

Guidance, Action, Projection (GAP) Meeting

February 2022

Executive Summary

On February 9, 2022, the Clinical Trials team convened the Guidance, Action, Projection (GAP) Meeting to identify Areas of Encouragement for 2023 and discuss funding mechanisms needed to promote the clinical research most likely to advance the Cystic Fibrosis Foundation (CFF) Mission. The agenda and invite list for the GAP Meeting were created by a meeting planning committee that included Drs. Ron Rubenstein, Andrea Kelly, Raksha Jain, and Michael Narkewicz, three cystic fibrosis (CF) community members: James Lawlor, Sylva Mazuera, and Shelby Luebbert, as well as six CFF staff members. The meeting attendees included 13 community members, 27 CF clinicians and researchers, 3 NIH Program Officers, and 19 CFF staff members representing the Cure, Care, and Community departments. The first half of the meeting was dedicated to breakout group discussions based on CF manifestations. Breakout group topics included airway, behavioral and neurocognitive, endocrine, gastrointestinal, and infection. The groups' goal was to identify the top Areas of Encouragement to be included the 2023 Clinical Research Programs' Request for Applications (RFAs) to drive research in those areas. The second half of the meeting was dedicated to discussion on recommended changes to the Clinical Research Award (CRA) and the Clinical Pilot and Feasibility Award (CP&FA), new RFAs to address specific topics, and other enhancements to the clinical research program to attract and obtain high-quality research that spans across the numerous complications associated with cystic fibrosis.

Areas of Encouragement

Areas of Encouragement are research topics that are considered gaps in our knowledge in the detection and monitoring, diagnosis, or treatment of a CF complication. Applicants for the CRA and the CP&FA are highly encouraged to submit research proposals that address one or more Areas of Encouragement. Introduced in 2018, the current Areas of Encouragement used in RFAs between 2018-2022 were developed by a Community Voice led survey. Moving forward, the Areas of Encouragement will be updated on a biennial basis during future GAP Meetings and will be informed by GAP meeting attendees, community surveys, CFF Workshop recommendations, and other areas of focus identified by guidelines committees or CFF/TDN research working groups.

2023 Areas of Encouragement

CF-RELATED DIABETES (CFRD): Research related to the screening and treatment of CFRD, including discovery and validation of novel biomarkers, when to initiate treatment, novel treatments, and personalized treatment approaches.

SEXUAL & REPRODUCTIVE HEALTH: Research related to fertility, pregnancy, parenthood, gonadal hormones and contraception, urinary incontinence, and sexual/reproductive health of all genders.

BONE HEALTH: Research related to bone accrual in growing children, factors that impact changes in bone density in adults, biomarkers to monitor changes in bone structure and impacts of CF therapies and other therapies on bone health.

DIET AND NUTRITION: Research related to the impact of diet on bone accrual/maintenance, CFRD risk and disease prevention/progression, metabolic syndrome, and the interplay between nutrition and CF symptoms and other co-morbidities.

GUT HEALTH: Research related to the development of relevant endpoints to study gut motility (e.g., gastroparesis).

LIVER & PANCREAS: Research related to the screening and monitoring for pancreatic and liver disease/complications, approaches to detect and treat non-cirrhotic portal hypertension, and to evaluate advanced liver disease.

IMAGING: Research related to the development or validation of novel imaging modalities to screen and/or monitor for pancreatic, liver, and lung disease/complications or response to therapy.

CANCER: Research related to understanding GI tract cancers, including incidence and natural history of GI cancers in CF and the impacts of modulators, endocrine malfunction, and other CF complications on cancer incidence.

REMOTE MONITORING: Research related to the development and use of remote endpoint or remote monitoring across a broad domain of CF complications/symptoms, including microorganism detection, sleep, diet, exercise, cough monitors, lung function, and other wearables.

EARLY LUNG DISEASE PROGRESSION: Research related to monitoring early lung disease progression for patients on modulator therapy that could lead to a better understanding of early benefits of modulator therapy or to create a decision tool on when to initiate modulator therapy.

ADVANCED LUNG DISEASE: Research related to the monitoring of disease progression, the identification of reversible disease, and understanding risk incurred prior to transplant for poor outcomes in Chronic Lung Allograft Dysfunction (CLAD).

