Castle IRB
www.castleirb.com
irbteam@castleirb.com
(888) 442-2472 (1-888-4-IBC-IRB)

Addressing Rare Disease Community Concerns: Evaluating the Latest FDA Guidance on Rare Disease Research

Research on treatments for rare diseases face unique barriers to meeting the general requirements for FDA approval due to "limited scientific knowledge, poorly understood natural history data, sample size constraints, and lack of drug development expertise (FDA 2023)", among many other challenges**.** Despite these barriers, rare disease organizations, families, and communities, are highly motivated and heavily invested in achieving successful treatments for themselves and their loved ones.

The FDA has recognized both the need for this research, **and** the challenges to implementing it, and in response has released guidance for sponsors on how to approach rare disease research several times. In December 2023, the FDA published a new guidance for sponsors of drugs for the treatment of rare diseases entitled "Rare Diseases: Considerations for the Development of Drugs and Biological Products", which is an update from earlier Draft FDA Guidance that had been published in 2019 and 2015. In addition, the FDA published Guidance for Industry "Human Gene Therapy for Rare Diseases" in January 2020, which is still effective and will be referenced in comparison to the new 2023 Guidance, below.

In the interim, the FDA, through its Center for Biologics Evaluation and Research (CBER) Office of Tissues and Advanced Therapies (OTAT) and Office of Therapeutic Products (OTP) launched numerous virtual series to engage with the rare disease patient population, including a town hall series, listening sessions, and workshops aimed at rare disease patients and their advocates. The FDA representatives would share information, ask for insights and recommendations, and elicit feedback on various issues throughout these forums. As Chair of Castle IRB, a central IRB that frequently reviews rare disease gene therapy protocols, I attended most of these sessions, taking notes on the concerns, interests, and insights of rare disease communities so that I could take them back to enhance our protocol reviews.

With the release of the FDA's new guidance, it is worth reflecting on the extent to which it is responsive to the concerns I heard raised by the rare disease communities in these listening sessions. The considerations listed below in no way exhaust the complex and nuanced concerns that rare disease community stakeholders voiced in the many sessions I attended. While I can't do justice to all the thoughts raised by these public sessions, I would like to analyze the recent guidance in light of some major issues that were raised and how I believe it is responding, or not, to them.

7 Issues raised by Rare Disease communities

1. Critique of placebo and sham procedures, suggest innovative study designs instead.

Patients and advocates voiced strong ethical objections to designing rare disease studies that randomize to placebo or sham procedures. Although willing to undertake risks for even a small possibility of benefit, they do not perceive placebos or sham procedures to be an ethical option, especially when time is of the essence and participating in one study could preclude them from participating in others. This is in contrast to the recommendation in earlier FDA Guidance, which recommends placebo controls "when feasible" (FDA 2020, 7).

Patients suggested more creative study designs where every participant is given some intervention or using natural histories as controls. They also suggested other innovative designs like platform, umbrella, or basket trials to compare different experimental treatments for the same disease, or the same treatment for different diseases as part of one trial. These designs, although posing regulatory and methodological challenges, have the possibility of addressing the challenges specifically posed by rare disease research (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9756081/).
This was generally mentioned in earlier FDA Guidance, where alternative trial designs that maximize data from a small and heterogenous group "should be considered" (FDA 2020, p. 8).

2. Critique of time it takes for clinical endpoints, suggests surrogate endpoints.

Due to the seriousness and often degenerative nature of many rare diseases, patients and their advocates also critiqued certain choices of clinical endpoints that took a long time to reach. In these cases, there were suggestions for surrogate endpoints that could establish efficacy sooner, expediting the research process for those desperate for drug development. Earlier FDA Guidance mentions the use of sufficiently justified surrogate endpoints to justify accelerated approval (FDA 2020, 10-11).

3. Critique of overly cautious risk assessment when no alternatives and serious disease.

A common critique of current study design is that the considerations of acceptable risks do not reflect the desperate and often degenerating situation of many patients with rare diseases. While risks should always be minimized, rare disease patients emphasized that when faced with a serious disease that frequently have no existing effective clinical alternatives, they are willing, and should be permitted, to take on what they consider acceptable risks which may be higher than what is seen as acceptable by sponsors and review bodies.

4. Critique of excluding more progressed patients (nonambulatory, etc.).

An issue that arose several times was the prioritization, or even exclusive access to studies for patients with less advanced disease. More progressed patients argued that they could still benefit from study interventions, and that understanding the impact of interventions on patients with more advanced disease is vital to progress in the field. Earlier FDA Guidance specifically encouraged enrolling patients with earlier stage disease in rare disease research (FDA 2020, p.6).

