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Office of Tissues and Advanced Therapies (OTAT)
Center or Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: FDA CBER OTAT Patient-Focused Drug Development Listening Meeting — Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on Cell and Gene Therapy Products (FDA-2023-N-0398)

Dear Dr. Rowzee,

The National Organization for Rare Disorders (NORD) appreciates this opportunity to provide comments in support of the U.S. Food and Drug Administration's (FDA) Patient Focused Drug Development Listening Meeting **'Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on Cell and Gene Therapy Products.'**

For nearly 40 years, NORD has been devoted to individuals with rare diseases and the organizations that serve them. NORD was founded after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing that landmark law. Our mission has always been and continues to be to improve the health and well-being of people with rare diseases by driving advances in care, research, and policy. Supporting patients, drug sponsors, and the FDA in patient-focused drug development (PFDD) activities has been a long-standing priority for NORD in pursuit of our ultimate goal - to improve the lives of individuals and families affected by rare diseases.

NORD applauds FDA's efforts to seek extensive comments and community engagement on post-market surveillance for cell and gene therapy products, and we greatly appreciated the public listening session on the topic last month. We offer written comments to extend and supplement our oral comments provided during the meeting and to assist FDA in ensuring that post-market surveillance will work for the unique challenges and needs of rare disease patients and their families. Our ultimate goal is to ensure that patient and family perspectives and preferences are adequately incorporated into each step of the drug development process.

1. Post-market surveillance should be designed to answer the key questions and concerns of rare disease patients, caregivers, and families considering these products as therapeutic options.

Gene therapy has been and continues to be a beacon of hope to many in the rare disease community. Among the more than 25 million Americans living with one or more of the over 7,000 known rare diseases, most don't have access to effective treatments. Very few rare diseases have cures,[1] and many lead to premature death in infancy or early childhood.[2] Most rare diseases are genetic or have a genetic component, and many are tied to single-gene defects that may eventually be repairable through cell or gene therapies. In fact, the more than a dozen gene therapies that have been FDA-approved to date have been for rare diseases. On the other hand, cell and gene therapies carry unique risks and potential unintended short and long-term consequences that must be carefully balanced.

Recommendation 1.a. Design post-market surveillance programs to help address the key questions patients considering cell and gene therapy must weigh.

Given the importance of cell and gene therapies to our community, NORD has periodically conducted surveys to better understand what information our community needs to make informed decisions concerning whether receiving a cell or gene therapy product is right for them. For many of the questions asked in our surveys, a definitive, clear-cut answer is still lacking. Long-term post-market surveillance will prove instrumental in answering these key questions, and it will be vitally important to carefully consider them when designing any post-market surveillance approaches for cell and gene therapies. This will help to ensure that as more cell and gene therapies become available to an ever-growing group of patients, the necessary evidence is collected to help patients and families navigate the complex decision-making about whether to receive these products. Concrete areas identified in our surveys where additional pre- and most-market data collection will be instrumental include:

- Is gene therapy a cure? How durable is the effect?
- Why are there variations in responses? What will be the impact on quality of life?
- Can the changes gene therapy causes be passed on to future generations?
- How long is the treatment, what does it entail, and does it reach every cell in the body?
- Is gene therapy safe? What are possible side effects?
- Who will be able to receive gene therapy? Will it be only those with severe or life-threatening disease?
- Can I receive a gene therapy multiple times?
- What is the difference between gene therapy and gene editing?
- Why does gene therapy cost so much? / Will insurance pay for it?

[1] https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0936-x
[2] https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01574-7

Recommendation 1.b. Make patient engagement and communication a central part of post-market surveillance for cell and gene therapies.

Given the importance of cell and gene therapies to the rare disease community, the evolving understanding of desired and off-target effects, and the complexity of the technology involved, effective post-market surveillance should be designed around a core of communication, patient engagement and empowerment. This will help ensure patients have the most complete understanding of known risk-benefit tradeoffs when they weigh decisions about whether to participate in gene therapy, while emerging risks and concerns can be addressed and timely incorporated in post-market surveillance.

Recommendation 1.c. Patient education must be closely integrated with the surveillance efforts.

