UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FDA CBER OTP Listening Meeting Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on Cell and Gene Therapy Products

April 27, 2023

Note: This document is not official FDA guidance.

Contents

Introduction

DR. VIJAY KUMAR: Hello, everyone; good afternoon. Thank you all for joining us for our public listening meeting on methods and approaches for capturing post-approval safety and efficacy data on cell and gene therapy products. Today's event is hosted by the Office of Therapeutic Products — or, as we usually say, OTP — within the Center for Biologics Evaluation (CBER) and Research at the Food and Drug Administration (FDA). My name is Dr. Vijay Kumar. I am a Medical Officer in the Division of General Medicine at OTP in CBER. I will also be your host for today's event.

I am pleased to welcome you all today as we hear from important stakeholders about various methods, approaches, logistics, privacy concerns, and other aspects related to efficacy and safety data collection in the post-approval setting for cell and gene therapies. As you all know, this is an important and exciting time in the gene and cell therapy space. With an increasing number of cell and gene therapy products in development and the potential for more of these products to become available to patients in the future, it is important to understand the full spectrum of long-term effects and collect accurate, timely, and comprehensive data to ensure these products remain safe, effective, and of high quality.

We know there is much to discuss here, and we recognize that today's meeting will likely generate additional ideas and comments; should this happen, we encourage you to submit your feedback to the public docket, which is available on Regulations.gov. The docket number is FDA-2023-N-0398 and will remain open until May 26, 2023.

We have a full agenda planned today. We will kick off today's meeting with opening remarks from Dr. Celia Witten, the Deputy Director of CBER and the Acting Director for OTP. We will then provide an overview of the meeting process and then move directly into the listening portion of the meeting. We will have four topics during today's meeting:

- Session 1: Alternative study designs, including decentralized studies
- Session 2: Development and establishment of product-based and/or disease-based registries
- Session 3: Real-world data (RWD) collected in clinical settings through digital health technologies (DHTs), electronic health records (EHRs), insurance claims databases, other administrative databases, and population-based data sources
- Session 4: Determination of specific safety or efficacy outcomes, such as development of malignancies, effects on fertility, or confirmation of benefits for which collection of post-approval safety or efficacy data may be necessary for cell or gene therapies

A quick note to our confirmed speakers: We will be providing you with access to your microphones and cameras during your session. Please stay tuned for more details in just a few minutes.

Before we get started, I would like to share a few notes. This event is being recorded. The recording will be posted on FDA's website in the next few weeks. We will also provide a transcript. Closed captioning for this event is available directly in Zoom. Lastly and as a reminder, please direct any comments related to the subject matter of today's meeting to the docket, and only use the chat box if you are experiencing technical difficulties. Once again, a note to those speaking at today's public listening meeting: We will be providing you access to your microphone and camera during your confirmed session and will be providing more details following today's opening remarks.

With that, I will turn it over to Dr. Witten. Dr. Witten, thank you so much for being here.

Opening Remarks

DR. CELIA WITTEN: Thank you, Dr. Kumar. Good afternoon, everyone. I'm Dr. Celia Witten, CBER's Deputy Director and Acting Director for the Office of Therapeutic Products.

As Dr. Kumar mentioned, our goal today is to discuss ways to collect accurate and comprehensive data about the long-term safety and effectiveness of these products after they have been approved and hear your perspective and concerns as key stakeholders in the cell and gene therapy space.

First, let's begin by talking about why today's topic is so important. The field of gene and cell therapy is evolving rapidly, with scientific discoveries opening new avenues to address difficult medical conditions that have few or no other available treatments, from rare inherited disorders to certain forms of cancer. There are more than 7,000 rare diseases affecting more than 30 million people just in the United States. Many of these rare diseases are life-threatening and have no effective treatments available. Although there is still much to learn and understand about rare diseases, we do know that about 80% of rare diseases are caused by single-gene defects, which gene therapy and, to some extent, cell therapy products are in a unique position to address. In fact, there are more than 2,000 investigational new drug applications for cell and gene therapies, demonstrating the fast-paced growth in these fields. Gene and cell therapy may transform our ability to provide care for patients living with difficult and often incurable medical conditions, and OTP is committed to facilitating the development of these innovative approaches to address significant unmet medical needs.

As new therapies are developed and approved, regulatory oversight is key to ensuring products are safe and effective. As many of you know, this is where OTP and FDA come in. FDA provides regulatory oversight for investigational therapies throughout the entire product lifecycle. That includes monitoring products after approval to assess their long-term safety and effectiveness, address any concerns that emerge, and potentially expand products used for new indications.

We work with sponsors of investigational products to provide input on all aspects of development, including chemistry, manufacturing, and controls; preclinical (animal) studies;

and clinical development — all of which are critical components of the drug development process. FDA's team of scientists and experts perform rigorous reviews of all available data to ensure that regulatory decisions are based on scientific evidence.

In addition, FDA aims to advance the state of the science by providing guidance and education to product developers and other stakeholders. We have more than 30 guidance documents on FDA.gov for gene and cell therapy product development; nearly half of them were developed in the last 5 years, further indicating the growth in these fields. And I'm pleased to share that today's meeting will help inform another guidance document focused on post-approval safety and efficacy data collection for gene and cell therapy products.

Finally, FDA recognizes that stakeholder and patient engagement are essential. We consistently and proactively communicate with patients, caregivers, and advocates to improve our understanding of patient needs, and we work with researchers and other product developers to support design of products that meet those needs.

What are the key characteristics of cell and gene therapies that set them apart from other medical products and make post-approval surveillance especially important? Unlike with small-molecule drugs, gene therapies often involve products and technologies for which there is comparatively little experience in terms of manufacturing, use, and monitoring. Administering gene therapies may involve invasive procedures — for example, using a catheter and MRI guidance to reach a particular region inside the brain. There are some possible added risks associated specifically with gene and cell therapies. In gene therapy, for example, the activity of the transgene may be difficult to control after it enters the recipient's cells, or it could cause a mutation in another gene, which might then be transmitted to the recipient's future children. Immune reactions are also common and could cause the body to reject a component of the product, such as the transplanted cells, a viral vector, or a transgenic protein.

Given their potential for long-lasting effects and the limited population that can be included in clinical trials, post-approval monitoring of cell and gene therapy products is especially important to ensure that they remain safe and effective over time. In some cases, approved products may require more extensive long-term surveillance to identify delayed adverse effects and verify the clinical benefit to patients. For example, FDA guidance for gene therapies utilizing integrating viral vectors calls for monitoring patients in the trial for 15 years.

In addition to clinical trial data, FDA also relies on real-world data and real-world evidence (RWE) to monitor and evaluate the safety of approved therapies, with the aim that this information will help advance the development of therapeutic products and strengthen regulatory oversight of medical products across their lifecycle. This data can be used to support a regulatory decision during the approval process, and it may also be used once a therapy is already approved to monitor the marketed therapy to satisfy drug post-approval study requirements.

While the terms *real-world data* and *real-world evidence* most likely are not new to you, I do want to take a moment to explain what they are and how these two concepts work together. Real-world data (RWD) refers to data relating to patient health status and the delivery of

health care. Examples of real-world data include data derived from electronic health records (EHRs), information in product and disease registries, medical insurance claims, patient-generated data, and data gathered from mobile devices and other digital health technologies (DHTs). Real-world evidence (RWE) is the clinical evidence derived from the analysis of real-world data about the usage and potential benefits or risks of a medical product or intervention. We at FDA have seen how real-world evidence can play a significant role in regulatory decision making when appropriate.

As you all know, the drug development process requires many more steps than what's included on this slide, and we recognize the process for gene and cell therapy product development is different based on the factors I mentioned previously. This is also true for post-marketing safety monitoring. After they are approved for use, therapeutic products are monitored for long-term effects and previously unknown side effects. Recipients of gene and cell therapy products are generally monitored for an extended period because of the potential for long-term risks associated with the products. Post-marketing surveillance is critical to help identify and understand any adverse effects that did not appear during the therapeutic development process. FDA uses this information to update drug labeling and, on rare occasions, to re-evaluate the approval or marketing decision. To deepen our understanding of the long-term risks and benefits of gene and cell therapy products, it's crucial that we capture precise, timely, and comprehensive data about the post-marketing safety and efficacy of these products.

