



November 30, 2018

Scott Gottlieb, M.D.
Commissioner Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2018-D-3124, Adaptive Designs for Clinical Trials of Drugs and Biologics; Draft Guidance for Industry

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

Dear Commissioner Gottlieb:

On behalf of the Cystic Fibrosis Foundation, we write to provide comments on FDA's draft guidance titled *Adaptive Designs for Clinical Trials of Drugs and Biologics; Draft Guidance for Industry*. We appreciate the opportunity to share our thoughts on this document and commend the agency for taking steps to update guidance as innovative adaptive trial designs become more widely used, especially in assessing products in development for rare disease populations.

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 over 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 to identification of new therapeutics to conducting clinical trials as well as 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 is experienced in employing more traditional adaptive design elements to monitor for efficacy and futility, in particular for longer, larger, or resource intensive studies. Our comments reflect our experience and observations in applying adaptive trial design elements in studies impacting the CF community.

Real world examples of clinical development plans

The acceptance of more novel clinical trial designs has been critical to removing some of the barriers rare disease communities face during the drug development process, and we expect broader use of

adaptive design elements to further benefit rare disease patients. It is therefore important to consider whether certain population characteristics for these groups may impact the use of different adaptive design features in clinical trials.

We appreciate FDA's inclusion of examples on appropriate applications for adaptive design elements and encourage the FDA to consider including additional real world examples of clinical development plans and pivotal trial designs that would be acceptable for regulatory purposes, especially for rare disease-specific issues such as small patient population and ethical concerns related to placebo use. Providing examples of adaptive designs that use external control groups from registries or prior completed trials would also be of great value to the rare disease community.

Adaptive designs applied in later phases of clinical development

This guidance primarily focuses discussion on the use of adaptive designs during early phases of development. While we appreciate the examples and discussion provided for early development applications, it would be beneficial to provide further discussion on how adaptive design elements may be used in late phase 2b and phase 3 clinical trials. We ask that the FDA consider providing examples on appropriate applications of adaptive elements in later phase trial designs.

Mechanisms for meeting with the FDA

We applaud the FDA for its recent unveiling of the Complex Innovative Trial Designs (CID) Pilot Meeting Program, which invites sponsors to apply for assistance in employing novel adaptive designs during the clinical trials process. Increasing the ways in which sponsors can interact with the agency is critical given that developing successful innovative designs requires more agency input to ensure that studies are carried out effectively and ethically. We look forward to learning from the case studies produced by this pilot program.

Unfortunately, given that the CID Pilot Program will only offer assistance to a handful of sponsors, we anticipate that this program alone will not be enough to meet the needs of the drug sponsor community. Planning for more complex adaptive trials is significantly more resource intensive, and phase 2 meetings are often too late to begin discussions with the agency on such designs. Sponsors may forgo the use of potentially beneficial adaptive designs where agency thinking is unclear to avoid product development delays.

Broader access to FDA staff and resources is needed as sponsors begin to test out more novel adaptive trial designs. Agency advice must also be accessible early enough in the product development process that it does not hamper development. We request that the FDA consider establishing additional mechanisms for sponsors to receive targeted advice on novel trial designs.

Aiding adaptive design use through data sharing

Increasing the accessibility of existing data will be critical for making adaptive clinical trials more efficient. Complex adaptive trial designs and necessary simulations for those studies rely heavily on robust data and assumptions that could be derived from prior successful studies. We encourage the FDA to explore ways to make data more accessible from prior completed trials of approved therapies as a

resource for planning future trials, and in particular the use of non-proprietary placebo group data from these trials.

Facilitating platform trials

There have been many examples of platform trials in oncology, with the National Cancer Institute (NCI) acting as a coordinating entity or funder for a number of these efforts. NCI provides stakeholders a venue to discuss these designs independent of a specific sponsor. However, fields outside of oncology lack a coordinating entity to assist in collaborative development of platform trials.

In the absence of any government agency or other body to support these types of trial designs, it will be difficult for other disease communities to leverage platform trial designs testing therapies from more than one sponsor. It may be of value for the FDA to play a role in supporting an honest broker structure for products outside of the oncology field in order to foster collaboration across sponsors.

We request the FDA to consider whether a mechanism within the agency may serve a coordinating role in platform trials. The FDA could additionally help facilitate platform trials or master protocols by making operational templates such as contracts, IRBs, consents, and protocols accessible to other sponsors and stakeholders to facilitate learning on how to negotiate and initiate these types of trials and save valuable time in coordinating across sponsors.

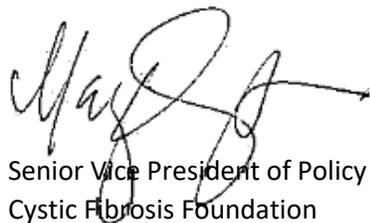
Non-inferiority testing and adaptive trials design

Non-inferiority testing can play an important role in validating second-to-market or novel therapies where a standard therapy is already in use. It is therefore important to understand how adaptive design use may impact evaluations of non-inferiority when comparing different treatments under one study design. Unfortunately, there is not much literature currently available that addresses adaptive or Bayesian methods for testing for non-inferiority. It may be beneficial for the FDA to include some discussion on these concerns in the guidance document.

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

Sincerely,

Mary Dwight



Senior Vice President of Policy and Advocacy
Cystic Fibrosis Foundation

Anthony Durmowicz, MD



Vice President of Clinical Development
Cystic Fibrosis Foundation