SUMMARY

FDA CBER OTAT Patient-Focused Drug Development Listening Meeting

Patient Perspectives on Gene Therapy Products

November 15, 2022

FDA

Table of Contents

NOTE: The report was originally released on May 15, 2023. This version includes minor edits for clarity and updated references.

Introduction

On November 15, 2022, the U.S. Food and Drug Administration's (FDA) Office of Tissues and Advanced Therapies (OTAT)[1] within the Center for Biologics Evaluation and Research (CBER) hosted a virtual patient-focused drug development (PFDD) listening meeting to gather patient perspectives on gene therapy products.

The FDA conducted the meeting as part of a commitment specified by the latest reauthorization of the Prescription Drug User Fee Act (PDUFA VII).[2] The seventh iteration of PDUFA provides the FDA with vital resources to expedite the development and evaluation of groundbreaking biological products, including gene therapies. The half-day meeting consisted of four sessions, providing a forum for patients, caregivers, patient advocates, and other essential stakeholders to share their insights and expectations regarding the risks and benefits of gene therapies, patient and caregiver participation in design and execution of clinical studies for gene therapy products, and current or future tools to improve the capture of patient experience data that are unique to gene therapy products. The goal of obtaining these perspectives was to inform the broad medical product research and development community and support the FDA's evaluation of safety and effectiveness for these products. This report summarizes the main topics and perspectives discussed during the meeting, supplemented by comments from Docket FDA-2022-N-2394, which was open from October 3, 2022, the date the meeting was announced, through December 15, 2022.

History of Gene Therapy and Patient-Focused Drug Development at the FDA

The FDA considers human gene therapy as a method of modifying a person's genes to cure or treat a disease. Techniques can involve either inactivating, repairing, or replacing problematic genes, or introducing new genes to help the body fight or treat diseases.[3] The FDA also considers genetically modified cells, such as chimeric antigen receptor (CAR) T-cells, to be human gene therapy products. Within FDA, CBER's OTAT provides regulatory oversight of human gene therapy products, including clinical trials, data integrity, and product manufacturing and quality, and provides guidance to developers throughout the clinical development process.

The concept of gene therapy has been extant since the development of recombinant DNA technology in the late 1970s, and the first gene therapy trial in humans was performed in 1990 at the National Institutes of Health Clinical

[1] On February 26, 2023, the Office of Tissues and Advanced Therapies (OTAT) became the Office of Therapeutic Products. As the public listening meeting was held on November 15, 2022, this summary report will refer to OTAT as the office sponsoring the meeting.

[2] PDUFA VII commitment letter, August 19, 2021.

[3] CBER. What is Gene Therapy? Updated July 25, 2018. Accessed April 18, 2023. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy.

Center.[4] Decades of continued advancement in the field allowed for approval of the first three gene therapy products in the United States — CAR T-cell products, Kymriah and Yescarta; and Luxturna, a directly administered gene therapy — in 2017. As of the date of publication of this summary report, the FDA has approved 12 gene therapy products, with more than 1,000 investigational gene therapy products under OTAT's regulatory purview.[5]

Gene therapy holds great promise for addressing serious medical conditions with few or no alternative treatments. Patient, advocate, and caregiver involvement is essential for advancing the state of the science for such conditions and for advancing gene therapy generally. The FDA seeks to understand patient stakeholder experiences, expectations, and preferences regarding risk-benefit considerations, clinical trial design, and treatment options. Patient input is vital for driving scientific advancements in this field and may support greater patient uptake of future marketed products.

Patient engagement at the FDA began in the 1980s during the HIV/AIDS pandemic, expanding to other health issues throughout the next decade. The FDA Patient Representative Program® was further expanded in the 2000s, allowing patients to serve as consultants to reviewers during review cycles. In 2012, FDA established the PFDD initiative under PDUFA V to help ensure patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated during drug development and evaluation.[6] The program systematically collects patient perspectives on disease symptoms, impacts on daily life, and treatment options across a range of diseases. Public meetings with patients and advocacy groups are held to discuss the impact of diseases and their treatments. In 2018, the FDA began issuing guidance documents to support collecting and using patient experience data in drug development and regulatory decision making.

In response to the 21st Century Cures Act of 2016 and PDUFA VI, FDA further enhanced patient engagement efforts.[7] In 2017, the Office of Patient Affairs was established within the Office of the Commissioner and led to an increase in patient engagement across all medical product centers. In addition to its Patient Engagement Program, CBER also participates in the Science of Patient

Gene therapy holds great promise for addressing serious medical conditions with few or no alternative treatments.

[4] Fatemeh Arabi, Vahid Mansouri, Naser Ahmadbeigi, Gene therapy clinical trials, where do we go? An overview, *Biomedicine & Pharmacotherapy*. Volume 153, 2022, 113324, ISSN 0753-3322, https://doi.org/10.1016/j.biopha.2022.113324

[5] CBER. Approved Cellular and Gene Therapy Products. Updated April 17, 2023. Accessed April 20, 2023. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.

[6] FDA. FDA-led Patient-Focused Drug Development (PFDD) Public Meetings. Updated February 23, 2023. Accessed July 11, 2023. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings#:~:text=From%202012%20to%202017%2C%20under,specific%20diseases%20and%20their%20treatments.

[7] FDA. 21st Century Cures Act. Updated January 31, 2020. Accessed April 24, 2023. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act.

Input (SPI) Initiative and has a dedicated Rare Disease program. The SPI Initiative aims to support studies on methods and tools to obtain robust patient input for reviews as well as provide reviewers with assistance in the regulatory review of patient input and patient-reported outcome (PRO) data. The Rare Disease program works to assist incorporation of patient perspectives in regulatory decision making for biologics to treat rare diseases.[8]

Meeting Overview

This virtual meeting provided the FDA the opportunity to hear directly from patients, caregivers, patient advocates, and other essential stakeholders. To raise awareness about the event, OTAT employed various promotional strategies. An outreach email was sent to a wide range of stakeholder groups, and an officewide email was circulated among OTAT colleagues, resulting in word of mouth being the leading referral source for the event. Additionally, OTAT leveraged social media platforms to publicize the event, using graphics and messages on CBER's Twitter account, which were shared by other FDA offices (Figure 1). The primary FDA LinkedIn account also promoted the listening meeting, leading to increased traffic from social media channels.