This is exactly why we're here today. With more and more cell and gene therapies expecting to become available for patients, understanding the long-term effects of these products will be key to ensuring they remain safe and effective. We want to hear from you about potential opportunities and pitfalls to enhance data collection for cell and gene therapy products in post-approval settings. As Dr. Kumar mentioned, throughout the four sessions today, we hope you will share your perspectives on refining product and disease registries, expanding data collection in clinical settings, drawing on alternative study designs to fill information gaps, and identifying long-term clinical outcomes that could constitute valuable primary endpoints to assess safety and efficacy. The fields of cell and gene therapy have much to offer, and OTP believes that your insight as key stakeholders will be instrumental to help accelerate the development of these innovative approaches.

The final thing I want to share with you today is how to stay in touch with us. OTP provides educational resources and hosts workshops about topics related to cell and gene therapies, including the OTP town halls and our educational webinar series on regenerative medicine. For the latest information on past and upcoming events, please visit our website. You can also subscribe to our newsletter to receive email updates from us, and of course, you can follow us on Twitter.

Thank you all for being here today. I'd like to now turn it over to Dr. Kumar.

DR. KUMAR: Thanks so much, Dr. Witten. We will now move into the public comment portion of today's meeting. Before we hear from our first speaker, I will give a brief overview of the meeting process. During this event, all microphones for the general audience will be muted. Because this is a listening meeting, we will not have a Q&A portion for the audience,

but we do appreciate your comments and encourage you to go to the docket if you would like to share specific feedback on these topics.

Speakers, we greatly appreciate your interest in speaking at today's meeting. During each session, I will introduce each speaker so that you can begin your presentation. When it is your turn to speak, you will be notified and asked to unmute yourself. You are also welcome to turn your camera on if you would like to do so. Once your presentation is done, please go back on mute so we can move on to the next speaker.

For those of you who submitted slides, your slide presentations have been added to this master slide deck. When speaking, please let us know when to advance the slides and say, "Next slide." Before you begin your presentation, please state your name and your affiliation.

To ensure transparency at this listening meeting, we encourage you to advise the audience of any financial relationship you may have with any firm, group, company, or product at the start of your presentation. If you do not have a financial relationship as such, you can simply make a statement to that effect.

Please keep the time limit in mind when speaking. Each speaker will have 5 minutes, and the clock will start once you have introduced yourself. We will give you a 30-second notice before your time is up so that you can then wrap up your presentation. If you run out of time, we encourage you to submit the remaining comments to the docket.

Lastly, each session will end with an opportunity for FDA to ask clarifying questions. I would like to take a moment to introduce the subject matter experts from FDA who are serving on today's panel:

- Dr. Meghna Alimchandani, the Deputy Director for the Division of Pharmacovigilance at the Office of Biostatistics and Pharmacovigilance (OBPV) within CBER
- Dr. Najat Bouchkouj, Medical Officer with the Division of Clinical Evaluation Hematology at the Office of Therapeutic Products within CBER
- Dr. Larissa Lapteva, the Associate Director of the Division of Clinical Evaluation General Medicine at the Office of Therapeutic Products within CBER
- Dr. Lei Xu, the Branch Chief for the Office of Clinical Evaluation at the Office of Therapeutic Products within CBER
- Dr. Zhenzhen Xu, the Team Lead for the Office of Biostatistics and Pharmacovigilance within CBER
- Dr. Osman Yogurtcu from the Office of Biostatistics and Pharmacovigilance within CBER

Thank you to our panelists for your time today.

Session 1: Alternative study designs, including decentralized studies

DR. KUMAR: We will now begin with Session 1, and the topic for this first session is alternative study designs, including decentralized studies. We have two confirmed speakers for this session, and each speaker will have 5 minutes. We will give you a 30-second notice before your time is up so that you can then wrap up your presentation. For those speakers who have submitted slides, we will advance the slides on your behalf; please just say, "Next slide." All speakers in Session 1 should now have access to their microphones and cameras; if not, please use the chat function to alert us. I would like to remind our speakers to please stay online after you speak and for the duration of your session in the event that the FDA panelists have questions for you at that end of the session.

Our first speaker is Mindy Cameron.

MS. MINDY CAMERON: Hello, everyone. My name is Mindy Cameron, and as you can see here, I have participated in many clinical research studies over the past 15 years or so, both as a patient and as a caregiver for my son, who is now 22 years old. I also work as a consultant in the pharma and biotech industry, and I am a patient innovator for Metadata Solutions, a global leader in life science technologies, including decentralized clinical trials, or DCTs. Thanks for this opportunity to discuss why decentralized and hybrid clinical trials must play a critical role in the long-term post-approval assessment of the efficacy and safety of gene and cell therapies.

Gene therapies are absolutely changing the course of devastating progressive and degenerative genetic diseases like the one that affects my own family, Duchenne muscular dystrophy (DMD). In addition to far healthier and longer lives, one of the most compelling aspects of gene therapy in DMD and other complex neuromuscular and neurological disorders is that patients may very well be freed from many of the lifestyle constraints that come with a condition that requires chronic medical care. In fact, it's my hope that patients who receive these cell and gene therapies may very well be out living productive lives instead of spending a lot of their time getting frequent clinical care.

While the need to monitor these potentially transformative gene and cell therapies in the long term is absolutely necessary, to be successful, we'll need to bring the research to the participants rather than expecting the patients to come and participate. Research tools like decentralized clinical trials can enable scientists, companies, health care providers, patients, regulators, and payors to easily collect data to further study these therapies in patients in their real lives, doing everyday activities and potentially living far longer. A commitment to monitor these therapies will also ultimately improve health outcomes as well as drive the evolution of the entire field of gene and cell therapies.

This slide is just an overview of how DCT tools can bring various aspects of clinical research to the very most important stakeholder: the patient. As you know, the COVID-19 pandemic abruptly prevented many clinical research participants from going to research sites and did much to speed the progress and adoption of DCTs. This happened to such a degree that many of the topics listed on this slide are very widely implemented now.

Basically, a decentralized clinical trial means you are conducting either the entire study or parts of the study away from a traditional clinical site. You incorporate things like video visits, home health care visits, wearable technologies, sensors, and apps through your telephone to do some of your clinical assessments. Patients can be alerted to something they need to do on their clinical trial directly from this app. There's a lot less back and forth between trial sites and patients. These tools also really help address some of the bigger challenges that we see in clinical research as a whole. The diversity of participants — when you're not expected to come into a clinic, you really do widen the scope of who can participate in your studies. Having things delivered directly to the home helps out families who may be juggling a variety of different lifestyles to make a clinical trial happen. Decentralized clinical trials really do bring the trials to the patients. The last challenge here, the long-term retention, is something that I think we really need to get at if we're going to consider long-term monitoring of these therapies.

So if we're thinking about decentralized clinical trials, why can't we think about decentralized therapy monitoring? Some of the same things: We can adapt therapy monitoring long term to patient lifestyles. Just don't make them come in; make this as easy as possible. In thinking about post-term approvals, it's easy to see why we're going to have to make this as quick, as easy, and as cheap as possible. These therapies truly do have potential to eradicate disease and suffering. I believe that the first among us to develop them, administer them, and receive them have a responsibility to remain engaged with this research over 15 years or perhaps even entire lifetimes. I think these decentralized clinical trial tools are going to make that a lot easier.

I also want to discuss some of the challenges, though, because I think, in order to get patients to buy into these long-term monitoring scenarios, they are going to have to be incentivized to do so. I believe that companies must be absolutely transparent in the limitations and the potential for long-term side effects so that patients are incentivized to stay in the loop and to stay followed. Lots of education around how we can keep patients incentivized to remain in the studies. How about paying them or taking care of some of their health care costs? On the last slide, I do talk a little bit about how to share data across the clinical research and the care teams that are taking care of these patients so patients can save time and money and resources by not having to conduct their clinical care and their research study care.

