

Clinical Trials in Pancreatitis: Opportunities and Challenges in the Design and Conduct of Patient-Focused Clinical Trials in Recurrent Acute and Chronic Pancreatitis

Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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Abstract: Recurrent acute pancreatitis and chronic pancreatitis represent high morbidity diseases, which are frequently associated with chronic abdominal pain, pancreatic insufficiencies, and reduced quality of life. Currently, there are no therapies to reverse or delay disease progression, and clinical trials are needed to investigate potential interventions that would address this important gap. This conference report provides details regarding information shared during a National Institute of Diabetes and Digestive and Kidney Diseases-sponsored workshop on Clinical Trials in Pan-

creatitis that sought to clearly delineate the current gaps and opportunities related to the design and conduct of patient-focused trials in recurrent acute pancreatitis and chronic pancreatitis. Key stakeholders including representatives from patient advocacy organizations, physician investigators (including clinical trialists), the US Food and Drug Administration, and the National Institutes of Health convened to discuss challenges and opportunities with particular emphasis on lessons learned from trials in participants with other painful conditions, as well as the value of incorporating the patient perspective throughout all stages of trials.

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Key Words: chronic pancreatitis, pain, recurrent acute pancreatitis, study design

Abbreviations: AP - acute pancreatitis, CP - chronic pancreatitis, RAP - recurrent acute pancreatitis, RCT - randomized controlled trial

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Pancreatitis is commonly categorized by disease onset, recurrence, and duration into acute pancreatitis (AP), recurrent AP (RAP), and chronic pancreatitis (CP). There are currently no US Food and Drug Administration (FDA)-approved therapies for the treatment of AP, RAP, or CP. Recognizing this unmet clinical need, the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH) sponsored a workshop on July 20, 2022, entitled, “Clinical Trials in Pancreatitis: Opportunities and Challenges in the Design and Conduct of Patient-Focused Clinical Trials in Recurrent Acute and Chronic Pancreatitis.” This builds on previous work from a related workshop in 2018 (“Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis: Knowledge Gaps and Research Opportunities”).^{1,2}

Recurrent AP and CP were selected as the focus of the current workshop because of the significant overlap in both clinical manifestations of disease and potential therapeutic targets between the conditions. The goals of the workshop were to convene key stakeholders including representatives from patient advocacy organizations, physician investigators (including clinical trialists), the FDA, and the NIH to promote collaboration and identify knowledge gaps and challenges to the design and conduct of clinical trials of RAP and CP and opportunities to advance the development of safe and effective therapies for patients.

PATIENT PERSPECTIVES ON CLINICAL TRIALS IN PANCREATITIS

Patients should be involved in the design, conduct, and dissemination of research that affects them. To that end, the National Pancreas Foundation (NPF) hosted an externally led Patient Focused Drug Development (PFDD) meeting in March 2020. Other supporting advocacy groups included Mission: Cure, the Rebecca's Wish Foundation, and the Familial Chylomicronemia Syndrome Foundation. Patient-Focused Drug Development is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. The PFDD meetings give key stakeholders, including medical product developers, health care providers, FDA, and other federal partners, an important opportunity to hear directly from patients, their families, caregivers, and patient advocates about the symptoms that matter most to them, the impact the disease has on patients' daily lives, and patients' experiences with current treatments.

Following the meeting, a Voice of the Patient meeting summary report was generated that captured the testimony shared by adult and pediatric patients and their caregivers during the meeting as well as the results of a survey about their experiences living with pancreatitis.³ Of the approximately 119 respondents, more than 75% reported experiencing pain, 41% experienced difficulties with nutrition and food issues, and 40% experienced nausea and fatigue.³ Quality-of-life issues included interference with social life and family, interference with work, and inability to engage in physical activities. These results corroborated a 2018 Mission: Cure survey of 145 individuals with CP in whom more than 90% reported pain as their principal symptom, with nausea and difficulty eating reported in more than 60% and chronic fatigue in more than 30%.⁴ When asked what patients want most, the PFDD survey revealed that better pain control was the highest priority,

followed by more empathy from and education for medical professionals, improved quality of life, and lower costs of medications.