The event focused on four key topics:

1. Patient and caregiver understanding and expectations of gene therapy risks and benefits
2. Patient and caregiver involvement in clinical study design and execution
3. Current tools and methods to capture patient experience data and any existing challenges or gaps to capturing patient experience data
4. Approaches to leveraging existing tools or opportunities for unique tools to capture patient experience data in gene therapy studies

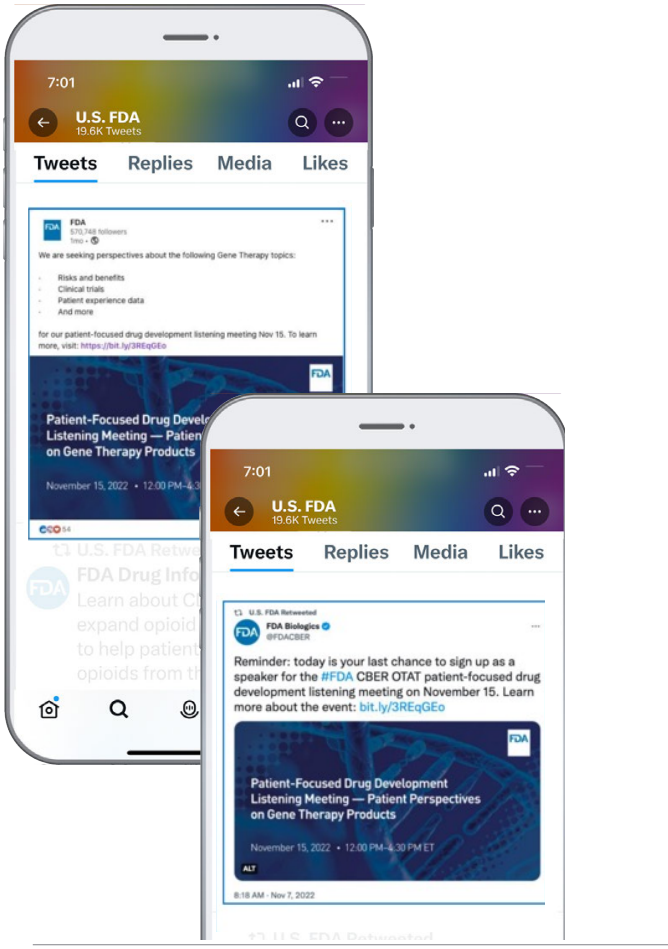
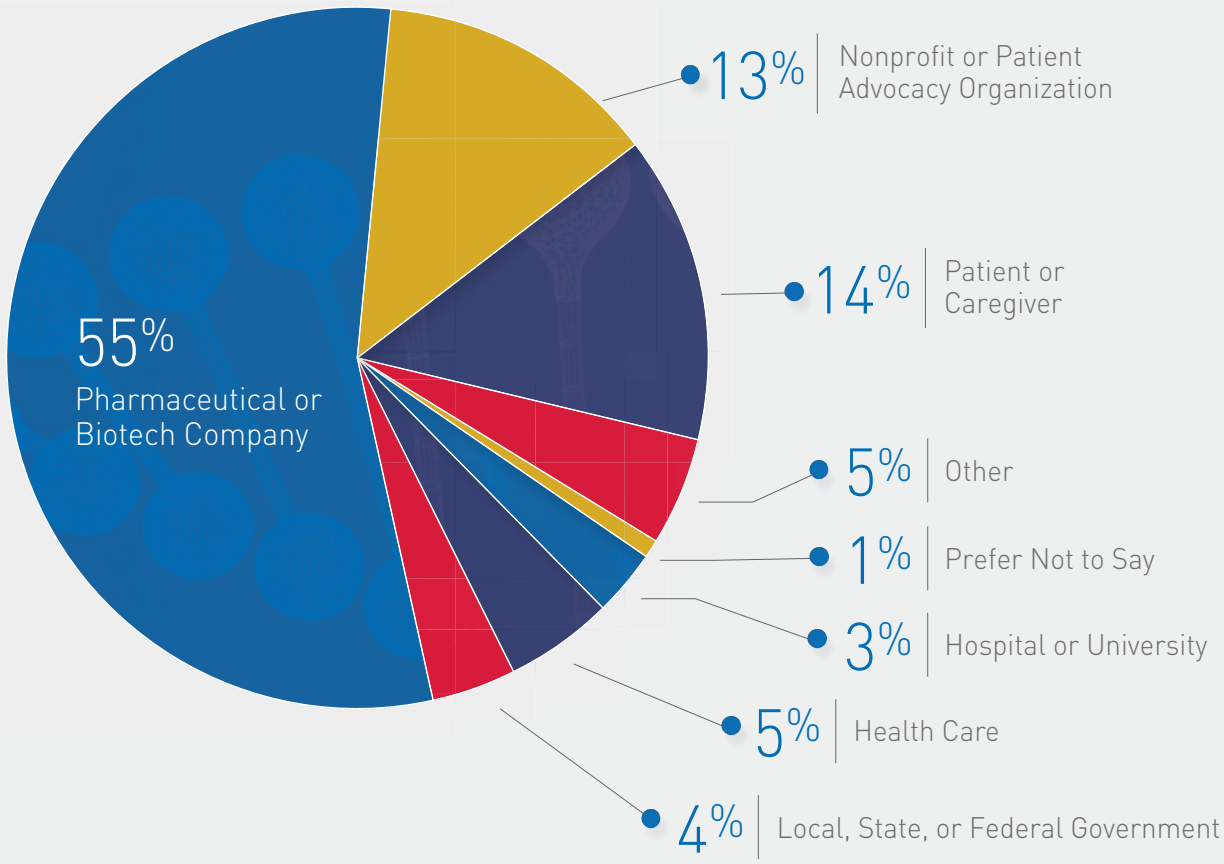


Figure 1. FDA Social Media Posts Promoting Workshop

[8] CBER. CBER Patient Engagement Program. Updated March 16, 2023. Accessed April 20, 2023. https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/center-biologics-evaluation-and-research-patient-engagement-program.

