



August 6, 2019

Ned Sharpless, MD  
Acting Commissioner  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993

Re: FDA-2019-D-1264, Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry

Filed electronically at <http://www.regulations.gov>

Dear Acting Commissioner Sharpless:

On behalf of the Cystic Fibrosis Foundation, I am writing to provide comments on FDA's draft guidance titled *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry*. I appreciate the opportunity to share the Foundation's thoughts on this document and commend the agency for offering practical advice to sponsors on how they can improve enrollment practices, especially for the purpose of supporting clinical trial enrollment for rare disease populations. As our letter details below, the FDA can offer further practical advice for drug sponsors on addressing challenges related to language barriers, reimbursement methods, reducing burden associated with trial visits, childcare costs, open-label studies, and pediatric trials consent.

**Background on Cystic Fibrosis and the CF Foundation**

The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis (CF) – a rare genetic disease that affects more than 30,000 people in the United States. The CF Foundation has been engaged in virtually every element of the research and development process from preclinical discovery, identification of new therapeutics, and conducting clinical trials to post-market surveillance and quality improvement studies.

While we have been fortunate as a community to have made great progress in the development of effective therapies for many people with CF, we are not yet done. The CF Foundation is dedicated to providing people with CF the opportunity to lead full, productive lives. To this end, the Foundation is funding research to develop new therapies as well as optimize existing treatments and standards of care. Additionally, the Foundation's Therapeutics Development Network (TDN) is the largest CF clinical trials network in the world. The TDN consists of 92 clinical research centers across the US and supported more than 60 multicenter trials in 2018 alone.

We are on the precipice of a big moment in the CF community; a new modulator therapy addressing the underlying cause of the disease was recently submitted to the FDA for review, and we expect that, if approved, 90% of people with CF will eventually benefit from a disease-modifying modulator therapy. This new therapy represents the achievement of a milestone inconceivable even just a decade ago, and we are now preparing for the impacts that the potential introduction of this new treatment will have on the research landscape for current and future CF therapies. Our comments reflect our extensive experience with CF clinical trials as well as our thoughts on CF population needs in both the present and in the near future.

### **Subpopulation challenges that impact CF clinical trial enrollment**

Not unlike other disease communities, CF has several subpopulations that face more onerous barriers to clinical trial participation than the average person. In particular, clinical trials for patients with CF can fail to effectively meet the needs of Spanish-speaking populations as well as those with limited or irregular income. However, we believe there are several actionable recommendations the Agency can make to drug sponsors to help improve access to clinical trials for these populations.

#### Addressing the needs of Spanish-speaking populations

For Spanish-speaking patients, language barriers remain a substantial challenge to clinical trial participation. For example, informed consent forms and other participant-facing study materials are often not translated into Spanish, and research sites may lack proper language supports for non-English speakers. These barriers prevent individuals who primarily speak Spanish, as well as other non-English speakers, from taking full advantage of opportunities to participate in clinical trials and as a result impacts the representativeness of the study population. The FDA should encourage sponsors to assess ways to make available resources and participant documents in languages other than English to make it feasible for more non-English speakers in the patient population to participate in trials.

#### Addressing the needs of individuals with limited or unreliable income

Patients with limited income as well as those without a reliable income source also face substantial barriers to clinical trial participation. Costs associated with clinical trials can be burdensome for many patients, but they may be especially challenging for low-income individuals. Delays in reimbursement for travel can severely impact a person's finances and ability to continue participation in the trial. The amount of time a patient must take off from work, school, child or elder care, or other commitments for clinical trial activities can also be a major deterrent to participation. As one patient with CF reported during a recent survey, "working full-time doesn't allow the flexibility to get off of work for extended periods of time. Traveling a far distance for multiple appointments is not sustainable when needing to reserve vacation days for health-related issues."

Travel can be especially challenging for patients with chronic diseases, and rare disease studies often require patients to travel much further than non-rare disease studies to reach a trial site. In a recent survey by the Foundation, 30 percent of respondents cited travel distance as a reason why they would not participate in a clinical trial. The concern that extensive travel may exacerbate health for those with chronic diseases is a further deterrent to trial participation. A patient with CF reported during a Foundation survey that, "travel can be exhausting, and [there is] more potential for illness." Additionally, patients with CF and other chronic diseases often travel a considerable distance to see

specialists for routine care and may be unable to further delay other life responsibilities for overburdensome clinical trial travel.