Recruitment and Retention

Many barriers can deter patients from participating in clinical trials, and systematic efforts are needed to optimize the participant's experience and reduce the burden of participation. Challenges in recruitment and retention can be categorized into common themes, including knowledge, provider-patient relationship, protocol design, and trial intervention.⁵ One knowledge barrier is that some individuals in the United States may harbor a cultural resistance to participation with a preference for standard-of-care approaches. Another knowledge barrier is a lack of provider and patient familiarity with applicable and ongoing research studies. In some cases, providers need to be educated on the study hypothesis itself, as many assumptions regarding the diagnosis and treatment of pancreatitis have been entrenched for decades despite limited evidence supporting this dogma (eg, the use of endoscopic sphincterotomy for pancreas divisum).⁶ A strong provider-patient relationship promotes engagement, but there is frequently a misalignment of incentives whereby health care providers are disincentivized by time and/or funding to introduce and enroll patients into clinical trials.⁷

Study protocols must balance the investigators' interests with feasibility of execution. Recruitment can be facilitated by use of digital media and the electronic medical record to confirm eligibility and even obtain informed consent; retention can be optimized by an appropriate balance of “check-ins” with minimal in-person visits throughout the trial. Other strategies to address patient engagement include appropriate monetary incentives for study participation, recruitment and engagement via social media, and collaboration with advocacy groups. Outcome selection is a key aspect of protocol optimization that is expanded further below. The study procedures, interventions, and potential benefits and risks of participation should be communicated clearly and in a balanced manner to ensure that patients are able to make an informed decision regarding whether to participate. Lastly, early patient education on the importance of and opportunities associated with participation in a clinical trial is critical to overcome some of these barriers.

DESIGN ELEMENTS FOR TRIALS IN PANCREATITIS

Defining Appropriate Patient Populations for Inclusion in Clinical Trials in Pancreatitis

Patient selection for clinical trials in RAP and CP follows the general principles of trial design, but there are additional unique considerations related to the heterogeneity in patient population and variable disease course. Selecting a clearly defined study population that is sufficiently symptomatic and likely to benefit from the drug or intervention may increase the likelihood of detecting a treatment effect and minimize the risk of false-negative results. Carefully considered and well-defined eligibility criteria can also minimize confounding through the reduction of undesired heterogeneity; there are many recent examples of this in RAP and CP.^{6,8–10} However, as eligibility criteria are narrowed, the burden of screening, proportion of screen failures, and risk for reducing the generalizability of study results are increased. Precise estimates are needed to better understand the variability in disease course, including variability in pain, and frequency and timeline of longer-term complications (eg, diabetes, exocrine pancreatic insufficiency, and recurrence of AP). Current data are limited, and clinical consensus recommendations have not been established to inform patient selection for clinical trials in pancreatitis, so this

is a high priority to permit efficient planning and successful execution of trials.

Outcome Measures in Recurrent Acute and Chronic Pancreatitis

Understanding a patient's comprehensive experience with treatments for RAP and CP requires a holistic approach toward selection and utilization of appropriate outcome measures. Outcomes should reflect areas of importance and relevance to different key stakeholders, including patients, researchers, clinicians, regulators, and study sponsors to understand whether an intervention is effective.

Optimal outcome assessment includes measurement across multiple domains, which may include clinical, humanistic, economic, and utilization measures.¹¹ Clinical outcomes describe or reflect how an individual feels, functions, or survives. Assessment of these outcomes can be made through report by a patient or a nonclinician observer or through performance-based assessments.^{12,13} Patient-reported outcomes (PROs) are a specific type of clinical outcome assessment (COA) that directly measure how patients feel or function through the assessment of clinical signs/symptoms directly from the patient about the status of their health condition without interpretation by a clinician or anyone else.^{10,14} Recent examples of CP-specific PROs to assess pain and quality of life have been developed for use in clinical practice¹⁵⁻¹⁷ but have not yet been systematically used in clinical trials. Despite recent progress in developing disease-specific outcome measures, there are still significant knowledge gaps, including assessment of other symptoms from patients, including nausea and lack of appetite, fatigue, and weight loss.³ There is almost a complete absence of the use of economic outcomes or health care resource utilization trials in RAP or CP.

