient collection of daily pain data; and (8) training of patients in the use of measurement scales.<sup>75</sup>

Finally, clinical trials need to be analyzed and presented in a format that will be clinically relevant. The analysis must plan for missing data including the use of mixed regression models and sensitivity analyses with different assumptions about missing data.<sup>76</sup> Presentation of data can include means and standard deviation but must also include responder analyses either using appropriate cutoff points within patients to identify responders<sup>60,77,78</sup> or by the presentation of data using cumulative distribution curves to display data at all possible levels of response.<sup>79</sup>

## CONSIDERATIONS FOR NATURAL HISTORY-CENTERED OUTCOME TRIALS

The time to disease progression in CP is variable and dependent on the age at presentation, presence of environmental risk factors, genetic mutations, integrity of the main pancreatic duct, and individual variability. While a large fraction of patients develops 1 or more clinical symptoms (eg, AP attack(s), new-onset

diabetes), individual events during short or intermediate time frame are infrequent and may have competing influences on disease course. Finally, as discussed previously, there are no well-accepted criteria to evaluate disease progression based on either clinical symptoms or imaging studies.

The goal of interventions to favorably alter the natural course of CP is to reduce development of functional derangements and morphologic destruction of the pancreas as well as the prevention and treatment of clinical symptoms. To effectively test promising treatments that may positively impact the course of CP, the duration of treatment and outcomes of interest need to be carefully chosen. Trials that evaluate clinical symptoms of CP can be conducted in a short (eg, pain, QOL) or intermediate (eg, frequency and severity of AP, hospitalizations, QOL) time frame. The duration of observation could be a few weeks to 6 to 12 months for short-term and 12 to 24 months for intermediate-term trials. Trials that evaluate for objective end points of disease progression, such as morphological disease progression, endocrine or exocrine insufficiency, pancreatitis-related death, and the development of pancreatic cancer, will need intermediate- to long-term observation period (3–5 or more years). As a result, these trials will be lengthy and costly.

To accelerate translational research, there is an urgent need to develop study designs or analytical methods that enable more rapid conduct of these trials. One approach is to use alternative end points that may change earlier than the recognizable progression events. End points consisting of longitudinal data of morphology, biomarkers, AP/recurrent AP, new-onset diabetes, and so on, can be used either individually or as a composite. However, it is not easy to define an objective composite end point that can be widely accepted. The CP Prognostic Score represents an attempt for such an approach.<sup>58</sup> Another approach is to validate short-term change in longitudinal data as a “surrogate” end point for long-term progression.<sup>80</sup> There are specific criteria for validating a surrogate end point: the surrogate end point and the long-term end point must have strong association; that association must be reproducible in the contexts of multiple studies, populations, and interventions; the variation of the association in various populations should be well understood.<sup>80,81</sup> In the case of translational research of CP, there are additional analytical challenges.

It is necessary to obtain large-enough longitudinal cohort data to study the validity of surrogate end points. The longitudinal adult CP cohort study of the Consortium for the Study of Pancreatitis, Diabetes, and Pancreatic Cancer will be an important data source, but other cohorts are also needed. Because CP is a multifaceted and heterogeneous disease, the short-term outcomes are both multivariate and longitudinal, with mixed data types (ie, continuous, categorical, recurrent episodes). Validating the short-term outcomes as surrogates for long-term outcomes requires joint modeling of multivariate longitudinal data with mixed data types and multivariate time-to-event data. Both statistical methods and software for this kind of analysis are being developed in other disease areas but have not been applied to CP. The longitudinal trajectory of these short-term outcomes may not be equal or proportional as CP progresses. For example, as CP progresses toward advanced stages, the inflammation in pancreatic tissue may increase initially and then decrease as fibrosis increases. This phenomenon causes difficulty in both composite end point definition and statistical modeling of surrogate end points. Proper metrics and methods are needed to evaluate the strength of association between short- and long-term outcomes, which constitutes part of the evidence of surrogate end point validation. Because both the short- and long-term outcomes are multivariate and longitudinal, it is necessary to define clinically interpretable features from the longitudinal data, with optimized prediction accuracy to the

long-term outcomes. Most surrogate end point methods were developed for evaluating a single end point, but multivariate surrogate end point should be considered for CP research due to the heterogeneity of the disease.

Successful establishment of a short- to intermediate-term outcome as a trial's end point, or validation of short- to intermediate-term outcomes as surrogate end points for the long-term outcome, will bring enormous benefits to the clinical research of CP: shorter-duration trials, faster pace of translational research, increased statistical power, reduced sample size and costs, and better understanding of the association among multiple progression indicators and multiple types of clinical events.

In conclusion, current treatment options for CP are generally limited to symptomatic management of disease manifestations, which have not yet been carefully defined or measured. This document frames the essential aspects of trial design, including the importance of understanding and including patient-centered outcomes, proposed methods to measure these outcomes, and study design considerations to facilitate future studies for treatment of pain and disease progression that produce drugs that most rapidly reach patients.

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