These challenges can be compounded by limited financial resources. It may not be feasible for patients with limited income to commit to paying for costly travel upfront, such as for flights to reach distant clinical trial sites, especially when they must rely on reimbursement well after the fact. Additionally, patients without access to reliable transportation may be more likely to cancel study visits or drop out because they are unable to travel to clinical trial sites.

The FDA should strongly encourage drug sponsors to make it a standard practice to compensate patients on the day of a visit. Reimbursement practices where patients receive money to help cover the cost of gas, rideshares, public transit, or other forms of travel prior to or at the time of visits can help reduce participation concerns as well as alleviate drop-out rates. Drug sponsors should also be encouraged to consider covering the costs for flights and hotels upfront for patients to make rare disease trial participation more accessible to individuals with limited income. Some clinical trial sites and drug sponsors have already made proactive reimbursement a standard practice, and there are tools and services already available to aid drug sponsors in this endeavor. For example, sponsors can contract with travel agencies to assist with travel and hotel reservations while covering these costs for participants upfront.

#### Tailoring trial visits to meet patient needs

We applaud the Agency for highlighting the importance of studying treatments in a patient population that is representative of the ultimate consumers of that treatment. An individual's circumstances in life should not prevent them from participating in clinical trials. Drug sponsors should aim to accommodate the widest pool of patients in the clinical trial design, including in the selection of exclusion criteria, and should consider how clinical trial designs may hinder or deter eligible patients from participating.

The FDA should further encourage sponsors to consider trial designs that minimize the number of visits, offer the widest window or time for study visits to occur in, consider more convenient and flexible hours for study visits, and use technological advances to collect study data in a more convenient location for the patient such as in their home. Again, there are tools and services already available for drug sponsors to reduce the burden of participation. For example, allowing patients to use at-home spirometry devices to measure lung function or visit local lab facilities rather than the study site for collection of blood samples can greatly reduce the burden of trial participation. Furthermore, drug sponsors should be mindful that trial duration can greatly impact patient burden.

#### **Childcare as an accepted non-coercive reimbursable expense**

For parents who are themselves participating in trials or who must accompany their child to a clinical trial visit, childcare costs associated with trial participation can become problematic. Reimbursement for costs associated with childcare will help reduce the overall cost burden of clinical trial participation for families and should not be considered by the FDA as resulting in undue influence on a patient. We strongly encourage the FDA to consider reimbursement for childcare an acceptable practice, and to encourage drug sponsors to incorporate reimbursement for childcare into their standard practices.

### **The importance of open-label extensions**

We appreciate the FDA's recommendation that sponsors consider making open-label extension studies available after early phase studies to encourage patients to participate in trials. Open-label extension studies are particularly important to rare disease communities, as these patients often have few treatment options available and some fear that they will not have access to the treatment after the trial ends. Drug sponsors can ensure that even those who have received a placebo during the trial gain access to the treatment early by offering an open-label extension.

For antibiotic drug development, open-label extensions are also key to ensuring continued treatment access for study participants. Due to the buildup of thick, sticky mucus in the lungs, people with CF are prone to intractable bacterial infections. For individuals in the CF community suffering from chronic infections, long-duration and multi-drug antibiotic treatment courses are often required. For example, treatment for nontuberculous mycobacteria (NTM) – a group of difficult-to-treat bacteria that commonly infect individuals with CF – typically requires a course of three antibiotics over the duration of a year or more. Open-label extensions ensure that trial participants maintain access to experimental therapies beyond the end of the trial phase when necessary, such as in the case of chronic administration for difficult-to-treat infections.

### **Special considerations for pediatric populations – starting early and challenges with consent logistics**

We appreciate the Agency's inclusion of recommendations to sponsors to consider pediatric patient needs early on in the drug development process. It is critical that drug sponsors think about the inclusion of pediatric and other special populations in clinical trials early, especially for therapies aimed at treating rare diseases where the intended population for the treatment often includes children. Starting clinical studies for pediatric patient trials early, such as pharmacokinetic studies, can help ensure that drugs are being tested with the ultimate population in mind.

Families can struggle to find the time for pediatric clinical trials due to competing obligations such as work or caring for siblings. As one parent during a CF Foundation survey described, "we don't have the time - both parents work full time and work opposite schedules, so coordinating time out of work is very difficult." A critical challenge drug sponsors can address for pediatric patients is the consent process. Both parents are often required to be present during the consent process when the study is considered to include greater than minimal risk, which can be particularly challenging when patients are required to travel a substantial distance to the clinical trial site. The added travel burden and increased costs associated with childcare for siblings of the trial subject can deter families from clinical trial participation. The FDA should encourage drug sponsors to consider methods for making the consent process for pediatric clinical trials more convenient and less burdensome for families while maintaining existing standards, such as by using tools like video conferencing to minimize excessive travel.