5. Critique of follow-ups that exclude from other trials.

An important point raised by patients in these venues was that while they acknowledged the importance of long-term follow-up for participants in rare disease research, they sometimes found that being in follow-up excluded them from participating in more trials. In the absence of effective clinical alternatives, many patients with rare diseases rely on continuous trial participation to attempt to improve research as well as their personal disease trajectory. Being excluded for years after a study's intervention has completed serves as a barrier to this.

6. Suggests patient engagement early.

While the rare disease community frequently acknowledged and appreciated the increasing avenues for patient engagement that the FDA and sponsors are incorporating into their processes, there was still concern that these avenues often engage patients too late in the study design process. The earlier patients are engaged, the more impact they have on the questions being asked, the design of the study, and the way it is reviewed.

7. Critique of clinical outcomes, suggests incorporating patient-reported outcomes.

Many patients challenged the relevance of using exclusively clinical outcomes to measure the effectiveness of gene therapy interventions and emphasized outcomes with more impact on quality of life from the patient perspective to be included. Earlier FDA Guidance gestures to the importance of patient experience, both in terms of asking for patient experience data to be collected and identifying aspects of the disease that are meaningful to the patient (FDA 2020, 11).

Relationship to New Guidance

In light of these concerns and earlier guidance, it is worthwhile to reflect on what the new 2023 FDA Guidance for Industry adds to the conversation. One major insight from this new guidance is its emphasis on flexibility and case-by-case considerations of what is required for rare disease studies. "The FDA recognizes that rare diseases are highly diverse with varying prevalence,

rates of progression, and degrees of heterogeneity. . .as such, no one program can be designed exactly like any other" (FDA 2023, 3).

This emphasis on study design flexibility in the new guidance specifically mentions potentially allowable adaptations in many of the ways desired by rare disease communities.

In response to critique #1 of use of placebos above, the new guidance allows study design flexibilities that, under certain conditions, can allow alternatives to using placebos or minimizing participant exposure to them. They also mention using natural history and registry-based studies to justify adapting the traditional design and phases of clinical trials. Similarly, in response to the #2 critique of slow achievement of clinical endpoints, the new guidance also allows that surrogate endpoints "may be considered" when the clinical endpoints are not feasible. In direct response to the challenge of how risk assessments were being made (critique #3) the new guidance acknowledges that greater risk and greater uncertainty may be acceptable when disease is serious, there are no acceptable alternatives, and "a substantial evidence standard has been met" (FDA 2023, 16-17). Finally, "practical considerations" may allow the inclusion of a broader range of disease stages, including different severities of disease and different severities of secondary conditions to the primary disease. In addition, the guidance allows the possibility of auxiliary safety cohorts and expanded access consisting of patients with the disease who may benefit but don't meet the study eligibility criteria. This responds directly to critique #4 above. Unfortunately, it doesn't address the concern about participation in one study excluding participants from participating in others afterwards (critique #5). This does not seem to be acknowledged or addressed by either the old or the new guidance, and should be addressed in the future.

This move toward flexibility acknowledges that rare disease research poses both practical and ethical challenges not shared by more traditional research approaches and makes space for the possibility of proceeding through the FDA process in different ways. On the other hand, the notion of flexibility, without clear understanding of the conditions under which it may be utilized, could be unsatisfactory to both sponsors and patients, putting the burden on

them to make the case for flexibility without adequate guidance on how to justify it. The guidance indicates that the FDA will have the authority when and how to allow flexibility, based on evidence and arguments made by patients and sponsors, but with little clarity on what will constitute an acceptable threshold of justification. It also creates a "black box" situation where research situations are addressed individually, with no transparency about how and whether similar issues are treated consistently or inconsistently, or the possibility from learning from those who have come before.

The other major shift in this guidance is the emphasis on patient involvement and patient-centered research. While mentioned briefly in earlier FDA Guidance, the 2023 guidance mentions it in a much more thoroughgoing fashion. It urges sponsors to engage with patient and caregiver concerns "early in the planning stages (FDA 2023, 12)", responding directly to critique #6 above. It also acknowledges that involving patients and caregivers "in the selection, development, or modification of existing clinical outcome assessment measures (FDA 2023, 13)" as well as assessing "aspects of the disease that are meaningful to the patient and caregivers (FDA 2023, 13)" can improve the chances of the program's success, directly responding to critique #7 above. In addition to these narrow areas, the new guidance added a section under "Additional Considerations" called "Participation of Patients, Caregivers, and Advocates" that encourages sponsors to involve these stakeholders in numerous ways.

This emphasis is welcome and reflects the expertise, agency, and power of rare disease communities to shape the research that impacts them. It does appear that most of the guidance emphasizes the relationship between sponsors and these stakeholders, leaving open the question of whether and how these stakeholder perspectives may impact the FDA review process itself. Especially when there is so much left unarticulated in the justifications for flexibility, and this flexibility is so central to the concerns of the rare disease community, I would hope that they would be at the table for some of these FDA determinations as well.