LUNG TRANSPLANT: Research related to understanding the usefulness, safety, and impact of modulator therapy post lung transplant, and the identification of therapies/treatment pathways that reduce CLAD post-transplant.

SINUS DISEASE: Research related to improving our understanding of CF sinus disease, including disease pathophysiology (of sinus disease and as surrogate for the lung), identification of best management practices, and impact of sinus disease management on health outcomes, including quality of life, lung disease outcomes, and transplant outcomes.

NEUROCOGNITIVE FUNCTIONING: Research related to advancing the general understanding of neurocognitive function in CF, including research to understand the impact of modulators on neurocognitive and mental health outcomes.

ANXIETY: Research related to the prevention/interventions for anxiety, including procedural distress/anxiety and medical trauma.

DEPRESSION: Research related to the prevention/intervention for depression, including resilience (self-care, wellness, etc.), suicide risk, and research related to improved understanding of the relationship between mental health and sustaining daily care (adherence).

SLEEP: Research related to the bi-directional impact of sleep disturbance/disorder on physical and mental health.

PAIN: Research related to the diagnosis and treatment approaches (psychological, pharmacological and wellness) to CF-related pain management

ANTIMICROBIAL MANGEMENT: Research related to the optimization of current antimicrobial therapies (e.g., improve understanding of drug-drug-interactions, treatment approaches, long-term impacts of therapies, antimicrobial stewardship, and eradication) in the current post-modulator population.

MICROORGANISM DETECTION: Research related to improving microorganism detection, including development of novel biomarkers, assays, and/or platforms and studies evaluating best approaches for detection (e.g., home collection of sputum, bronchoalveolar lavage fluid (BALF), etc.) and/or assessments of specimen quality and processing requirements needed for research.

MICROORGANISM RELEVANCE & SURVEILLANCE: Research related to microorganism relevance and surveillance, including improving our knowledge of which species are pathogenic, how surveillance samples/studies may help understand disease heterogeneity (relevance of dental disease, sinus disease, etc.), and potential shifts in pathogens (microbiome shifts vs. pathogenic organisms) in the post-modulator era.

INFLAMMATION: Research related to understanding the role and relevance of inflammation in lung disease presence, severity, and progression; innovative ways to detect and monitor inflammation that reflects lung disease severity and progression; role of biomarkers as outcome measures for future CF clinical trials targeting infection and/or inflammation.

Recommended Changes to Current RFAs & Clinical Research Program

During the second half of the meeting, the group discussed the current RFAs under the Clinical Research Programs to ensure they were appropriate to attract the research identified to be Areas of Encouragement. Several attendees noted that the cost of projects related to certain outcome measures, particularly imaging, would be higher than the budget level of the current pilot RFA. There were also several suggestions to increase the funding level to support larger pilot studies that may require multiple sites. This need for multi-site clinical studies continues to grow particularly to study complications of CF that may be less common and as highly effective modulator therapy (HEMT) continues to impact the trajectory of CF.

It was also noted that several Areas of Encouragement require the expertise of specialists that may be outside of the CF community or unfamiliar with the disease. To help attract new researchers, particularly those in fields that may have limited protected time to conduct research, it was suggested that the Clinical Research Award have a multiple-PI option similar to the NIH funding mechanism.

ACTIONS:

- We plan to increase the budget let of the Clinical Pilot and Feasibility Award to include \$80,000 for up to two years (+12% IDC) for single center projects and up to \$150,000 for up to two years for multi-center projects (+12% IDC). Studies involving more expensive outcome measures may request a budget waiver to submit proposals above the funding thresholds and will be evaluated on a case-by-case basis. These changes will go into effect in 2023.

- We plan to develop a method to support projects that have multiple-PIs on the application for a Clinical Research Award. We hope to have this new opportunity for 2023 proposals.