There is a key opportunity to develop a “core outcome set,” an agreed minimum set of constructs or domains (ie, outcomes) that should be measured and reported in all clinical trials of a specific disease or trial population,¹⁸ for RAP and CP.¹⁹ Several notable efforts have been made in developing core outcome sets in pain (eg, IMPPACT, Ped-IMPPACT) that provide a useful foundation.^{20,21} Standardization of outcome domains and measurement tools for clinical trials of treatments for RAP and CP would enhance the quality of the evidence for treatments, strengthen systematic reviews of CP interventions, and help clinicians make evidence-based treatment decisions for this patient population.

Regulatory Aspects of Drug Development in Recurrent Acute and Chronic Pancreatitis

There are important regulatory considerations for drug development in RAP and CP.² In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled trials. Adequate and well-controlled trials include a clear statement of objectives, appropriate control for comparison, selection of patients with the disease or who are at risk of developing the disease, methods to minimize bias, well-defined and reliable methods for assessment of response, and adequate methods of analysis.

A goal of drug development is to demonstrate the clinical benefit of the therapy on a meaningful aspect(s) of how a patient feels, functions, or survives as a result of treatment.^{10,13,14,22} Well-defined end points and outcome assessments specific to pancreatitis have not been established to assess disease activity or progression. Other outcomes, such as irreversible morbidity or mor-

tality, may not be feasible to assess because of the extensive time and resources needed to adequately conduct and power investigations.

Clinical trials for gastrointestinal disorders frequently utilize end points based on COAs. Of the various COAs, PRO assessments have been most commonly used to support drug approvals. Sponsors may obtain advice on the development and implementation of COAs through medical product development within an individual development program; through the Center for Drug Evaluation and Research's COA Qualification Program, which is considered a precompetitive space that potentially results in a qualification statement from the FDA for use of the COA in a particular context of use; or through critical path innovation meetings or other such nonbinding informal meetings with relevant FDA experts. In addition, several resources to promote the development of PRO assessments have been developed by the FDA and are publicly available. For example, the roadmap to patient-focused outcome measurement in clinical trials is shown in Figure 1.²³ Regardless of the pathway utilized, it is essential to ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into these assessments.