I think I'm out of time, but I only scratched the surface, and I'm looking forward to hearing more about what others say today. Thank you very much.

DR. KUMAR: Thank you, Mindy. Our next speaker is Barbara Isquith Arone from IQVIA.

MS. BARBARA ISQUITH ARONE: Hello, everybody. Good afternoon. My name is Barbara Arone. I have spent the past 20 years working in the generation of real-world evidence to answer regulator, payor, provider, and patient questions of critical importance to patient care. My contact information can be found on this slide.

Over the course of the past 2 years, our organization has dedicated quite a bit of time to thinking about how to best design studies for cell and gene therapy long-term follow-up, both in the post-trial and the post-commercial population. I've laid out here for you a few

considerations that we've been thinking about as we have come along this journey with a number of different partner organizations.

First and foremost, we speak about cell and gene therapy as if it were a single type of treatment, but in fact, these treatments are quite nuanced. When you're talking with a company that has a cell therapy versus a gene therapy or a gene-editing therapy, each of these are quite different, and the expectations of impact to patients over the long term can be quite varied. My colleague Diego Correa will speak about this a bit more in the discussion on outcomes later this afternoon.

We're also looking at a very wide swath of therapeutic areas. Some of these treatments are in pediatric populations, as Mindy was showing us, where, through the course of treatment, these patients will grow and mature and enter adulthood, passing different lines of informed consent along the way and moving quite dynamically through life and through the health care system.

Some of these therapeutic areas, especially in the oncology arena, are expected to have very high mortality, and patient survival may never reach the 15-year limit that we're looking to collect data over. Companies have also invested millions of dollars in building post-trial long-term surveillance programs, and those investments will continue even after products are commercialized.

There's also a growing number of products with the expectation of retreatment. Patients initially exposed in a clinical trial might need to be in a long-term follow-up and then require retreatment with the commercial product, at which point they would need to be followed through the commercial pathway. From an operational standpoint, it does not make sense to run these programs in parallel with each other, and the expectation of many organizations is that eventually those efforts will merge.

When IQVIA looks at these programs, we've developed a methodology for reviewing factors that contribute to design and operational strategy. It rests on the patient's journey, the expected patient survival, the data needs, and the mechanism of action for the therapy.

We start with an analysis, first and foremost, of the patient journey. How will the patient move through the health care system after the time of their treatment? Will patients return to their local treating physician? Do they travel hundreds of miles to the treatment center in order to receive the treatment? When they do go back to their home territory, what type of doctors will they see and on what frequency? Understanding where the patient will be seen and by whom contributes to our thinking about how to design a patient-centric study solution.

The second thing we look at is the data that's needed to perform the long-term safety and efficacy analysis. What are we worried about? Are we looking for long-term malignancies? Are we looking for all-cause mortality? Do we have to measure treatment persistence — and how best to do that?

Once we have determined what data needs to be collected and what the patient journey looks like, we can then assign data sources for each of these types of data. Where will the patient be, and how can we generate that data during the course of their standard-of-care visits? Is there a

way for us to obtain that data out of the standard-of-care workflow, or are we going to have to do additional data collection? By looking at the patient journey and the data type, as well as the best data source, you can begin to pull together a design that's sensitive to those issues. My colleague Ian Bonzani is going to speak more about this question later this afternoon in the section on data sources.

This methodology also surfaces for us very quickly when a decentralized data collection strategy would be beneficial. By allowing the patient journey to drive these operational decisions, we can focus on designs that will be most easily incorporated into patient care, and we have the highest probability of a successful, robust data collection. The focus on journey can help us balance tools like decentralized study collection — that make it easier for data to be collected in rural populations, for example — with clinical support from local treating professionals who already interact with the patients in their own community.

As we have looked at this effort, the one piece of advice that we have given to each and every organization we've talked to is that they need to look at their initial designs for the long-term follow-up as a first pass. They have to build evolution and flexibility into the designs. Fifteen years is a very long time; there will be changes in technology, changes in patient expectations, new therapeutic uses for the products, and new regulatory guidance. We work with companies to anticipate the need for flexibility and build in program evolution so that these programs can continue to grow and change while still protecting the scientific endpoints.

I don't know that our industry has ever been more challenged to collect truly critical information over such long periods of time. The logistic and operational aspects are not to be underestimated, and meetings like this today can help us surface the issues and begin to work toward solutions. I look forward to answering any questions.

DR. KUMAR: Thank you, Mindy and Barbara, for sharing your perspectives on this topic. I will now open it up to the FDA panel to ask any clarifying or follow-up questions.

FDA Questions

DR. LARISSA LAPTEVA: Thank you for these presentations; they are very informative, and we appreciate your participation in the meeting. I have a quick question for the last speaker of the session.

The aspects that you have outlined about decentralized clinical trials are very much on the point of all of the different challenges and opportunities that we see with these trials, to truly make trial content patient-centric. It takes a village and it takes a lot of effort to actually make a study like this, have it conducted, and ensure that credible data come out of the trial that uses one or more — or sometimes many — elements of decentralization.

My question for you would be, "Where do you see the biggest challenges in trying to introduce elements of decentralization in post-marketing data collection?" I recognize that this is probably a very large question, but based on your experience and your research of the topic,

maybe you could outline at least a couple of the biggest challenges that you see. Thank you.

MS. ARONE: I think that one of the biggest challenges we have — and this is part of the reason why we start thinking about it at patient journey — is that *decentralized* just means we're taking it away from the clinical trial site; we're not implying where it's going. One version of decentralized is like what Mindy was talking about when she was talking about decentralized clinical trials, where you do videoconferences, you might send home health nursing, and it's quite interventional in nature, meaning that lots has to happen to collect the data. Another version of decentralized data collection would be to find the data that's already being produced in the health care system. These are patients who, after treatment, will continue to see a physician of some sort, whether it's a primary care physician or a specialty physician, for their lifetime.

So the question about what the biggest challenge is — there is no one answer to where you're going to find that decentralized data, and you have to let the therapeutic area and the product itself help guide you to where the patient is going to be. Then the question becomes, "Can you find the access to the data in a timely fashion and robust enough in the native data production of moving through the health care system, or are you going to need to do something more in order to collect the information?" That's the reason why the way we've thought about it is to think about patient journey — to think about the data that you need and then how you can get that data that you need in the patient journey or whether you need to step outside the patient journey and do more to collect that information.

I think the biggest challenge is that in every scenario, because we don't have enough patterns yet to say we have patterns, you are designing something that is very bespoke to the therapeutic area, the type of treatment, and the patient journey. I think that's the biggest challenge right now: We haven't done enough of this to see the patterns. I imagine the patterns will emerge, but we haven't done enough of it yet to see them.

DR. LAPTEVA: Thank you very much for sharing your thoughts, and thank you for pioneering the field.

DR. KUMAR: Thank you. Dr. Alimchandani, you had a question?

DR. MEGHNA ALIMCHANDANI: Yes, a question for the second speaker: I think you mentioned that post-trial and post-commercial populations will eventually overlap, and I was wondering if you could comment and elaborate on that a little bit more.

MS. ARONE: This is something that I think a lot of the pharma companies are struggling with right now: They have patients coming out of the post-trial population, they're designing long-term follow-ups to follow these patients for 15 years, and they're certainly hoping to reach a commercial population within that 15-year time window. Whatever they are designing as their long-term follow-up for their trial population, they're trying to balance their activities and the cost of those activities to what they might need to do in the post-commercial population.

There is a lot of discussion among companies of how to design something that will do the long-term follow-up of the clinical trial population and be able to incorporate the patients once

the product becomes commercially available. How can we merge those two workstreams together? Now, you might not need to collect the same data on both populations, but a lot of the activities and the questions about patient journey are going to be the same. There is a lot of discussion right now about how to bring those two workstreams together in a useful fashion, because 15 years is a very, very long time for your post-trial population, and you certainly hope that those products are coming to market within that window.