Figure 2. Registration Breakdown



The number of **attendees totaled 816**, representing a **61% attendance rate**. The number of registrants and the attendance rate exceeded prior RegenMedEd patient-focused events hosted by OTAT, which had an average of more than 503 registrants and a 60% attendance rate.

Forty-six patients, caregivers, and advocates expressed interest in speaking at the event. Each session featured a diverse range of participants, underscoring the enthusiasm of patients and advocates to engage directly with the FDA and their peers. More than 1,300 people registered for the event, with 55% affiliated with the industry and 27% identifying as patients, caregivers, or members of patient advocacy organizations or nonprofits. Figure 2 represents a breakdown of registrant affiliations.

For each topic, patient, caregiver, patient advocate, and other stakeholder speakers (Appendix 2) presented their perspectives during topic-specific sessions. Each session ended with an opportunity for a panel of OTAT subject matter experts (Appendix 2) to ask the speakers clarifying questions. To supplement the input gathered at the meeting, stakeholders were encouraged to submit comments on the topics to a public docket, which was open until December 15, 2022. Twenty comments were submitted to the public docket, including perspectives from patients, caregivers, and advocacy groups (Appendix 1).

SESSION 1

Patient and Caregiver Understanding of Gene Therapy Risks and Benefits

Gene therapy carries tremendous potential for transforming the treatment landscape for a variety of serious diseases. However, it is essential for patients and caregivers to understand the associated risks and benefits to make well-informed health care decisions. One of the primary risks is the possibility of adverse reactions or side effects, which can range from mild to life-threatening or fatal. Despite the risks, gene therapy has the potential to greatly benefit patients, especially those with genetic disorders lacking effective treatments.

Stakeholder Perspectives on Understanding Gene Therapy Risks and Benefits

Seventeen speakers (Appendix 2) provided comments in this session:

- The president of Project Alive, an organization dedicated to raising awareness about Hunter syndrome, spoke on the potential benefits of gene therapy as a treatment for this rare genetic disorder. **She emphasized the need to understand the community's knowledge and willingness to participate in gene therapy clinical trials**.
- The Chief Science Officer of the Foundation for Angelman Syndrome Therapeutics (FAST) and mother of an affected child discussed the attitudes toward gene therapy for Angelman syndrome (AS). **She highlighted the need for more education on risks and benefits and the trust the AS community** has in patient advocacy groups.
- A cofounder of the Gaucher Community Alliance and executive board member of the International Gaucher Alliance (IGA) discussed how IGA conducted focus groups in 2021 and an international survey in 2022 to **gather community input for developing educational programs about gene therapy**.
- A man with severe hemophilia who underwent gene therapy shared his experience, detailing what his life was like both before and after treatment. He stressed the significance of education and **suggested that clinical trial organizations provide support materials to help patients understand the treatment process**.
- A mother of two young adults who live with Duchenne muscular dystrophy (DMD) detailed her experience caring for them over the past two decades. She **highlighted the importance of early access to innovative therapies to stabilize disease progression and produce a higher patient benefit**.

- The Scientific Director for the Dravet Syndrome Foundation (DSF) discussed the externally led PFDD[9] meeting that DSF held to hear from the community regarding disease burden, current treatments, and future treatments, emphasizing that **98% of caregivers were interested in gene therapy**.
- A man with two sons who have DMD spoke about his experience trying to enroll them in clinical trials, saying that some of the FDA requirements for pediatric involvement in these clinical trials had made it difficult. He **suggested that the FDA expand the inclusion criteria for these pediatric clinical trials**.
- A patient and PhD candidate with Friedreich's ataxia (FA), now unable to walk without a walker, **spoke about her experience with the disease**. She expressed a desire for gene therapy treatment but disagreed with the FDA's guidance on gene therapy treatments that call for a unilateral neuronal injection, emphasizing that not all areas of the brain function bilaterally.
- The founder of Teach RARE, father to a daughter with aromatic L-amino acid decarboxylase (AADC) deficiency, an ultra-rare disorder, spoke about his and his wife's experience caring for their daughter both before and after gene therapy. He **emphasized the importance of early intervention for rare genetic disorders**.
- The president and CEO of the Shwachman-Diamond Syndrome Alliance, and mother of a child with Shwachman-Diamond syndrome (SDS), a disease characterized by a very high risk of developing leukemia, spoke about her experience caring for her child. She emphasized that **SDS is a great candidate for gene therapy**, with the bone marrow as a primary target.
- A patient with mucopolysaccharidoses (MPS) and member of the National MPS Society spoke about her lifelong experience with the disease, mentioning that she has received nine surgeries to manage bone and joint pain. She said that **gene therapy holds great promise and may be the only modality that could treat the underlying cause of the disease**.
- A man with hemophilia spoke about his and his family's experience, emphasizing who he is as a person outside of his condition. He said that **gene therapy changed his life but that everyone's experience with risk and involvement in clinical trials is personal and differs from person to person**.
- A man with hemophilia who volunteers with the Hemophilia Foundation of America spoke about his experience with the disorder, having **elected not to receive the gene therapy offered to him**. He detailed what factors caused him to make that decision, primarily the lack of long-term safety and efficacy data.
- A scientist with the Jain Foundation living with limb-girdle muscular dystrophy (LGMD) R2 spoke about how **gene therapy is the only treatment modality that could treat the underlying cause of the disease rather than the symptoms**. He emphasized the need to make gene therapy available for as many diseases as possible as soon as possible and encouraged the FDA to partner with other federal agencies and advocacy organizations to make this a reality.

[9] FDA User Fee Programs. Externally-led Patient-Focused Drug Development Meetings. Updated July 29, 2023. Accessed April 20, 2022. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings.