CLINICAL TRIAL DESIGN

Key Considerations and Insights From Pain Trials

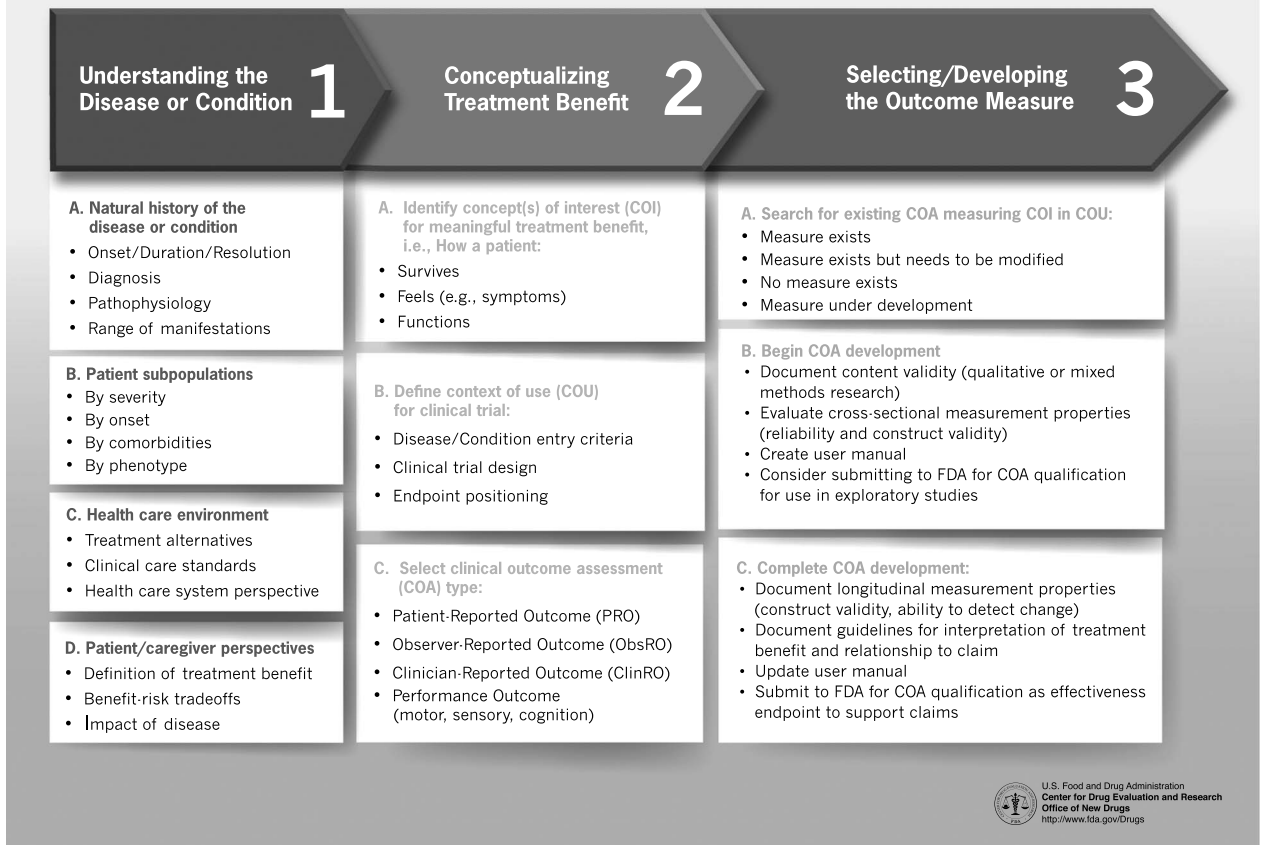
Beneficial insights into clinical trial design for RAP and CP may be gained by reviewing challenges that have been identified related to the design, execution, analysis, and interpretation of clinical trials that assess pain-related outcomes in other diseases. These challenges include (1) failure to translate results from pre-clinical models to human pain conditions; (2) the magnitudes of treatment effects reported in analgesic trials seem to have decreased over the past few decades; (3) sample sizes have often been too small to detect modest but clinically meaningful treatment effects; (4) existing pain COAs have limitations; (5) the optimal pain phenotypes may not have been studied; and (6) changes have occurred in the approaches used for conducting clinical trials and in the patients enrolled, and there may have been increases in participant misbehavior (eg, misrepresenting symptoms) and investigator misconduct. One particular threat to identifying a true benefit relates to the generally high placebo responses seen in most pain trials.

To address challenges in the design, conduct, and analysis of pain clinical trials, various factors should be considered.²⁴⁻³⁰ These include increased attention to (1) patient selection and training; (2) adequate blinding of participants, investigators, and outcome assessors; (3) mitigation of treatment nonadherence; (4) prespecification of outcomes, analyses, and accommodation of intercurrent events and missing data; (5) reducing placebo group responses by minimizing placebo effects and participant expectations to the greatest extent possible; (6) distinguishing clinically meaningful within-participant improvements from clinically meaningful group differences in clinical trials; (7) engaging patient partners throughout all stages of developing pain treatments; and (8) analyzing heterogeneity of treatment effects, a crucial basis for the development of precision pain treatments. An evidence-based approach to the design of clinical trials, especially when involving pain treatments, has the potential to increase assay sensitivity (ie, the ability to detect a true benefit when present) and informativeness, thereby accelerating the availability of novel treatments for patients with painful RAP or CP.²⁸