### **Exclusion criteria based on health status**

We applaud the FDA for calling on sponsors to assess whether any exclusion criteria may be unnecessarily prohibiting certain groups from participating in clinical trials. A common criticism we hear from the CF community is that people at the extremes of disease state are unfairly excluded from clinical trials.

Patients want to participate in clinical trials, and for many people with CF clinical trials represent an important opportunity to access potentially life-changing treatments and prevent further health decline. Trials also present a valued opportunity for individuals to contribute to advances that can benefit the broader disease community.

We recognize that certain exclusions, such as in the case of CF research where often individuals with a lung function measure of less than 40 percent FEV1 or greater than 90 percent FEV1, can help to ensure that clinical trials are best situated to demonstrate efficacy and prevent certain patients from being exposed to undue risk. Adaptive trial designs and expanded population study extensions can play a role in minimizing unnecessary restrictions by enrolling ideal patients during earlier phases and allowing for individuals outside of a particular range of metrics to participate during expansion phases.

### **CF is a shifting population – future challenges**

Historically, the CF population has responded to clinical trial enrollment needs with strong interest and participation rates. However, this may change as population characteristics evolve. Individuals with CF who are able to take modulator therapies will likely be healthier and have slower disease progression compared with those who are unable to take these treatments. Additionally, we expect that many in the population with established disease will continue to experience health complications that must be addressed with other therapies.

The CF clinical trials of the future will be impacted by this diverging population – those without effective modulators or with established disease who may have a greater desire to enroll in future clinical trials, and those who are healthier thanks to early intervention with modulator therapies but who may be less inclined to participate in trials. Drug sponsors will need to consider how shifting population characteristics in CF and other diseases can and should impact clinical trial designs.

### **Patients who are healthier may be less willing to participate in clinical trials**

Enrollment challenges for people with CF who have gained access to modulators at a young age will likely look similar to challenges faced when engaging patients in the general population who do not have CF or other life-threatening, chronic diseases.

As people with CF become healthier, they will likely have busier lives with more responsibilities and commitments related to work, children, elder care, community involvement and more – activities that healthier populations engage in more readily than those with chronic, debilitating diseases and which drug sponsors must contend with when designing and enrolling participants from the general population in studies.

Additionally, patients with CF may be less willing to participate in clinical trials if it impacts their ability to remain on the therapies that have resulted in significant health gains. When asked about willingness to participate in a clinical trial during a Foundation survey, one patient stated, “I would definitely be hesitant to give up a highly effective CFTR modulator.” Trial designs that allow patients to stay on some or all of their current therapies while participating in clinical trials will be especially critical for engaging CF patients on effective modulator therapies. When it is not possible for patients to remain on current therapies, both drug sponsors and the Agency should be mindful of the duration patients will have to be

off existing therapies and make a good faith effort to minimize the length of the washout period where appropriate.

Patients without effective therapies or with advanced disease will face new challenges

Patients with CF who do not have access to modulators or who already have established disease will face enrollment challenges more along the lines of what we see in the CF population today. Patients who are sicker tend to be more interested in participating in trials, but we expect there will be added barriers to reaching this population as it becomes smaller and more disperse.

Trial sponsors will likely need to rely more on referrals to connect patients to clinical trial sites as fewer CF patients lack treatment options for the underlying genetic defect. Additionally, the CF population without access to effective modulators will consist mostly of individuals with rare or nonsense mutations.

Subpopulations in CF affected by mutations that are more challenging to address will have very different therapeutic development needs compared with subpopulations that have effective modulators already available. It is important to note that disease subpopulations may have important differences from one another that warrant consideration during the trial design and enrollment process.

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Once again, we commend the FDA for its request for comments on this draft guidance document. There are important opportunities for discussion and collaboration regarding improving clinical trial enrollment practices, and we look forward to working alongside the FDA in the future in this endeavor.

Sincerely,

Mary Dwight

A handwritten signature in black ink, appearing to read 'Mary Dwight', with a stylized flourish at the end.

Senior Vice President of Policy and Advocacy  
Cystic Fibrosis Foundation