To help patients and caregivers become fully informed and make sound personal health care decisions regarding gene therapy products, it is essential to increase awareness and understanding of the technology among patients and their families.

- The founder of SCID Angels For Life Foundation, mother to two children with severe combined immune deficiency (SCID), a disease characterized by a malfunctioning immune system at birth, **spoke about her difficult experience in getting diagnoses and treatment for her children**; one passed away as an infant, while the other has been able to receive lifesaving care.
- A man who has received gene therapy for the treatment of hemophilia B spoke about his lived experience both before and after treatment, saying that it changed his life significantly. He **emphasized that there is a risk of the unknown when receiving these treatments and that the patients have to be the ones to ask the questions**.
- A mother of four children, two of whom suffer from CLN2 Batten disease, discussed the devastating effects of this always fatal neurodegenerative disease. She acknowledged gene therapy's risks and potential challenges but stressed that the **greatest risk is the risk of doing nothing.**

Following the public presentations, OTAT panelists (Appendix 2) asked the participants about the challenges they faced in finding information about gene therapy and whether the FDA could create reading materials to help patients garner more information in the future. The speakers highlighted various issues, such as a lack of education, fear of the unknown, equity problems, language barriers, and a gap in knowledge among clinicians. Some of the patients' care occurs in the hospital setting, where urgent medical situations take priority, leaving little room for education. Additionally, some patients cannot access information because of their location, education level, or socioeconomic status, and therefore, using tools such as visual aids could make the information more accessible. The speakers suggested that advocacy groups could play a significant role in providing information as trusted neutral parties and that FDA educational videos, workshops, and conferences posted on YouTube are a good source of easy-to-follow and understandable information.

Stakeholder Perspectives on Understanding Gene Therapy Risks and Benefits

Session 1 of the meeting and comments received from the docket provided insights into public views on comprehending the risks and benefits of gene therapy. The perspectives presented on these topics are summarized below.

Increasing Awareness and Understanding of the Technology

To help patients and caregivers become fully informed and make sound personal health care decisions regarding gene therapy products, it is essential to increase awareness and understanding of the technology among patients and their families. One way to achieve this is

through educational initiatives that aim to provide a clear and accurate understanding of basic gene therapy information, how the products work, and their potential risks and benefits. Educational initiatives can take various forms, including online resources, workshops, seminars, and patient support groups.

Several participants emphasized the importance of obtaining reliable education on the risks and benefits of gene therapy from neutral advocates they trust. Educational efforts should address the importance of quality of life (QoL) and the perception of risks when designing clinical trials. There is urgency to identify better measures to establish a better QoL and increase the willingness to participate in clinical trials. A comprehensive understanding of the benefits and risks of gene therapies compared with traditional therapies is vital for informed decision making.

Increasing Awareness and Understanding of Clinical Trials

Clinical trial participation is critical to advancing the field of gene therapy and bringing effective treatments to patients. However, participation in clinical trials can be challenging, particularly for patients with rare genetic disorders. Many patients may be hesitant to participate because of concerns about safety, the unknown long-term effects of the treatment, or fear of participating in clinical trials with sham or placebo controls.

To increase participation in gene therapy clinical trials, it is vital to engage with patient advocacy groups and other patient-focused organizations. These groups can help raise awareness about clinical trials and the importance of participation and provide support and resources to patients and their families throughout the process.

Assessing Attitudes Concerning Risks and Benefits

Advocacy organizations representing a wide range of therapeutic areas have conducted research assessing attitudes concerning risks and benefits of gene therapy products. Focus groups, surveys, and PFDD listening sessions conducted to assess community attitudes and understanding of gene therapy have delved into patients' experiences with decision making concerning risks and benefits, as well as life post-gene therapy. Patients and caregivers are willing to accept considerable risk and uncertainty for a therapy that slows disease progression. Caregivers' concerns revolved around the method of administration, the permanence of treatment, and the effectiveness of alleviating symptoms. Once a gene therapy is approved, patients and caregivers are generally highly willing to undergo treatment, believing that the most significant risk lies in inaction.

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SESSION 2

Patient and Caregiver Involvement in Clinical Study Design and Execution

High-quality research focusing on the perspectives and experiences of patients and caregivers is essential for meaningful incorporation of patient preference information into the design of clinical studies for gene therapy products. Clinical trials designed with patient perspectives in mind may facilitate patient enrollment and minimize the burden of participation in clinical trials.[6]

To start the session, 13 presenters (Appendix 2) provided comments:

- A mother of a daughter with CLN2 Batten disease discussed the need for **more patient involvement in clinical trial design and execution, emphasizing the importance of collaboration between scientists, drug development teams, and families to identify meaningful endpoints and assessments**. Enhanced incorporation of the patient's voice in drug development can ensure faster approvals while measuring safety for rare diseases.
- A representative of the community supporting aspartylglucosaminuria, an ultra-rare neurodevelopmental disorder, **highlighted that lack of funding and commercial interest in ultra-rare diseases** has made it difficult for patients to access gene therapy. She shared her experience founding the Rare Trait Hope Fund and raising money for the pre-IND (investigational new drug) stage of drug development.
- The founder of The Speak Foundation spoke on the gene therapy development challenges with potential products for LGMD, including patient recruitment and variability within subtypes. She discussed **proposed solutions such as natural history studies as external controls for trials, surrogate endpoints and biomarkers, incorporation of patient-reported outcome (PRO) measures, and more platform approaches for subtypes**.
- The mother of two children with SLC13A5 citrate transporter disorder shared her family's journey with an ultra-rare disease. She founded the TESS Research Foundation for SLC13A5 Epilepsy to fund the preclinical development of gene therapy treatments. She **stressed that patients and caregivers are the experts in the disease, and their input is critical in clinical trial design and execution**.
- A father of a daughter with WOREE (WWOX-related epileptic encephalopathy) syndrome, who is founder and president of the WWOX Foundation, spoke on the challenges faced by ultra-rare disease patients and their families. He expressed concern regarding the appropriateness of traditional clinical trial models for novel interventions such as gene therapy and **worried about the potential requirement for placebo and sham arms in study design, robbing participants (in this case, children) of their only chance**.