Proof-of-Concept and Feasibility Studies

Considering the substantial efforts needed to conduct large, definitive trials in pancreatitis, proof-of-concept studies (also

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials



U.S. Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of New Drugs
<http://www.fda.gov/Drugs>

FIGURE 1. Summary of the US FDA's roadmap to patient-focused outcome measurement in clinical trials²³

called pilot studies) may be particularly useful to (1) demonstrate feasibility in recruiting patients from the target population, (2) demonstrate feasibility and guide future methodology of trials to evaluate a certain treatment strategy (eg, pharmacogenomics), and/or (3) identify early evidence of efficacy of a new intervention. Proof-of-concept studies involve efficient research strategies such as small sample sizes and brief duration of follow-up but must be carefully designed to have high predictive value and to determine whether larger, more intricate clinical trials are warranted. To this end, proof-of-concept trials should be designed to maximize assay sensitivity. Trial features that seem to be associated with high assay sensitivity include trial conduct in sites with extensive research experience, small numbers of research sites, and training trial participants regarding outcome ratings. For the sake of simplicity and efficiency, it is ideal for the proof-of-concept study to consist of the new intervention versus placebo; however, a third arm with active control, or in select situations replacement of a placebo with a standard-of-care arm, can also be considered. Inclusion of an active control arm may serve to confirm the trial's assay sensitivity, which is important in situations where the investigational treatment fails to separate from placebo.

Proof-of-concept trials may require unique considerations for (a) study population, (b) intervention characteristics, (c) comparator control interventions, and (d) trial outcome. Feasibility, or pilot, clinical trials are proof-of-concept trials that may be designed

to emulate a larger planned confirmatory trial. In pilot trials, assessments of trial elements such as (1) recruitment, (2) compliance with the trial protocol by participants and research personnel, and (3) completeness of trial outcome data capture can inform the design and feasibility of subsequent trials. A thorough understanding of the potential, and limitations, of proof-of-concept trials as informed by past experiences in different therapeutic areas may serve to guide improved progress in clinical research and development.

Randomized Controlled Trials

Randomized controlled clinical trials are needed to identify effective and safe treatments in RAP and CP. In addition, they will provide the foundation for the development of evidence-based treatment recommendations, which have the potential to inform and improve clinical practice. Regardless of the disease or clinical trial intervention, the validity and impact of all randomized controlled trials (RCTs) depend on (1) selecting an important and timely clinical question, (2) designing a study that maximizes validity by minimizing bias, and (3) executing the study using an infrastructure that promotes efficient and rigorous conduct with protection against the inherent threats to an RCT. The first element is achieved by testing hypotheses with strong preliminary data, including from pilot clinical or preclinical studies, and that would have a significant impact on clinical practice. Minimizing bias in a clinical trial involves several considerations including

eligibility, end points, sample size estimation, randomization, and blinding. The latter is particularly relevant for trials that assess invasive treatments, wherein masking (blinding) is more important, but more difficult to establish.

End points (outcomes) in an RCT are linked to blinding because more subjective end points (eg, abdominal pain) require more extensive efforts to maintain masking. Masking aims to minimize bias at 3 levels, namely, the patient, the treating clinician(s), and the outcome assessor(s). At the patient level, knowledge of study group assignment may influence a participant's interpretation of symptoms, their threshold to seek medical attention, and their disposition when responding to study questionnaires. For treating clinicians, unmasking may lead to differential care of participants, resulting in unequal cointerventions between study groups. Lastly, outcome assessors who are aware of study group assignment may interpret clinical and laboratory findings differentially. Because investigators are generally incentivized by "positive" study results, unblinded adjudicators may unconsciously interpret information in favor of the intervention.