MS. CAMERON: I would just add that that's absolutely the biggest challenge. A person in a trial is committed to a certain amount of follow-up, but when you have the commercial patients, are they going to be entered into a mandatory study? How does that work? I do think that maybe some of these may need to be studied even longer than 15 years; we might be looking at patients over an entire lifetime.

MS. ARONE: I think the retreatment is really bringing that up as a significant possibility.

DR. ALIMCHANDANI: Thank you so much for your comments.

DR. KUMAR: Thank you both. Dr. Najat Bouchkouj, did you have a clarifying question?

DR. NAJAT BOUCHKOUJ: Not anymore. My questions were answered; thank you.

DR. KUMAR: Thank you. Any other FDA panelists have additional questions?

DR. OSMAN YOGURTCU: Hi, this is Osman Yogurtcu from CBER OBPV. My question is for Mindy Cameron. Thanks a lot for sharing your experiences. In order to obtain high-quality and sufficient real-world data in decentralized clinical trials, as you would appreciate, patients need to take on more responsibility. Based on your experience, how can we support patients to ensure they provide relevant data that meets the quality and quantity standards, presumably for many years?

MS. CAMERON: As my colleague said, most of these patients will require continued standard care for their disease state, so there's one way. It's my hope, obviously, that children treated with gene therapies will grow up, and these decisions to be in the clinical trial really weren't even made by them, so post-trial follow-up to a young adult, hopefully in his 20s or 30s, is going to be challenging. I just believe that we're going to have to make it as easy as possible with wearable technologies; we're going to have to be savvier about what kinds of data are collected through just patient-reported outcomes.

But I also think it all needs to happen in real time. Rather than have your patient come in once every 5 years, you need to check in with them more frequently than that. If we do have emergent side effects that we can't foresee, we'll need to be able to communicate with these patients rapidly and get their responses rapidly so that, if we do need to do data collection in a hurry, we've got the capability to do that. And I don't think coming into a clinic once a year is really going to be enough.

DR. YOGURTCU: Thank you so much.

Session 2: Development and establishment of product-based and/or disease-based registries

DR. KUMAR: Thank you. If there are no additional questions from the FDA panelists, we will move to the second topic of the meeting: development and establishment of product-based and/or disease-based registries.

We have nine speakers for this session, and each speaker will have 5 minutes. We will give you a 30-second notice before your time is up so that you can then wrap up your presentation. If you have not completed your slides, you can submit the information to the docket. For those speakers who have submitted the slides, we will advance the slides on your behalf; please just say, "Next slide." All speakers in Session 2 should now have access to their microphones and cameras; if not, please use the chat function to alert us. I would like to remind our speakers to please stay online after you speak and for the duration of your session in the event that the FDA panelists have questions for you at the end of the session.

Our first speaker is Bill Wood from the American Society of Hematology (ASH) Research Collaborative.

DR. WILLIAM WOOD: Thank you, Dr. Kumar. My name is Dr. Bill Wood. I'm a hematologist at the University of North Carolina at Chapel Hill. I also serve as a senior medical advisor for the ASH Research Collaborative and chair the Data Hub Oversight Group for the ASH Research Collaborative. I will be presenting some comments over the next few minutes. I'm joined at today's session by my colleague Dr. Sam Rubinstein, also a hematologist at the University of North Carolina. He will be available to answer questions, should they come up, at the end of the session.

I'd like to take the opportunity to introduce the audience and some of my colleagues at FDA to the ASH Research Collaborative and the work that we're doing in this area. This is a topic that is of keen importance to us because of the disease focus that we have currently. The ASH Research Collaborative is a supporting organization to the American Society of Hematology. Its primary goals are to accelerate progress in hematology by fostering collaborative partnerships throughout the environment and ultimately to improve the lives of people affected by blood diseases.

At the core of what we do at the ASH Research Collaborative is our data hub.

Our data hub is a real-world data evidence generation system. Our data hub has primary focus areas currently in sickle cell disease and multiple myeloma. These are disease areas, as you know, that are of critical importance to the field of cell and gene therapy. For those disease networks that we have, we have different sites that are participating by providing data from a variety of different sources. We also have data that are provided directly from patients themselves. These data come to our central hub and then are used for a variety of purposes, importantly to accelerate research and to enhance collaborative clinical care across participating sites.

I just wanted to spend a minute to talk about how our EHR data come into the hub. We follow coverage standards, and we use the Observational Medical Outcomes Partnership Common Data Model or Fast Healthcare Interoperability Resources (FHIR)[1]-based application programming interface transmission of our EHR data. We're able to merge those data with flat files that are oftentimes locally curated at our participating sites. These data come into the hub; they actually can then go back out to the sites via our prepopulated electronic case report forms (CRFs). At that point, our sites are able to validate the prepopulated data and complete missing data, should that be an issue. This is also a critical opportunity for additional elements that may be important for prospective evidence generation to be added so they can be brought into the forms and then brought back to the data hub. This is important as well in the context of cell and gene therapy, where certain data elements may not otherwise be routinely collected as part of standard EHR data transmission.

I wanted to draw the group's attention to a recent initiative that we were privileged to cosponsor along with the Innovative Genomics Institute (IGI). This initiative was around accelerating innovations for sickle cell disease with real-world evidence, and we focused specifically on the area of cell and gene therapy, so the insights we generated from this initiative were applicable to multiple myeloma and other areas in hematology. Two of the main topics that we addressed were reflected here in these workgroup reports around real-world data needs for genomic therapies, as well as a workgroup that focused on developing a coordinated registry network. I would direct the group's attention to the URL that I provided here in the slide; please do take a look at the reports that we've generated. We hope these will be useful to FDA, sponsors, and others as you're considering the types of data points that are important for real-world evidence generation in this space.

I also wanted to comment that ASH as an organization also has its own interests in the area of cell and gene therapy. It achieves this interest through a variety of structures, one of which is a subcommittee on emerging gene and cell therapies. You can see here the goals of the subcommittee, which were around understanding the state of the science, advancing the use of immunotherapies for treatment of nonmalignant hematologic diseases, educating investigators about clustered regularly interspaced short palindromic repeats (CRISPR) gene editing, providing physicians with information on cell therapy, and advocating for improved patient access.

In conclusion, I would just note that ASH and the ASH Research Collaborative have a strong interest in the safety and efficacy of cell and gene therapy products. I again wanted to emphasize the work that we did with the IGI and would encourage anyone interested to please read the reports that are available on the website. I would note that the ASH Research Collaborative Data Hub can be a resource for industry, FDA, and others to efficiently collect postapproval cell and gene therapy product data, especially in multiple myeloma and sickle cell disease.

We welcome your interest. I would be happy to answer follow-up questions, and I would encourage anyone interested to please reach out to me afterwards. There are opportunities for collaboration and partnership. Thank you again.

DR. KUMAR: Thank you, Bill. Our next speaker is Leonard Valentino from the National Hemophilia Foundation.

DR. LEONARD VALENTINO: Good afternoon. I'm Len Valentino, a hematologist and President and Chief Executive Officer at the National Hemophilia Foundation. Here are my disclosures, which are none; the opinions in this presentation are my own and not necessarily reflective of those of the Board. The mission of the National Hemophilia Foundation has as its bottom line ensuring that people and families with inheritable blood disorders can thrive.

I wanted to provide a brief introduction to hemophilia, as that will be the topic that I will focus on. Hemophilia is a bleeding disorder due to the lack of clotting factor VIII or factor IX. The most common serious inheritable bleeding disorder, hemophilia affects more than an estimated 1.125 million males worldwide; about 40% of those have a severe form of the disease. It's estimated that for each male with hemophilia, there are approximately 1.6 affected females. The estimated global prevalence of hemophilia is about 3.2 million.