- The mother of a son with CLN2 Batten disease who is founder of the Juju and Friends CLN2 Warrior Foundation stressed the importance of patient and public education to raise awareness about the risks and benefits of cell and gene therapies. The **primary goal of patient involvement should focus on meeting the priorities, preferences, and needs of those affected the most, but patient involvement in clinical trials often occurs too late in the research process**.
- The mother of a son with LGMD who volunteers with the LGMD2D Foundation and The Speak Foundation expressed the eagerness of the community to learn more about gene therapy, the potential side effects, and the risks. The community **supports a safe yet faster process to make gene therapy treatment available to patients to help slow down or stop disease progression.**
- The mother of a son with Edwards syndrome (trisomy 18), who is also the CEO and president of The E.WE Foundation, **emphasized the need for patient participation in the research process at an early stage**. By having patient partners in clinical study design and execution, the clinical development process can transform from one directed by sponsors and investigators to one driven by the needs of patients and their caregivers.
- A patient with LGMD 2D shared his experience as the first person globally to receive an investigational gene therapy for any muscular dystrophy. He **emphasized the need for quicker approval of gene therapy treatments** by discussing the tremendous impact of the disease on his family, including the death of two sisters. There is an urgency to find a cure for 2D, and he called for companies to prioritize research in rare diseases such as 2D.
- A patient with DMD discussed his experience as a rare disease advocate and highlighted the importance of including the entire patient population in clinical trials. He pointed out that **trials for progressive diseases often exclude patients further along in disease progression**. To overcome the travel difficulties of patients with complex needs, he suggested having multiple trial locations, local lab options, and travel assistance programs.
- The parents of two children with FA shared their concerns about clinical trial design and execution for gene therapy trials. They **emphasized the importance of including children in research and advocated for their involvement in the design and execution of clinical trials**. They urged the FDA to consider the power of natural history studies over sham surgery as a control method.
- The director of SCID Angels for Life Foundation discussed the urgent need for better treatments for SCID, also known as "bubble boy disease." She **expressed the need for financial incentives to support orphan drug status for new cellular therapies and fast-tracking successful treatments so that patients with rare diseases** such as SCID are not left behind.

After the speaker presentations, the OTAT panelists asked participants about their perspectives on patient and clinical experiences, as well as barriers to participating in gene therapy clinical trials. One of the speakers mentioned that the placebo-controlled trial design for ultra-rare diseases, especially in LGMD, is a huge impediment for any rare disease. Another participant raised concerns about the financial viability of studies, stating that the traditional method is not working for gene therapy and cellular therapies. One speaker emphasized the lack of available gene therapy trials for her son to participate in and the need for more innovative trial designs. Another participant highlighted the need to weigh the benefit to a single system, where the biggest barrier to entry is the follow-up period in progressive diseases that may preclude participation in other clinical trials.

Stakeholder Perspectives on Involvement in Clinical Study Design and Execution

Perspectives on patient and caregiver involvement in the design and execution of clinical trials were collected during the second session and from docket comments. The following summarizes public views on these topics.

An Earlier, Collaborative Approach

Early inclusion of patients as partners in the research process can significantly contribute to the design of clinical trials that address their unmet needs and objectives. Patient involvement in clinical trials should be earlier in the research cycle to avoid conducting clinical studies that only prioritize objectives and clinically relevant problems. Primary goals should instead focus on addressing the priorities, preferences, and needs of individuals at risk or whose quality of life has been negatively affected by symptoms or treatment burdens.

Effective gene therapy development requires a collaborative approach, engaging patients, patient advocates, researchers, clinicians, and regulatory and industry partners. With adequate support, both the general public and patients could become aware of these therapies, understand the complexities involved, and actively participate in discussions. Patients and caregivers at the listening meeting highlighted the importance of their involvement in gene therapy development through advocacy with biotech companies and staying informed during the FDA review process. Participants discussed challenges in drug development, such as patient recruitment for clinical trials involving ultra-rare diseases and meeting specific inclusion criteria. They also suggested that the agency consider regulatory flexibility to facilitate earlier treatment access.

Trial Design Considerations

For rapidly progressing diseases with a 5-year trajectory, reevaluating the required follow-up period for children treated with gene therapies and the exclusion from future trials once a gene therapy is received is vital, particularly in the context of rare degenerative diseases. Trial design should encompass multiple outcome measures and endpoints, including those related to QoL. Furthermore, trial design should incorporate therapies that enhance life skills and milestones.

Another concern is the use of sham and placebo controls in clinical trial design. A sham control involves mimicking a procedure, such as surgery or injection, without administering the treatment being tested. A placebo control involves administering an inactive substance, such as a saline injection or sugar pill, instead of the treatment being tested. Both sham and placebo controls are used to create a comparison group that receives no therapy to measure treatment effectiveness. The use of such controls in clinical trials raises ethical, scientific, and practical factors that should be considered.

Effective gene therapy development requires a collaborative approach, engaging patients, patient advocates, researchers, clinicians, and regulatory and industry partners.

SESSION 3

Current Tools or Methods to Capture Patient Experience Data and Any Existing Challenges or Gaps to Capturing Patient Experience Data

Patient experience data is a critical input in developing and evaluating new gene therapies, ensuring that a patient's needs and preferences are considered throughout the process. In this session, participants discussed the existing toolkit and resources for capturing patient experience data and highlighted gaps in data collection, emphasizing the need for a more comprehensive understanding of patient experiences.

The 21st Century Cures Act[7] expands previous work to support collection of patient experience data by various individuals and organizations, including patients, family members and caregivers, patient advocacy groups, disease research foundations, researchers, and drug manufacturers. The aim of collecting such data is to gain insight into the impact of a disease or therapy on patients' lives, as well as their preferences for treatment options. During the meeting, the FDA sought to understand how participants utilize these tools and the challenges they face in doing so, with the goal of identifying any gaps that need to be addressed.