Innovative and Complex Trial Designs

Alternative designs to the standard, 2-arm, placebo-controlled RCT are gaining popularity in other areas of biomedicine and could also be considered for trials in RAP and CP. These designs can address some of the challenges in traditional RCTs such as lack of representativeness to population, small sample bias, and incorrect statistical inferences. Alternative trial designs including pragmatic, cluster randomized, adaptive, and hybrid effectiveness-

implementation designs can be used to generate knowledge in an efficient manner (Table 1). These trial designs can help address gaps in translation to practice. For example, pragmatic clinical trials are appropriate designs for answering questions about whether a treatment works in the real world (under routine conditions) and thus help to address the gap between highly controlled trials and clinical practice. Common elements of pragmatic trials include less restrictive inclusion/exclusion criteria, enrollment and intervention in real-world care settings or the home, and use of real-world data (eg, electronic health record). Technology can be used in important ways to increase reach and equity in trial participation and to conduct remote assessment and intervention.

Importantly, the translational pipeline should not be viewed as a linear series of stages, because it is often necessary and acceptable to return to previous stages or pursue multiple stages concurrently. An example of this would include a hybrid effectiveness-implementation trial that studies implementation while also collecting additional effectiveness data. The combination of these data can address how clinical outcomes relate to levels of adoption of an intervention in practice and be used to guide the selection and refinement of the intervention.

ADDITIONAL CONSIDERATIONS

Design and Conduct of Clinical Trials in Children and Adolescents

Pancreatitis affects patients across the life span, and there is an expanding literature base related to the epidemiology of

TABLE 1. Innovative Clinical Trial Designs and Their Potential Uses in Trials in Pancreatitis

Trial Design	General Features and Characteristics	Advantages/Uses
Pragmatic clinical trials	<ul style="list-style-type: none"> • Less restrictive eligibility criteria • Enrollment and intervention in real-world care settings or home • Use of real-world data (eg, electronic health record) • Flexibility in treatment delivery 	<ul style="list-style-type: none"> • Helpful to understand if a treatment works under routine conditions • Lower risk of failure to transfer study findings into patient care
Cluster-randomized design	<ul style="list-style-type: none"> • Randomization occurs at the group (eg, clinic) rather than individual level 	<ul style="list-style-type: none"> • Useful when individual participant randomization is either inconvenient or not feasible (eg, testing a new process of care) • Useful for studying bundled interventions
Stepped wedge cluster randomized trial	<ul style="list-style-type: none"> • Clusters randomly cross-over from control to intervention • All cluster groups eventually receive intervention 	<ul style="list-style-type: none"> • May be more appealing to sites as they will all receive intervention • Allows for longer-term longitudinal observations of intervention • Advantage when logistical concerns mean that implementation needs to be staggered
Adaptive trials (eg, SMART [Sequential Multiple Assignment Randomized Trial])	<ul style="list-style-type: none"> • Interventions and/or randomization structure altered based on early response according to predetermined rules • Decision points are defined about when to offer different interventions (eg, if a participant does not respond positively to the initial treatment) • Specify the factors that indicate a change in treatment is needed (ie, the tailoring variables) (eg, response on primary outcome or is experiencing unwanted adverse effects) 	<ul style="list-style-type: none"> • Useful to answer complex questions related to sequence of interventions that mimics clinical decision-making • More efficient design to test multiple interventions with a smaller sample size • Can identify benefits/harm to smaller subgroups
Hybrid effectiveness-implementation design	<ul style="list-style-type: none"> • Designed to identify barriers and facilitators to implementation of an intervention in real-world settings • Can use qualitative and quantitative measurements from administrative and participant report data • Collects additional effectiveness data in population of interest 	<ul style="list-style-type: none"> • An efficient model to simultaneously assess implementation and effectiveness • Advances the pace at which the intervention may be successfully disseminated

pediatric-onset AP, recurrent AP, and CP. Genetic abnormalities are found in approximately half of all pediatric patients with RAP and CP, and almost one-quarter of individuals in these groups experience chronic pain.³¹ There is an increasing recognition from stakeholders (including the NIH) of the need to study this disease in children and adolescents to close longstanding knowledge gaps. Diagnosed pediatric RAP and CP are not as prevalent as in adults, and there are far fewer treatment centers, so rigorous multisite studies are needed to advance the field.