The treatment of hemophilia over the past 75 years has improved the life expectancy and quality of life of people with hemophilia in the developed world. However, in the worldwide population of hemophilia, about 70% of people do not have access to therapy, and it's in the low- and low-middle-income countries where ethical allocation of novel treatments and potentially curative gene therapy for almost 3 million people worldwide has not been thoroughly debated.

How can we achieve treatment for hemophilia? In the past, this has been achieved through standard and extended half-life products, which you see towards the left-hand portion of this slide. With the introduction of non-factor therapies administered subcutaneously, the burden of treatment has been decreased. However, lifestyle modifications continue to be necessary. With the advent of cell and gene therapy, with hemophilia gene therapy for hemophilia A and B, we're hopeful that a new paradigm can be reached.

Of course, it's important that we collect appropriate data. A core outcome set was created and published by Iorio and colleagues in 2018. This core outcomes set, the coreHEM Core Outcome Set, focused on patient-important outcomes, such as the frequency of bleeding and the duration of expression of a gene therapy product. However, the factor activity level, an important biomarker, was also critical in the understanding of outcomes, as well as utilization of the health care system, mental health, and chronic pain.

Now, all of this needs to be achieved by preparing the community. Preparing the hemophilia community for gene therapy involves training and education of health care providers on hemophilia gene therapy, as well as training and education of all stakeholders on shared decision making. We believe that it's important that the facilities that administer a hemophilia gene therapy, whether it be for hemophilia A or B, should be experienced in the process and

understand the procedures necessary and potentially be certified. The federally recognized hemophilia treatment centers should be the sites of care for hemophilia gene therapy, as they have the knowledge and expertise in evaluating, administering, and managing people with hemophilia, and most importantly, they're accustomed to collecting long-term real-world data. The individuals receiving a gene therapy product should be enrolled into a registry in order to collect robust real-world data, including adverse events. This will be the topic of my colleague Donna Coffin's presentation towards the end of this session.

On the next slide, you can see some of the components that go into a risk analysis for any novel gene therapy. There are certain things that we know that we know, such as steroid toxicity, the increase in transaminase levels due to liver toxicity, and of course the peri-injection reactions. Towards the right upper corner of this slide, there are many things we know we don't know, such as the significance of those elevated liver enzymes in the first year, the late liver enzyme increases, and of course the consequences of vector integration. In the lower left-hand corner, there are many things that we have forgotten that we knew, such as that adeno-associated virus (AAV) vectors do in fact integrate and that liver toxicity and liver failure may be a possibility with these types of therapies. In the lower right-hand corner is, of course, the most perplexing situation: what we don't know we don't know. These are, of course, the unknowns that need to be captured through real-world data collection: complications such as thrombotic microangiopathy, complement activation, dorsal root ganglion toxicity, hemophagocytic lymphohistiocytosis, and of course what's next.

In my conclusion on the next slide, I'd like to thank you for allowing me to provide input on the use of real-world, timely data, evidence that's provided from registries, for capturing post-approval safety and efficacy data for hemophilia gene therapy products. Thank you again.

DR. KUMAR: Thank you, Leonard. Our next speaker is Karin Hoelzer from the National Organization for Rare Disorders (NORD).

DR. KARIN HOELZER: Thank you very much. Good afternoon, everyone. I would like to thank FDA for holding today's public listening session, as well as for all the patient outreach over the years.

I am here representing NORD, the National Organization for Rare Disorders. NORD is a unique umbrella organization for about 330 disease-specific rare disease organizations in the rare disease space. We were established 40 years ago, after the Orphan Drug Act passed, to formalize the coalition of rare disease groups that were instrumental in getting this landmark law passed. Our mission is and has always been to improve the health and well-being of people with rare diseases by driving advances in care, research, and policy.

Cell and gene therapies have tremendous potential for our community. Of the 25 to 30 million Americans living with rare diseases, the vast majority do not have FDA-approved treatments. As we heard already in the last session, many of our rare diseases lead to debilitating disease and premature death in infants and young children. On the brighter side, many of our rare diseases are genetic or have a genetic component, which makes gene and cell therapies so promising for our community.

When I think about the concept of post-marketing surveillance, I start with what our patients need to know if they are considering whether to receive cell or gene therapy. Over the years, NORD has conducted a number of surveys of our community, and the questions on the slide that you see are how this applies to you. We have a lot of questions around the impact of the cell and gene therapy on the quality of life, the durability of effect, and what it really means for the impact on the patient and the family in the short and long terms. Obviously, safety and effectiveness are key questions for our community, as are family planning and potential impact on future generations. We also have questions around equity and who will be able to receive cell and gene therapies.

Thinking about the role of patient registries in long-term surveillance for cell and gene therapy, we see tremendous benefit. NORD has, for many years, worked with many of the rare disease patient advocacy groups to help them stand up and operate patient registries, and we see, again, tremendous benefit. But thinking about the unique use case of cell and gene therapies and the long-term monitoring that will be required, on this slide, you see some of the key considerations we hope FDA will take into consideration when thinking about how to take this approach.

The first question is, "What should be the role of patients and caregivers in both designing and operating the registries?" Through our long experience, we know that there's tremendous benefit and power in engaging patients and caregivers in the registries and oftentimes having the registries run and operated by patients for patients. But we also realize that many of our communities need support, tools, and resources in order to develop the registries and make sure that the registries are fit for purpose and actually fit the regulatory grade.

When we think about the sheer number of cell and gene therapies that are in development, we know that a disease-by-disease specific approach for registries will not be feasible or efficient. We've been using a platform for many years, and we see tremendous benefit in having a platform that will be adaptable across disease areas. But we know that there are considerable questions around diversity, equity, and inclusion when we think about these registries, in particular for our patients' communities, which oftentimes face additional and particular challenges with regard to access to these registries, including oftentimes limitations, et cetera.

We've already heard about the need for long-term participant engagement in the registries and really intentionally thinking about how to ensure the participants will be engaged in the registry long term. We see tremendous value in thinking about registries not just as a role for post-marketing surveillance but also for patient education, engagement, and empowerment. We already heard about the importance of patients seeing a value out of the time and effort that they dedicate to participating in a registry.

I would be remiss if I did not talk at least briefly about the other data sources for post-marketing surveillance. We know registries have a tremendous potential, but they're only one part of the puzzle. We know that when we talk about rare diseases, we do discuss data and disease progressions that are usually incompletely characterized. We know real-world data have severe limitations for our diseases because of things like the lack of disease-specific International Classification of Diseases, 10th Revision (ICD-10) codes for many of our

diseases. We know the clinical presentation of our diseases is often complex and heterogeneous, and all these sectors make it very difficult to do very robust post-marketing surveillance. We also know patient perspectives on key issues, such as risk-benefit trade-offs, are diverse and can change and evolve over time. We know many of our patients still face a long diagnostic odyssey before they finally arrive at the right diagnosis, and you already heard about the burden of patients participating in clinical trials, as well as in seeking the specialized care that they need.

DR. KUMAR: Your time is running out. Can you wrap up and submit your comments to the docket?

DR. HOELZER: Absolutely. I would just like to thank everyone. My contact information is here. Thank you.

DR. KUMAR: Thank you, Karin. Our next speaker is Chris Jones from Red Nucleus.

MR. CHRIS JONES: Good afternoon, everyone; it's nice to be here today. Thank you to FDA for organizing the conversation. I'd say it's moderately therapeutic to be able to share thoughts about our daily travails and how to make studies better in the gene therapy space and in the rare disease space. I lead our clinical division of Red Nucleus, and that's my only affiliation as an employee of that group to disclose. I've been working in the rare disease space for over 20 years in various capacities and, in one form or another, have been doing digital projects.

I want to share some thoughts and maybe build on some of the ideas shared both in registries as well as in the alternative design space. We sort of chose the registry space thinking about long-term follow-up. We do support several sponsors working in gene therapy, including in some of their Phase 1, 2, and 3 studies, as well as in their post-approval planning. Those of us in the rare space — and I know probably in FDA as well in your reviews — have seen anecdotal videos for years of rare patients. We've spent about the last six or seven years trying to see if we can build a system and a process that support structured video for quantifiable change over time, and that longitudinal aspect will fit very well with all of the topics of registries and long-term follow-up in gene therapy.