Three presenters (Appendix 2) provided comments for this session:

- A mother of a daughter with CLN2 Batten disease discussed the challenges of capturing patient experience data within a small community. She **called for families to partner with researchers, industry, and the FDA** to address these challenges **and funnel patient experience data into the evaluation of gene therapy products and the design of clinical trials**.
- A gynecologic oncologist, who is also a patient and a relative of a patient with cancer, shared her interest in the future of gene therapy. As a researcher, she discussed the difficulties in recruiting patients for gene therapy studies, especially for people with devastating diseases in advanced stages. She **called for the FDA to provide guidance on best practice strategies and future visions for postmarketing surveillance and research capturing systems**.
- A mother of a child with SYNGAP1, and President/CEO of the SYNGAP1 Foundation, highlighted that patients with autism and sensory issues might struggle to participate in needed measures, which could affect data collection. She **emphasized the importance of engaging patients in learning more about gene therapy and providing data for natural history studies**.

During the panelist question period, the participants were asked about their experiences in searching for information on gene therapy and the challenges they encountered in understanding it. The issue of equity was raised, with differing levels of education and language barriers being mentioned as significant obstacles.

Participants highlighted that even a basic understanding of genetics and gene therapy is difficult to comprehend, and the fear of side effects and the unknowns of gene therapy also pose a challenge. While natural history studies and epidemiology were recognized as crucial, participants acknowledged the difficulty in communicating these concepts to the general population. Participants also communicated during the Q&A discussion that clinicians can lack knowledge of gene therapy, which creates a gap in communication with patients. Finally, advocacy groups were recognized as a valuable resource for providing information as a neutral party. One participant suggested the development of educational materials, such as the videos posted by the FDA on YouTube, as an effective way to communicate information.

Stakeholder Perspectives on Current Patient Experience Data Capturing Tools or Methods and Any Existing Challenges or Gaps to Capturing Patient Experience Data

Session 3 speakers as well as submissions to the docket presented perspectives on the tools for collecting patient experience data and their associated challenges, offering valuable insights on identifying gaps and addressing them. The views presented on these topics are summarized below.

Tools or Methods for Collecting Patient Experience Data

Current tools and methods for capturing patient experience data encompass a variety of approaches. A natural history study collects information about the natural history of a disease in the absence of an intervention, from the disease's onset until either its resolution or the individual's death. Although knowledge of a disease's natural history can benefit drug development for many disorders and conditions, natural history information is usually not available or is incomplete for most rare diseases; therefore, natural history information is particularly needed for these diseases.[10] Participants in the meeting suggested adopting natural history studies as external trial controls and utilizing more innovative designs for ultra-rare diseases.

Another essential method for capturing patient experience data is using PRO measures. These questionnaires and other tools, completed by

Although knowledge of a disease's natural history can benefit drug development for many disorders and conditions, natural history information is not usually available or is incomplete for most rare diseases; therefore, natural history information is particularly needed for these diseases.

[10] FDA. Rare Diseases: Natural History Studies for Drug Development. Draft Guidance for Industry. Published March 2019. Accessed April 20, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development.

patients, assess their health, quality of life, and/or functional status, providing insights into patients' perspectives on treatment effectiveness, symptom severity, and daily life impact. Participants suggested incorporating more PROs emphasizing vital aspects, such as breathing issues, an outcome measure that patients sometimes feel is overlooked.

Qualitative research methods, such as in-depth interviews, focus groups, QoL assessments, and narrative techniques, offer rich information on patients' experiences, perceptions, and values. These methods allow patients to share their perspectives on their disease and treatment options in their own words and provide a more detailed understanding of their experiences. Qualitative research can potentially uncover nuances and complexities that might be missed in quantitative assessments, providing a more comprehensive understanding of patient experiences and improving patient-centered care.

Challenges or Gaps With Capturing Patient Experience Data

Despite these tools and methods, several challenges and gaps in capturing patient experience data persist. One speaker discussed the challenges of capturing patient experience data in small, resource-limited populations like parents of children with CLN2 Batten disease. The primary data sources (e.g., doctors, other parents of children with CLN2 disease, biotechnology company surveys) are often privileged and not transparently shared. Gaps in data meaningful to gene therapy trials exist, and the challenges include a disconnect between frontline care and drug development and inequity in resources. Families can partner with researchers, industry, and the FDA to overcome these hurdles in collecting patient experience data. Addressing these challenges and gaps will enable more effective capture and use of patient experience data, ultimately leading to more informed decisions and the development of therapies that better address patients' needs and preferences.

Gaps in data meaningful to gene therapy trials exist, and the challenges include a disconnect between frontline care and drug development and inequity in resources.

SESSION 4

Approaches to Leveraging Existing Tools or Opportunities for Unique Tools to Capture Patient Experience Data in Gene Therapy Studies

Effectively capturing patient experience data in gene therapy studies is essential for developing therapies that address patients' needs and preferences. During Session 4, presenters expressed their views on implementing approaches to better collect patient experience data in gene therapy research.

Five presenters (Appendix 2) provided comments to begin the session:

- The chief advocacy officer from Parent Project Muscular Dystrophy (PPMD), an advocacy organization for DMD, discussed unique tools and approaches for applying patient experience data. As an example, he **presented results from a study on maximum acceptable risk tolerable to adults with DMD and caregivers for non-curative, time-limited gene therapy, demonstrating a willingness by most to accept risk**.
- The CEO of the Friedreich's Ataxia Research Alliance (FARA) **emphasized the need to reduce the gap between non-interventional data and adaptive trial designs**. She discussed FARA's 20-year prospective longitudinal non-interventional observational trial and stressed that such natural history data could supplement control or comparator arms, using novel methods such as Bayesian methods to borrow historical data.
- The CEO of the EveryLife Foundation for Rare Diseases, which works to advance the equitable development of and access to lifesaving diagnoses, treatments, and cures, **discussed the importance of patient experience data in rare disease therapy development**. She suggested that the FDA lay out clear actions to help reconcile the different approaches between Center for Drug Evaluation and Research (CDER) and CBER to help standardize the agency's rare disease guidance, PFDD meetings, and review activities.
- A patient with severe hemophilia who received gene therapy shared his personal experience with gene therapy and **stressed the importance of considering the whole patient when evaluating gene therapy benefits**. He urged researchers to capture patient experience data in gene therapy trials as the impact of gene therapy on his life went beyond the data.
- A mother of two daughters with CLN2 Batten disease who is a career registered nurse shared her perspective on patient experience data during gene therapy studies. She expressed gratitude for the detailed review process and urged researchers and clinicians to closely partner with the community. She **emphasized that time is of the essence and called for simplified, standardized, and streamlined data collection processes**.