Children and adolescents are considered a vulnerable study population, and therefore, special protections are required for inclusion in clinical trials. Protections for children in research extend beyond the general obligations and protections for ethical research in adults.³² A unique aspect of clinical trials in children is that participation requires permission from the patient's parent or legal guardian, and there may be unique motivations that influence family decisions to agree or decline participation.³³ Inclusion of children in research requires partnering with investigators with expertise in pediatrics in addition to appropriate community and/or advocacy representatives.

Scientific Public-Private Partnerships and Consortia

Patient advocacy organizations play an important role in the development, conduct, and dissemination of clinical trials through their engagement with patients, regulators, scientists, and industry. Two of these organizations are highlighted below.

The NPF has a mission to provide hope for those suffering from pancreatitis and pancreatic cancer through funding cutting-edge research, advocating for new and better therapies, and providing support and education for patients, caregivers, and health care professionals. The NPF has been committed to supporting high-quality research in RAP and CP through many activities such as convening stakeholders, ensuring patient input to clinical trial design, facilitating inclusion of participants across all demographics (eg, Black/African American initiative), informing regulatory agencies, providing research funding, attracting new investigators to the field, and facilitating best practices and novel treatment approaches.

Mission: Cure is a nonprofit organization dedicated to improving the lives of people suffering from RAP and CP by partnering to develop effective therapies in under 10 years. Some of their activities include recruiting impact investors and helping them find projects and companies that promise to significantly impact patient outcomes and are commercially viable, pitching life sciences and biotechnology companies to invest in pancreatitis (citing the significant unmet need and the commercial opportunity), surveying patients to identify priority outcomes and identifying validated instruments, and creating a resource to help drug developers select appropriate preclinical models. Recently, Mission: Cure received funding from the Chan-Zuckerberg Initiative Science program to mobilize stakeholders to develop therapies for RAP and CP.

Ethics in Clinical Trials

The ethical principles described in the Belmont Report provide governance to ethics in clinical trials.³⁴ Specifically, there should be aspirations to simultaneously pursue the respect for persons, beneficence, and justice. Participant selection should be fair, and participation voluntary. Historically, emphasis has been given to avoid financial compensation that may be perceived as unduly influencing decisions to participate in a clinical trial. Recent thinking suggests this protectionism is unnecessary and that compensation is consistent with beneficence and justice (ie, ensuring that

research participation is available not only to those who can afford the time and incidental expenses).³⁵

One recruitment consideration relevant to RAP and CP is the inclusion of participants with substance use disorders. Trials in participants who have a history of substance use disorders may not raise immediate ethical concerns, although depending on the type of intervention/treatment being studied and the abuse potential, this history may impact eligibility. In contrast, patients with active substance use are often categorically excluded. This may primarily be identified as an issue of beneficence and minimizing potential harms, but it can also raise questions of justice in excluding individuals who may benefit from research both directly and indirectly.³⁵ Lastly, if genetic testing is included as part of the trial, participants should be properly informed about how the results will be shared, preferably by either a trained clinician or genetic counselor.

Opportunities for Investigators for Conducting Clinical Trials in Pancreatitis: Preclinical and Observational Studies

Preclinical studies in animal models and observational clinical research provide important data to guide the development of therapeutics for RAP and CP and identify elements central to the design of clinical trials. There are ongoing efforts to improve and utilize preclinical models of the pancreatitis spectrum to recapitulate the human disease and its varied clinical manifestations.³⁶ This work is helpful to prioritize promising interventions.