I just have a few slides to illustrate some of what we're trying to think about with the sponsors on how to structure and make things patient focused, as Mindy was talking about, and provide qualified processes and quality data that can be used for all the stakeholders in the post-approval setting. With that overview and intro, just a couple of slides to go through some of the topics and issues that we see in these studies.

I'll just talk you through a little bit of an example of what we've been doing in video with the iTakeControl platform. We've been capturing at-home video; we started with Duchenne muscular dystrophy and looked at activities of mobility that can be captured by caregivers and patients at home. This illustration here, working left to right: First of all, I want to start with the concept of how we structure video capture and how we deal with caregivers and at-home scenarios for virtual or decentralized or long-term follow-up designs. The first thing is training and being specific, being standard, and being clear and simple on what kind of assessment we

want to do. We have a range of different assessments that can be done, but we want to educate anybody participating in a trial, including site coordinators and the principal investigators (PIs) but also the participants and caregivers, on how to perform a task, what they are expected to do, and where the camera is. And all of that gets standardized. Everything is captured within a system, so we're not dealing with files that are coming in from outside a system. We have controls over what is actual study data or long-term follow-up data.

This particular screenshot on the second part there illustrates automated blurring. Anytime we're talking about video, the first questions we get are around protected health information (PHI), confidentiality, security, and all of that. Applying artificial intelligence (AI), blurring, and facial recognition is very doable, and combining that with a quality control, confidentiality is maintained. Consent is also obtained, of course, in the normal course of institutional review board (IRB) oversight for any data in the study, including the videos.

Looking at the third and fourth screenshots, just to illustrate what happens as we do these kinds of things, the payoff is really rating and quantifying this data. Whether it's date analysis, whether it's rise-from-floor, whether it's 6-minute walk, 10-meter walk, the Baileys for pediatric and developmental milestones — all of these rubrics can be rated and scored. Obviously, it needs to be disease-specific, and we can talk about that as an interesting topic, especially in the rare space, where we're looking at either adapting validated instruments or we're talking about novel endpoint development in order to really show what happens to patients on a therapy over time, from a visual evidence standpoint, and quantifying that with the scoring and rating, and all of this within a 21 CFR part 11 audit trail system. We're all familiar with telemedicine in the clinical setting; having a conversation with a physician or clinician is pretty established at this point. But having the audit trail, the structure, the visit IDs, the metadata around a video recording is crucial for you all, because all that data will wrap up with a particular video and scoring and datasets.

DR. KUMAR: Chris, your time is up. Can you submit your comments to the docket?

MR. JONES: I can. I just want to thank you for the conversation today. This was just a telemedicine example of the same topics on things like clinician global impression of severity or change. Thank you, Dr. Kumar.

DR. KUMAR: Thank you, Chris. Our next speaker is Barbara Isquith Arone from IQVIA.

MS. ARONE: Hello, everybody; thank you for having me back for this second topic. Disease and product registries are a very natural fit for the type of long-term follow-up that we think about in the post-commercial space. This presents an amazing opportunity to leverage the existing thinking and, in some cases, the existing structure to accomplish the data collection that we need.

On one side, the opportunity is great. Registries typically rely on standard-of-care data, so there's minimal to no intervention beyond the patient's standard care. There are many operational approaches — which we heard about from some of the other speakers — for registries, from direct site-based data entry, patient-generated data, electronic health record

data... In addition, disease registries have the added benefit of capturing untreated patients to provide valuable contextualization of events and outcomes for patients who have been exposed to gene therapy.

There are, however, some significant challenges. Registries in their native state will not have specialty tests, specialty imaging, or any measurement of treatment persistence unless those imaging tests or treatment persistence have become a part of the standard-of-care therapy. Data entry into registries can also be periodic in nature, either flowing with the patient's expected visit schedule or, in some instances, flowing in one time per year per patient. So it is unlikely that registries in their current state would provide us with the speed of insights, specifically on safety endpoints, that would be desired in cell and gene therapy long-term follow-up. This is not to say that existing registries are insufficient. They could, of course, be modified to be able to better match these efforts. But modifying the existing programs may be challenging to achieve in a timely manner.

One of the ideas I'd like to raise today for the Agency's consideration is multisponsor product registry solutions. If there are multiple products within the same therapeutic area or with the same general mechanism of action, could all of those products be managed under a single multisponsor solution? Multisponsor solutions reduce the burden on physicians; however, they do increase the complexity and the delivery of those programs. The data governance can be complex and also quite complicated, and the collaborations between companies can be fraught in the best of times. I have worked on a few multi-sponsor solutions before; they were always mandated by regulators — enforced collaboration, as it were — but I do think it's an interesting idea for us to consider when we think about the burden of these programs on physicians and treating centers.

Disease registries are especially intriguing and worth considering under certain circumstances. If the treatments are for rare or ultrarare disease populations, as presented by the speaker from NORD, it is possible that there might already be a registry that exists for patients with this condition. Depending upon the percentage of patients who we could reasonably expect to be treated with the therapy, we could see the addition of an arm of registry to capture additional information on these patients under the umbrella operations of the registry in general. It's likely that patients would be treated at one or two treatment centers in any one region of the country, and then when they return to their home physicians, their home physician might already be participating in the disease registry and entering information about those patients. Again, the disease registry also gives you the opportunity to compare treated patients to the cohort of patients within the disease registry that are untreated, essentially creating a pool of patients with which you can contextualize the patients exposed to the gene therapy. I think this could be a really interesting partnership for industry and advocacy organizations, which have a strong hand in the rare disease community.

One current challenge for the collection of data in the post-commercial space is that we are looking at post-trial data collection guidance and applying those rules to this effort. If those are the rules that we're operating under, registries will struggle to meet the bar for data quality and data immediacy. Through pilot and demonstration projects, clear goals around data latency

and data quality could be tested to assess the gaps and to help organizations explore solutions to enable existing registries so that they have mechanisms in place to produce high-quality, timely data and insights. These demonstration programs would allow product owners to engage with regulatory, patient, physician, and payor stakeholders to assess the success and the limitations of these types of solutions. As an industry, we look forward to partnering and establishment of appropriate solutions as we move forward in this journey together.

DR. KUMAR: Thank you, Barbara. Our next speaker is Joe Franklin from Verily.

MR. JOE FRANKLIN: Hi, I'm Joe Franklin, Head of Strategic Affairs at Verily. It's a real privilege to be able to be here to present today on this very important topic, and many thanks to FDA, to the other presenters, and, of course, to everybody listening in. I just want to emphasize, as an important disclosure, that I'm an employee of Verily.

The focus today is on post-approval data for cell and gene therapy products. I want to emphasize that this is part of a broader trend in the evidence generation landscape. I find it helpful to quickly step back and look at the context in broad terms.

On the left hand of this slide is the canonical approach to evidence generation, represented in a chart. This is for a drug or biologic product. You can see there are successively larger preapproval studies, and if they show that a product is safe and effective, it results in approval. After approval, there may be a Phase 4 study or a post-market study, maybe a registry. Historically, the vast majority of the use of the product is not part of any systematic data collection, and the experiences of the patients in this data void are lost from the perspective, at least, of informing regulatory or care decisions.

More and more, we as a community are developing the tools to fill this data void through more efficient evidence generation. As we've heard today, efficient and broad evidence generation like this is especially critical for cell and gene therapies. We know FDA has emphasized the need for long-term follow-up and guidance, and this is part of existing approvals. Outside of FDA, it's very reasonable to expect that over time, increasingly, payors will have expectations of post-approval evidence generation. On top of these factors, the number of licensed cell and gene therapies is anticipated to rapidly increase. This all begs the question, "How do we, as a community, generate post-market data efficiently and in a way that reflects the diversity of the population that needs an intervention and that reflects patient experience in addition to other critical outcomes?"