During the subsequent engagement by FDA panelists, the speakers were asked about patient perspectives on gene therapy development and clinical trial participation during Session 4. The discussion included consideration of tools to understand patient tolerance for risk and acceptable levels of risk weighed with gene therapy benefits. The use of stated preference methods was suggested, along with the importance of utilizing patient preference information to better understand the community's preferences. The discussion also included gene therapy misconceptions, such as the expectation that the therapies will be curative. Ongoing education for patients and physicians was suggested as a way to address such misconceptions. The participants commended advocacy groups for their efforts in patient education and their sacrifices to move therapies forward.

Stakeholder Perspectives on Leveraging Existing Tools or Discovering Opportunities for Unique Tools to Capture Patient Experience Data in Gene Therapy Studies

Insights on leveraging existing patient experience data capturing tools and uncovering opportunities for unique tools to capture data were gathered during the fourth session and from docket comments. The following summarizes public perspectives on these topics.

The following data collection tools to better understand patient risk tolerance and uncover misconceptions to develop better educational methods were discussed:

- **Threshold technique:** This approach helps determine the maximum acceptable risk for adults with DMD and caregivers for a non-curative, time-limited gene therapy. By understanding patients' and caregivers' risk tolerance, researchers can better tailor therapies and inform policy solutions that reflect unmet needs and urgency.
- **Utilizing existing tools:** Researchers can utilize existing databases and clinical endpoints, including biomarkers, clinical manifestations, and narrow endpoints, to gather patient experience data and inform the development of gene therapies.
- **Unique tools on the horizon:** The advent of artificial intelligence and other emerging technologies presents new opportunities for capturing patient experience data in innovative ways, enhancing the overall understanding of patient needs and preferences.

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Conclusions

The virtual PFDD listening meeting organized by CBER provided valuable insights into the perspectives of patients, caregivers, and other stakeholders on gene therapy products. It facilitated a comprehensive discussion on understanding gene therapy risks and benefits, patient and caregiver involvement in clinical study design and execution, challenges and gaps in capturing patient experience data, and approaches to leveraging existing tools while looking for opportunities for unique tools in gene therapy studies. The FDA and other stakeholders can continue to advance patient-centered research and increase efficiency in the development and evaluation of gene therapies that genuinely address patients' needs and preferences by building on the insights gained from this meeting.

Appendix 1: Docket Comments

To supplement the input gathered at the listening meeting, stakeholders were encouraged to submit comments to Docket FDA-2022-N-2394, which was open from October 3, 2022, to December 15, 2022. The comments are summarized below:

- A mom of a woman with the ultra-rare genetic condition of aromatic L-amino acid decarboxylase (AADC) deficiency. Diagnosed in 1995, her daughter was the fourth child to ever be diagnosed. She founded the AADC Family Network to provide support and resources to other families caring for loved ones with AADC. She calls for the FDA's support, guidance, and flexibility throughout the orphan drug regulatory process as the AADC Family Network partners with biotech companies to develop potential therapies for the condition.
- Submitted by the EveryLife Foundation for Rare Diseases, which advocates for impactful, science-driven legislation and policy that advances equitable development and access to lifesaving diagnoses, treatments, and cures. They note that the FDA and Congress have recognized a need for nuanced approaches, given the unique nature of genetic conditions, and that the FDA has demonstrated commitment to patient-oriented translational science. They also mentioned that the PDUFA VII commitment did not mention specifics on addressing the need and that there appears to be a discordance between how CDER and CBER approach therapeutic development, suggesting the creation of a center that focuses solely on rare diseases.
- A mom of two kids with metachromatic leukodystrophy (MLD), one of whom was able to receive gene therapy treatment and one of whom is in hospice care. She wishes that the disease were caught earlier in her oldest daughter so both of them could live longer lives, suggesting that MLD be added to the newborn screening panel.
- A mom of a child with AADC who was enrolled in gene therapy at 18 months old with excellent results, and a member of the advocacy organization Teach RARE. Since AADC is a rare disease, it is difficult to gain attention for research and funding, but she hopes the FDA will take action; gene therapy for AADC is approved in the European Union and the United Kingdom but not yet in the United States.
- A mom of a son diagnosed with CLN2 Batten disease, which took a year and a half to diagnose. She stresses that there are no FDA-approved therapies for 95% of all rare diseases and urges the FDA to establish a Rare Disease Center of Excellence to fund regulatory science and support development of therapies for rare diseases. This would be a response to the Speeding Therapy Access Today (STAT) Act of 2021.
- Submitted by the Friedreich's Ataxia Research Alliance (FARA). The FA community wants to participate in clinical trials for gene therapy but is concerned that participation in a gene therapy trial would interfere with participation in future trials. They have concerns with the FDA's guidance on gene therapy, as well as the use of sham (placebo) surgeries in trials. They suggest the use of natural history and non-interventional data, as well as reducing the number of participants, time, and resources needed to conduct trials.
- A patient with X-linked hypophosphatemia, a nonfatal, progressive, lifelong disease that significantly reduces quality of life, stresses that quality of life matters in the risk-benefit assessment, in addition to fatality, and that quality of life should be looked at over the whole lifespan, not just at the time of diagnosis. He makes two suggestions: one, that FDA require sponsors to certify in the product applications that they have had conversations with the patient community, and two, to change

the rule that patient advocates cannot attend sponsor meetings with the FDA unless the sponsor itself invites patient advocates.