A key pre-requisite for such a learning, continuous-feedback system will be effective patient education to translate and contextualize the results of post-market surveillance. To date, NORD has developed a variety of educational resources to help patients, families, healthcare providers, and the public learn about this emerging therapeutic area including the basics of gene therapy, how it is currently used and its potential for future therapies for rare diseases. Our introductory resources include FAQs,[3] a video series,[4] and a podcast,[5] supplemented with downloadable written materials.[6] These introductory resources are complemented by a webinar series, workshop recordings, and a continuing medical education series we co-crated with Platform Q Health and the American Society of Gene & Cell Therapy (ASGCT), which are all accessible through our website.[7] This type of foundational content can help set a baseline for patients and families unfamiliar with cell and gene therapies, and provide necessary context. Moreover, based on our experience developing this content, as well as based on patient feedback we have received, we recommend short materials with clearly defined content; a curricular approach that combines different learning formats and speaks to the diversity of adult learners; and content that heavily leverages storytelling. NORD would be delighted to continue the discussion about how best to incorporate education and communication as central components of the post-market surveillance systems for cell and gene therapies.

2. Leverage FDA's new congressional authority and establish a 'platform' program for post-market surveillance registries for cell and gene products.

Given the small patient populations; length of necessary follow-up; medical complexity and heterogeneity of most rare diseases; range of potential adverse events; and lack of disease-specific ICD-10 codes that complicate the use of claims and EHR data as RWE, patient and/or product registries will likely play a key role in post-market surveillance for cell and gene therapies.

[3] https://rarediseases.org/gene-therapy/frequently-asked-questions/
[4] https://rarediseases.org/gene-therapy/resources/
[5] https://podcasts.apple.com/us/podcast/ungeeking-the-speak-dr-rachel-bailey-talks-gene-therapy-101/id1511001441?i=1000515121374
[6] https://rarediseases.org/wp-content/uploads/2022/03/NRD-2241-Gene-Therapy-Sell-Sheet_FNL.pdf
[7] https://rarediseases.org/gene-therapy/resources/

Of the more than 7,000 known rare diseases the vast majority still do not have an FDA-approved therapy. Developing post-market surveillance systems one disease at a time will be wholly inefficient and, at times, impossible given the small patient populations. Standardization of registries across products and diseases, and a 'platform' approach to these registries will be vital to handle both the number and diversity of cell and gene therapies that are currently in development and the limited capacity in many rare disease communities to stand up *de novo* registries. A 'platform' approach will allow for pooling or contrasting of data across diseases where appropriate, cut down on the cost of registry maintenance and updates over the decades of follow-up, and allow for standardization and harmonization across manufacturers and regulatory bodies. Moreover, careful design, user experience testing, and continuous evaluation can help alleviate concerns about accessibility by historically marginalized groups and others who may be disproportionately affected by access challenges including issues such as lack of broadband internet access, visual impairment, or language barriers.

3. Build capacity to ensure the patient communities can be integral partners in the registry program

When considering the sheer complexity of developing post-market surveillance systems that follow individual patients for decades or throughout their entire life, patients, caregivers, and advocates must play a vital role in their design and execution: patient and caregiver groups have the trust of the community and understand the questions and concerns that motivate participation in the registry year after year. Patient groups also have the necessary contacts and know how to reach their members and their families and how to communicate effectively and efficiently with the patients and families. Moreover, patient groups are often the first to hear of new safety or efficacy concerns in their community. While pharmaceutical companies may grow, contract, merge, be acquired, shift focus, or go bankrupt in the decades of follow-up after a patient receives a cell or gene therapy, patients and families will continue to be left with the risks and benefits of their treatments, for better or for worse.

Through NORD's IAMRARE registry program[8] and our RareLaunch Research Ready[9] curriculum, we have extensive experience helping patient groups develop, implement, and analyze patient registries that are by patients and for patients. Based on these experiences, we understand how powerful patient-led patient registries are - and how much support many patient groups need at every step of the process to ensure the registries are of regulatory grade and sustainable. This includes, among other issues, setting up informed consent processes, managing data sharing agreements, and navigating Institutional Review Boards (IRBs), designing and pilot-testing the surveys in English and potentially additional languages, recruiting participants, capturing and curating the data, and conducting the data analysis.

To help build the necessary capacity and ensure patients and families can be effective partners in this process, more clarity is needed now about key questions including:

- What is the role of patients and caregivers in designing, operating, and analyzing the registry?
- Who owns the data, and who has access rights (and to what data)?
- What role will disease-agnostic registries/ gene therapy platform-specific registries play?
- What funding models will allow for financial sustainability today and in the future?