Combining different sources of data that provide information about a patient's longitudinal health journey is a key feature of a modern registry. I think it's great that this public meeting includes this section specifically on registries, as many of my fellow presenters have touched on. Critically, a registry needs to satisfy several criteria. It needs to be able to generate robust insights from a combination of datasets and provide different types of longitudinal data. It needs to include patient-centric data; this means working with real patients, as per registry. It needs to generate evidence that reflects the diversity of the population. Especially for monitoring safety events, it also needs to support rapid turnaround of high-priority data elements.

A participant can decide to enter a registry and provide informed consent to collect information for the study. This enrollment and consent can happen at different points along the timeline, including when a patient is diagnosed with a disease, when a patient receives an approved product, or when a participant enrolls in a randomized clinical study (RCT). Fundamentally, a registry needs to be efficient in this way. For patients enrolled in a clinical study, the registry and the clinical study use the same or at least overlapping data sources. The patients' health history can inform of the evidence generation in the RCT, and for follow-up purposes the registry can provide that data in the post-marketing context or the post-trial context for long-term follow-up, including monitoring for safety events and durability of clinical effects. For patients that are receiving an approved product in a normal clinical setting, it's really important to be able to pull in the data sources that can provide follow-up evidence generation efficiently and monitor outcomes efficiently, including from EHR and other RWD data sources. Perhaps most fundamentally from a patient-centric perspective, a modern registry needs to allow patient-centered data collection through robust means — sensor-based or PRO-based measurements — to understand the experience of a real patient and allow some of this data to be collected in a convenient manner for patients, including at home.

Finally, from an efficiency perspective, I want to emphasize that it's really important that registries and registry-based studies be designed to generate evidence for multiple purposes. This is something good to think about prospectively. This includes both regulatory review purposes, regulatory follow-up from a post-approval perspective, as well as coverage and payment. On the regulatory side, of course, registries should be designed to meet post-approval expectations or requirements for post-marketing safety and effectiveness, depending on the unique circumstances of the licensure of the products, whether it's accelerated approval, needing post-approval confirmatory study, et cetera. Secondly, a registry should be designed to provide evidence for other purposes, especially payment and coverage decisions, which is becoming critical as payors consider novel payment methods or models that take into account long-term outcomes. A registry that combines real-world data with patient-centric data is really important here, because the relevant data is challenging to provide from individual data sources by themselves.

Hopefully, this was a helpful brief overview. I really thank FDA again for this public meeting and look forward to answering any questions.

DR. KUMAR: Thank you, Joe. I see that several of you have been posting comments to the chat. Please also post your comments to the docket. Our next speaker is Halina Malina from Axanton Technology GmbH.

MS. HALINA MALINA: Hello, everybody. I don't have slides, so please pay attention to what I say, because I will say something completely different.

We consider that disease grows by protein modification, not by gene modification. So when we have chemical substances, they will modify the regulatory sequences of protein covalently and in a reversible way. These kinds of sequences are not degraded in our body, but they will still be found in our blood and the cells. So the problem is not the gene at first; the upstream problem is modification of proteins. When we have a modified cell membrane, the caspases

will be activated and the cell is degraded, but only cytoskeleton lead to cross-linking.

This kind of mechanism of disease we have in all diseases associated with aging: We have cross-linking of protein in Alzheimer's, in Parkinson's, in cardiovascular disease, and in retinal degeneration, and anybody can try to make regenerative therapy. We have an antidote against the modified protein, and this antidote we call MEMS: Molecule Establishing Membrane Signaling. If you put MEMS on the cells, on the primary cell culture, the cell will regenerate. If you put it on your skin, the skin will regenerate. I tried it first on my lupus or neurological dermatitis; it was something which nobody knows how to heal and what it really was. It healed my disease. There are so many people who have the problem with diseases which are completely unknown, so these people use MEMS for many years. We don't do any gene modification. We should remove that modified protein by the antidote against this modified protein. You take only 5 micrograms of MEMS sublingually and your body is regenerated systemically. It is enough to take only 5 micrograms of MEMS per week and your body is regenerated, and you prevent cardiovascular disease, you prevent infection, you prevent Alzheimer's, and you prevent Parkinson's — but, of course, in an early stage, if the organ is regenerated it is ready for transplantation.

So we have a mechanism which is not healed currently, which is not targeted at all, because we target lupus from the transplantation of the organ, the cells — and finally the transplanted cells are put into the tissue with the modified protein, and these stem cells degenerate. Now, all of the stem cells are infected very easily, because if you have modified protein in the cell membrane, your immunity is very low, and you should remove them before.

So we have science applied now. Nobody would like to hear this, because we have known this for 15 years and nobody is interested. We have only family money. We are working with our private money. No company until now would like to help or would like to develop the product. The product is really completely new, and it is a new approach to prevent all diseases.

DR. KUMAR: Halina, you are running out of time. Can you wrap up and submit your comments to the docket?

MS. MALINA: Of course. Thank you.

DR. KUMAR: Thank you. Our next speaker is Donna Coffin from the World Federation of Hemophilia.

MS. DONNA COFFIN: Thank you, and good afternoon, everybody. I'd like to thank the organizers of this meeting for inviting the World Federation of Hemophilia to present today. My name is Donna Coffin, and I am the Director of Research working on the Gene Therapy Registry (GTR), which is what I'll discuss today. I have no conflicts of interest as a full-time employee of the WFH; we are a nonprofit advocacy organization.

Just a little bit of background for gene therapy for hemophilia: The current gene therapies in Phase 3 are AAV-based. We have two products that are approved, not yet in use, because they're still going through the reimbursement process — one for hemophilia A and one for hemophilia B — and several others that are in Phase 3 clinical trials.

We have been working on a global prospective observational registry aimed at collecting long-term safety and efficacy data on all people with hemophilia who receive gene therapy. This is a multi-sponsor initiative, so we have all of the manufacturers who are in Phase 3 clinical trials part of this initiative. The aim was that we would not have to have individual product-based registries; we would all use the same database, and each of the manufacturers would be able to obtain the data that they need for their regulatory needs through the Gene Therapy Registry. We have been collaborating with patients, health care providers, industry sponsors, and the regulatory bodies — FDA and the European Medicines Agency (EMA) — on establishing this project.

The protocol and the core dataset are both completed, and both were informed by patients, health care providers, FDA provided comments, and the EMA. We're currently undergoing EMA qualification as a data source for EMA regulatory purposes. They have a very formal process where you can submit your core dataset and the protocol, they evaluate it, and if deemed high quality and useful for their purposes, they will grant a qualification accreditation.

The objectives are to determine the long-term safety and efficacy of gene therapy for hemophilia. We're also looking at the long-term quality of life and the burden of disease post-gene therapy infusion.

Because this is a global registry, we're working with national registries that already exist. For countries that have their own national registry, we're working with those registries to try to link data rather than go directly to the treatment centers and have the treatment centers enter the data. We think it would just be easier for everybody if we could link data. If there is no national registry in a country, we'll go directly to the treatment center and have them enter the data directly. That's for post-approval patients.

We're also aiming to enroll all of the clinical trial patients into the registry. This is patients who received these products or AAV gene therapies in the past via clinical trials and, very importantly, patients who are in Phase 4 studies that will be starting up soon. We also want to make sure that all of the patient data from the Phase 4 studies gets into the registries as well so that we have a complete, robust database of gene therapy data.

This is a figure — just how the data will flow. On the left we have our hemophilia treatment centers; this is in the event that a country has a national registry. They will enter their data into the national registry, and we're working with the national registries to provide them with our core dataset, so as they build out the gene therapy component of the registry, they'll have our core dataset and align as much as they can with what the global Gene Therapy Registry is looking for. The data will go from the treatment center to the national registry and be sent over to the Gene Therapy Registry on a regular basis. We'll work with each registry individually; ideally, it would be an overnight thing, and every night they would just download the data, but that will be determined. In the global GTR, we'll have the combined global dataset, so we'll be able to look at data from different countries on different products. The adverse events of interest and serious adverse events that are entered in the GTR will be flagged and sent immediately to the individual manufacturer of that product, and each of the industry partners will get their product-specific data as well for their needs.