- Submitted by the Jain Foundation, an advocacy organization for limb girdle muscular dystrophies (LGMD), for which there are currently no available treatments. They stress that patients are willing to assume risk and that the FDA should rely on surrogate endpoints, natural history studies, and external controls in lieu of placebos and apply its accelerated approval pathway for gene therapies for LGMD. They also stress the importance of better education and guidance for those suffering with LGMD and their caregivers.
- Submitted by the Alliance for Regenerative Medicine (ARM), a leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM requests that the FDA to hold a public forum after publication of the report for this workshop, addressing specifics with how patient experience data is being used in product reviews.
- Submitted by the National Organization for Rare Disorders (NORD), which has created educational resources to help patients, families, health care providers, and the public learn about gene therapy. They would like to partner with the FDA to expand these resources.
- Mom of a daughter with WOREE syndrome and founder and president of the WWOX Foundation (Australia). She has some concerns with current clinical development programs for gene therapies, imploring the FDA to "make the journey to a clinical trial as frictionless, fair, and quick as possible."
- Submitted by the Cystic Fibrosis Foundation. They suggest the FDA work with patients and patient advocates to identify and draft materials and language suggestions that are geared more toward the public, as most materials are geared toward industry and regulatory professionals at this time. They suggest the FDA incorporate PFDD provisions proposed in the Cures 2.0 Act to require sponsors to collect patient experience data during clinical trials and FDA to consider those data in regulatory decision making.
- Two poster presentations were submitted by the FamilieSCN2A Foundation. One was titled "More than Seizures: Expressive Communication as a Clinical Trial Outcome for SCN2A-Developmental and Epileptic Encephalopathie" and showed that improved communication in patients was a critically important goal for improvement and should be considered as an endpoint in clinical trials. The other was entitled "Phenotypic Heterogeneity in SCN2A-Developmental & Epileptic Encephalopathy: A Function of Function," hypothesizing that different genetic variants are associated with different forms of epilepsy or autism spectrum disorder. The results indicated the NaV1.2 protein for future trials.
- Submitted by Parent Project Muscular Dystrophy, which fights to end DMD. They stress the need for more patient experience data and encourage CBER to consider incorporating it into product labeling. They also urge CBER to develop a guidance related to developing gene therapies in DMD.
- Submitted by FasterCures, Milken Institute, an organization whose goal is to save lives by speeding up scientific advancement. They point out that the misinformation regarding COVID-19 indicated that there is a public fear of gene therapy (i.e., misinformation about the vaccine modifying genetics) and suggest that the FDA make credible information about gene therapies easier for the public to find. They implore the FDA to identify and work toward filling areas where current educational resources do not match the need for information, including in provider education, as they claim that medical school curriculum is lagging behind innovation.

- Submitted by the International Foundation for CDKL5 Research (IFCR), an organization run by caretakers and patients with CDKL5 deficiency disorder (CDD), one of the few orphan diseases to have an FDA-approved therapy. They state that risk tolerance and the definition of "meaningful change" for patients depend on age and disease severity and that any improvements in developmental milestones would be impactful.
- Submitted by Pharmaceutical Research and Manufacturers of America (PhRMA), which provides potential treatments for patients with unmet medical needs, as well as cost savings for patients and caregivers. They encourage the use of COA data, specifically PROs, to support development of cell and gene therapies, specifically in the domains of function and quality of life. They also stress that patient risk tolerance is not static and changes with age, disease progression, and treatment factors, as well as addressing COA in the pediatric population, as a lot of gene therapies are intended for children.

Appendix 2: Speakers and OTAT Panelists

Speakers

Session 1:

1. Kim Stephens, Project Alive
2. Allyson Berent, Foundation for Angelman Syndrome Therapeutics
3. Aviva Rosenberg, International Gaucher Alliance and Gaucher Community Alliance
4. James Rippy
5. Jennifer McNary
6. Veronica Hood, Dravet Syndrome Foundation
7. Tushar Tangsali
8. Shandra Trantham, Friedreich's Ataxia Research Alliance
9. Richard Poulin, Teach RARE
10. Eszter Hars, Shwachman-Diamond Syndrome Alliance
11. Jenny Kleine, National MPS Society
12. Robert Wiseman Jr.
13. William Hubbert, Hemophilia Foundation of America
14. Bradley Williams
15. Heather Smith
16. Ryan Hallock
17. Suzette James, CLN2 Batten Disease Community

Session 2:

1. Corrin Jackson, CLN2 Batten Disease Community
2. Julia Taravella, Rare Trait Hope Fund
3. Kathryn Bryant Knudson, The Speak Foundation
4. Kim Nye, TESS Research Foundation
5. Johann Mentz, WWOX Foundation
6. Cristina Rosa, Juju and Friends CLN2 Warrior Foundation
7. Rachel DeConti
8. Sarita Edwards, The E.WE Foundation
9. Donavon Decker
10. Colin Werth
11. Randy and Maureen Juip, Friedreich's Ataxia Research Alliance
12. Barb Ballard, SCID Angels for Life

Session 3:

1. Claudia Fennell, CLN2 Batten Disease Community
2. Ying Huang
3. Monica Dudley-Weldon

Session 4:

1. Ryan Fischer, Parent Project Muscular Dystrophy
2. Jennifer Farmer, Friedreich's Ataxia Research Alliance
3. Annie Kennedy, EveryLife Foundation for Rare Diseases
4. Andrew Wayne
5. Amanda Beedle, CLN2 Batten Disease Community

OTAT Panelists

1. Dr. Najat Bouchkouj, Medical Officer, Malignant Hematology Branch
2. Dr. Jasmine Gatti, Clinical Team Leader, General Medicine Branch 2
3. Dr. Elizabeth Hart, Branch Chief, General Medicine Branch 1
4. Dr. Yuxia Jia, Medical Officer, Oncology Branch
5. Dr. Larissa Lapteva, Associate Director, Division of Clinical Evaluation and Pharmacology/Toxicology