[8] https://rarediseases.org/advancing-research/patient-registry-program/
[9] https://learn.rarediseases.org/courses/rarelaunch-research-ready/

- What is the long-term responsibility of manufacturers to maintain post-market surveillance domestically and internationally, including if products may not/ no longer be on the US market?
- What minimum requirements are needed to ensure the registry is and continues to be fit for purpose and of regulatory grade (in the US as well as in other jurisdictions)?
- How can we ensure diversity, equity, and inclusion is integral to the registry platform and program?
- Which strategies will be effective at encouraging long-term participant engagement?
- What is the role of the registry program in patient education, engagement, and empowerment?

4. Ensure patients are fully invested in and benefit from the registry program to make long-term follow-up feasible

Designing a system intended to follow individual patients for decades or throughout their life is a formidable challenge. Ensuring patients are invested in and directly benefit from the data collected as part of the post-market surveillance system will likely be key to long-term success. This will include making patient engagement central to every step of the registry program; designing registries to answer key questions among the patient community; and leveraging post-market surveillance to inform the development of new and better cell and gene therapies. Experience shows that patients and families that have gone through the process can be one of the best sources of information for gene therapy patients and that rare disease communities often take a leading role in attracting the attention from researchers and sponsors and play a key role in bringing the product to market. Therefore, the registries have the potential to become central sources of information for rare disease patients, sponsors pursuing cell and gene therapies for additional rare diseases, and the rare disease community writ large. This role, in turn, will be vital to ensure the surveillance efforts will be able to continue over multiple decades of follow-up, as pediatric patients grow up, age out of pediatric provider networks, and leave their families' insurance plans; as patients relocate across state lines and countries; and as federal agencies, private-sector companies, health IT networks, and our nation's healthcare system continue to evolve.

5. Develop today's post-market surveillance systems to they can help generate data for tomorrow's cell and gene therapies

Post-market surveillance can play a pivotal role in informing the developing of future cell and gene therapies, including for 'offshoot' gene therapies that are based on the same vector and platform manufacturing technology as the originator product while addressing new diseases or conditions. Designing today's registries with tomorrow's purposes in mind will be vital to long-term success; it also provides an opportunity to ensure tomorrow's cell and gene therapy development programs are truly patient-centered and guided by the priorities of the patient communities. Areas where post-market surveillance data can inform the patient-centered development of new cell and gene therapies include:

- Defining outcomes meaningful to patients including the completeness and durability of effect
- Informed consent, ethical considerations, and effective study communication
- Communicating patient expectations for participation in the gene therapy trial including preparation for trial participation, recovery, durability of effect, etc.
- Designing trials that work for patients (e.g., diagnosis, inclusion /exclusion criteria, patient burden)

- Communicating safety considerations including long-term health risks and vector cross-reactivity
- Support for long-term follow-up and living after gene therapy
- Long-term access to transformative therapies

6. Leverage all available data streams, and intentionally try to build in redundancies to future-prove surveillance systems

As mentioned before, building a post-market surveillance system to follow a small number of individual patients for decades, with each individual patient lost-to-follow-up potentially detrimental to the overall surveillance efforts, is a formidable effort. At the same time, data on most rare diseases are still lacking, their natural history and disease progression incompletely characterized. Similarly, real-world data sources are still subject to several severe limitations, which are magnified for most rare diseases. Moreover, the clinical manifestation for most rare diseases is complex and heterogenous, and the long diagnostic odyssey means that too many potential patients cannot fully benefit from the available treatments. Additionally, patients vary considerably in their diagnostic journey and often have undergone a range of ineffective therapies and interventions that may impact their disease trajectory. To develop a post-market surveillance system that can overcome these challenges will mean leveraging and integrating all available data sources and to pool and integrate across diseases and products where possible. Given the length of follow-up, building redundancies where possible will be important to reduce dependencies on the continued availability of one single tool, product, or organization, including one registry, HER, or claims system.

Moreover, gene therapy trials have so far only been conducted in small population groups for limited amounts of time, thus limiting the ability to learn from, standardize and validate existing tools and approaches. Given the increasing availability of gene therapies, strategies and approaches to validate existing tools pre- and post-market across disease areas and specific therapies will be particularly important. Equally important will be a re-evaluation and updating of these tools as the first gene therapy patients gain increasing experience in living with the gene therapy and experience increasing opportunities to re-consider their experiences and decision-making processes around gene therapy.

We thank the Agency again for the opportunity to comment and look forward to working with FDA to ensure rare disease patients can fully participate in and benefit from today's, as well as future, cell and gene therapies.

Sincerely,

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National Organization for Rare Disorders