Ongoing observational studies, such as PROCEED and INSPPIRE, provide opportunities to inform clinical trial design, including feasibility of recruitment, precise estimates of event rates, and baseline variability in outcomes of interest.^{37,38} Furthermore, data collected in these studies may be used for the development of biomarkers or prediction models to identify high-risk groups of individuals who may be more likely to benefit from a specific intervention.

One challenge facing the design and conduct of clinical trials of CP is that important disease progression outcomes (eg, development of fibrosis, exocrine pancreatic insufficiency, diabetes mellitus, and pancreatic ductal adenocarcinoma) develop slowly over years and are not feasible to assess in short-term studies. Biomarkers that respond more rapidly may be beneficial for inclusion in proof-of-concept studies; however, current biomarkers have not been adequately characterized or demonstrated to be predictive of clinical outcomes. Furthermore, the data needed to inform the use of a biomarker may depend on the intended context of use (eg, diagnostic, predictive, disease monitoring, response to treatment). Establishing consensus recommendations for standard assessments, including biomarkers, in both early- and late-phase trials, may promote the identification of promising evaluations. Consortia dedicated to clinical and translational research in RAP and CP have been developed worldwide, and it is hopeful that progress will be accelerated over the next decade.³⁷⁻⁴¹

CONCLUSIONS

In summary, although there are many challenges facing clinical trials for RAP and CP in adults and children, several opportunities for the advancement the field were identified during the workshop (Table 2). These include additional collaborative efforts to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into clinical trial and drug development and evaluation; identification of appropriate eligibility criteria to inform trial populations; considerations of trial and overall program design elements to increase the likelihood that interpretable data will be generated; leveraging

TABLE 2. Selected Knowledge Gaps and Opportunities to Advance the Field of Clinical Trials in RAP and CP

Patient Perspectives on Clinical Trials in Pancreatitis

- Generate additional qualitative and quantitative data to clarify motivations and barriers to participating in clinical trials in both adult and pediatric patients
- Obtain additional input regarding tolerable risk profiles for varying levels of improvement in pain and other symptoms
- Understand patient perspectives on nutritional problems and benefits sought from treatments
- Understand best practices for working with patient advocacy groups to disseminate information regarding clinical trials, including availability of open trials and study findings

Clinical Trial Design

- Develop standardized study definitions of RAP and CP, including symptoms and clinical events
- Clearly define participant populations of interest, taking into consideration feasibility, homogeneity of the population, and generalizability of results
- Develop core outcome sets for clinical trials in RAP and CP for adult and pediatric patients
- Identify and implement methods to reduce participation burden (eg, use of technology to identify participants, obtain consent, and collect patient-reported outcomes)
- Consider opportunities for implementation of proof-of-concept studies
- Use alternative and innovative trial designs for more efficient studies across the translational pipeline
- Encourage clinical trials in pediatrics and consider novel design approaches to address small samples
- Innovate on the process of funding, regulating, and administering clinical trials to
 - Minimize the administrative burden on clinical centers
 - Optimize direct-to-patient engagement with support of advocacy groups
 - Multiyear competitive enrollment contracts to incentivize sites to meet or exceed their enrollment targets

Additional Considerations

- Develop and/or optimize preclinical models to identify potential therapeutic targets and prioritize therapeutic interventions in RAP and CP
- Promote standardized assessment and collection of biosamples for correlative biomarker and translational analyses
- Pursue collaborations with investors (including federal, pharmaceutical, and/or life sciences investors) to accelerate the preclinical and clinical trial pipeline
- Realign incentives to advance promising repurposed therapies

strategies and gaining insight from clinical trials that have assessed pain-related outcomes; and identification of available resources to support the development of assessments of clinical benefit for use in clinical trials. Progress in this field will require sustained efforts from all stakeholders, including patients, patient advocates, researchers, clinicians, regulatory agencies, and industry. The organizational and statistical infrastructure of recently launched consortia can facilitate efforts to address the existing knowledge gaps and promote the design and conduct of clinical trials that are able to identify safe and efficacious therapies for our patients and resolve the unmet medical needs they face.

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