The GAP attendees also discussed ways to improve the quality of proposals, particularly proposals from young investigators or those who may be new to CF research. Many members noted that there are opportunities to leverage the Letter of Intent (LOI) phase to provide better feedback to the applicant and to suggest possible consultants or mentors to aid the applicant in future submissions. In addition to leveraging the LOI, the group recommended that we offer modest support for the development of a research study. Attendees also encouraged us to increase the visibility of CFF resources, including National Resource Centers and Community Voice, and to increase the transparency of our clinical research portfolio. It was noted several times during the meeting that the utilization of Community Voice or other patient and family groups be encouraged and should include meaningful engagement and input of the target population in the design, conduct and interpretation of the study findings. For example, early consultation with the target population about (1) clinical endpoints that are meaningful to them and (2) protocol burden and steps that could be taken to make research participation more feasible may improve the success of a study in recruiting subjects, particularly for minority and marginalized populations.

There was a brief discussion on the role of the Clinical Research Programs to receive Quality Improvement and Implementation Science research proposals. It was noted that those types of research fall outside of the scope of the Clinical Research Programs and should be re-directed to other CFF programs.

ACTIONS:

- We plan to revise the LOI portion of our RFA guidelines to better obtain details and justification on outcome measures and plans to include underrepresented minorities in relevant grant applications. This change will go into effect 2023 RFAs.
- We plan to revise the LOI reviewer critiques template to include a section for mentorship/consultation suggestions and guidance to evaluate DEI plans in grant submissions. We plan to work with the External Racial Justice Working Group to obtain pertinent resources to educate our reviewers on DEI in research. We hope to use this new reviewer template for the 2023 RFAs.
- We plan to work with our Communications team to develop ways to increase visibility of our current CFF resources, including NRCs and Community Voice. We plan to reach out to GAP attendees for feedback on implementation plans.
- We are currently conducting a needs assessment with the CF Community to understand what level of transparency is desired/needed. We plan to reach out to GAP attendees to discuss researcher needs.
- We plan to develop an Idea Development Award RFA for 2023. The intent of the Idea Development Award is to provide support for a one-year planning period for a multi-center study or a study investigating a CF complication that requires outside expertise/consultation.

Recommended Special Topic RFAs

During the meeting, there was robust discussion regarding the paucity of data related to health disparities across the broad range of cystic fibrosis complications, including infection and pathogen acquisition and liver disease. It was also noted that we should encourage community-based

participation throughout the study (e.g., patient partners, focus groups, etc.) and encourage thoughtful strategies for the inclusion of minority and marginalized populations, including BIPOC and those not eligible on modulators.

ACTION:

- Working with the External Racial Justice Working Group, we will develop a Health Disparities Special Topic RFA for 2023. The details regarding this RFA are still under development but expected to be announced during the summer 2022.

Recommended Workshop

During the meeting, there was discussion surrounding the need for a workshop dedicated to inflammation in CF. Meeting attendees recommended the effort should include a partnership with basic science researchers and clinical researchers to identify key questions that will improve our understanding of the relationship between infection and inflammation, autoimmune disorder co-morbidities, and other complications associated with systemic and localized inflammation. Recommendations generated from the workshop attendees will be used to inform the next steps for the CF Foundation to seek and obtain research that addresses those key questions.

ACTION:

- We plan to hold an Inflammation Workshop in the first half of 2023. Planning for this workshop will commence in September 2022. Planning will involve representation from both the basic and clinical research community as well as CF community members.

Other Recommendations for Attracting New Researchers/Mentorship/Consultation Recommendations

The last portion of the meeting was used to discuss other ways to attract new researchers to CF and to connect them with resources and/or consultants to aide with study design and grant writing. One suggestion was to create CF Research Ambassadors who are researchers that may attend non-CF specific conferences or meetings and can share their CFF Funding research. It was noted that CFF Guideline Committees often present their work at conferences. There was also a recommendation to develop a list of established CF investigators who are willing to serve as consultants to researchers who are new to CF. Many meeting attendees also noted the importance of consultation with a biostatistician during the development of a study as well as sufficient level of effort for the duration of the project. It was recommended that CFF develop a biostatistician core as a resource to CF researchers.

ACTIONS:

- We plan to develop a list of established investigators who are willing to serve as consultants for study design and proposal submission. We will work with the TDN, National Resources Centers, CFF Research Working Groups, and the CFF Networks to develop a list that is broad in specialties and research interests. We will work with our Communications team to identify the best way to make this information easily accessible.
- We will continue to discuss ways to build a biostatistician core or other means to attract biostatistician to CF and connect them with CF researchers.