DR. KUMAR: Donna, you are running out of time. Can you wrap up and submit your comments to the docket?

MS. COFFIN: Yes, I can, thank you. We have clinician-reported and patient-reported data through an app, and I'll wrap up there. Thank you very much for your time.

DR. KUMAR: Thank you, Donna. This concludes the speaker portion of our second session. Thank you to all of the session speakers for sharing your perspectives on this topic. I will now open it up to the FDA panel to ask any clarifying or follow-up questions.

FDA Questions

DR. BOUCHKOUJ: Perhaps I can ask my question to Dr. Hoelzer, the speaker from NORD. Thank you for the presentation. As we all know, patient education is incredibly important and can be the cornerstone of many public health initiatives. Can you just speak to the use of digital technologies, such as social media and so on, as a tool for patient education regarding patient registries, especially the young adult patient population with rare diseases?

MS. HOELZER: Absolutely. Thank you very much for bringing that up. Patient education, especially around registries, has been a long-term priority for NORD. As part of the Rare Disease Cures Accelerator, we have been working with the Critical Path Institute (C-Path) under a grant from FDA to really create patient-focused education specifically around registries.

What we are learning is that having a mixture of media, having animated short videos, leveraging social media and influencers all have been tremendously helpful in making sure that we raise awareness, that we bring patient advocacy groups up to be what we call *research-ready* so that they can really take a leading role in designing the questionnaires and making sure that the patient registry really captures what matters most to the patient community, and absolutely, social media are a very important tool for engaging our membership and for disseminating information. It always strikes me how many educational materials are out there that are really good quality but that are not easy to find and that therefore don't get the use that they would deserve.

DR. BOUCHKOUJ: Thank you.

DR. KUMAR: Dr. Alimchandani, you had a question?

DR. ALIMCHANDANI: I had a couple of questions. My first question was for Dr. Wood, the first speaker for this session. You showed us a model of the EHR data submission process and how it feeds into the CRFs. Have you used a similar method to feed adverse event reports into MedWatch forms and into our FDA pharmacovigilance databases, such as the FDA Adverse Event Reporting System (FAERS)?

DR. WOOD: Thank you for the question, and I see my colleague Dr. Rubinstein is here as

well; thank you. We have not done that to date. I appreciate the opportunity, though. I think we're always looking for ways to leverage our technology to meet additional reporting requirements, but that's not something that we've done to date. Thank you for the question.

DR. ALIMCHANDANI: Thank you. I had another question for Ms. Donna Coffin, the last speaker of the session. For the global registries — that's a really exciting concept — what was the length of follow-up time that you were thinking? Is it going to be a 15-year follow-up per patient? More, less? Any comments on that? Thanks.

MS. COFFIN: For us, we would like lifelong follow-up. We understand that it may be very difficult over time. We're trying to incorporate aspects like a patient engagement tool, where they can enter their data themselves online later on if need be, but we're aiming for lifelong.

DR. ALIMCHANDANI: Can you comment on some of the barriers and challenges of the multi-sponsor registry with this concept of the global registry?

MS. COFFIN: There's lots of barriers and challenges. I have to say, we are working very well together with the industry sponsors; we meet on a monthly basis together, and we brainstorm on many different parts of the registry. They understand the value of this global registry; it helps them as well, so I think that for them, it's easy to work with. The challenge is getting the registries from around the world; there are a lot of different registries and stakeholders to work with, so there's a lot of work. Everybody is on board with the idea; it's just the actual getting the work done and going through all of the paperwork in every single country to get them up and running.

DR. ALIMCHANDANI: Thank you.

DR. KUMAR: Thank you. Do any of the other FDA panelists have additional questions?

DR. YOGURTCU: Quick question for Chris Jones from Red Nucleus. Thank you for the presentation — very exciting work. Where are the patient iTC data stored, and who has ownership of the data? Also, do you think you may lose medically useful information due to face blurring, and if so, how would you remedy that?

MR. JONES: I'll try to take that in order; correct me or catch me if I miss something. Our particular platform is all on Amazon Web Services (AWS), but all the controls and role-based permissions are very typical of a clinical trial technology, so what sites see are very different than what patients or a sponsor would see. All of that is standard design and using AWS, if that's what you're asking from a technology perspective. For controls, storage, and configuration, the sponsor designs the requirements, and then we implement those controls with all the standard documentation, audits, and study standard operating procedures (SOPs).

Facial blurring — that's a great question; thank you for asking it — that's also kind of related to 21 CFR Part 11. We always keep all copies of a video submitted, including the unblurred and the blurred. Let's say we're dealing with infants or young children and communication skills or we're following a toy block or language or movement in the face: Raters and scorers in the consent process are able to see the unblurred, and the blurred is used for all other

purposes — essentially all those who wouldn't be permitted to see the face. So that's how we control that process. Thanks for the question.

DR. YOGURTCU: Thank you so much.

DR. KUMAR: Thank you to all of our speakers thus far for sharing your perspectives; we appreciate you being here with us today. We will now take a 10-minute break and begin our third session at 1:50 p.m.

Session 3: Real-world data collected in clinical settings

DR. KUMAR: Welcome back from the break, and once again, thank you, everyone, for joining us for today's public listening meeting on methods and approaches for capturing post-approval safety and efficacy data on cell and gene therapy products. We have two remaining sessions today. As a reminder, we do have a docket open where anyone can provide additional input. To access the docket, please visit Regulations.gov and type in the docket number, which is FDA-2023-N-0398. The docket will remain open until May 26, 2023.

We will now move on to our third session for today's listening meeting, which is on real-world data collected in clinical settings through digital health technologies, electronic health records, insurance claims databases, other administrative databases, and population databases.

We have eight speakers for this session, and each speaker will have 5 minutes. We will give you a 30-second notice before your time is up so that you can then wrap up your presentation. For those speakers who have submitted slides, we will advance the slides on your behalf; please just say, "Next slide." All speakers in Session 3 should now have access to their microphone and cameras; if not, please use the chat function to alert us. I would like to remind our speakers to please stay online after you speak and for the duration of your session in the event that FDA panelists have questions for you at the end of the session.

Our first speaker is Cristina Vargas from Juju and Friends CLN2 Warrior Foundation.

MS. CRISTINA VARGAS: Hello, everybody. My name's Cristina Vargas, and I value the opportunity to be able to talk with FDA today. I just want to state that I have no financial obligations or any connections to any companies or groups. I lead the patient organization of Juju and Friends CLN2 Warrior Foundation, which serves the rare disease community. Given that my son Juju has CLN2 Batten disease, I'm a full-time caregiver, and these subjects have a very sentimental undertone.

The following issues are just a few of the many significant issues that parents in the rare disease community face. Since lives are at stake and time is of the essence, parents and organizations work extremely hard to have their voices be heard. As a result, I have high hopes that the outcome of these open meetings will lead to great collaborations.

So whose responsibility is it to collect data? It's not obvious who's responsible for developing

data platforms that specify the required data components to be gathered. While gathering data is frequently necessary for product developers to be able to meet FDA approval requirements or any contractual obligations to payors, the data generated through these have other activity collections that should also be relevant to a wider range of stakeholders in order to be able to advance knowledge and in order to be able to guide any health care decisions. This is also the case in post-approval study requirements, and the coordination of data-gathering efforts by a mutual third party is desired, but choosing the correct organization to undertake this can be difficult in and of itself.

The following should be addressed while gathering data for clinical trials:

- Expanding the number of studies. This is crucial because of Batten disease rarity. One way to achieve this goal is to be able to have joint strategies, such as providing financing for patients to be able to travel abroad.
- The importance of early intervention for the greatest results. Several studies target older individuals; however, this is unsuitable for diseases that have an early start, such as my son Juju's disease and many other rare diseases.
- The requirement for outcome metrics that are in line with these patient impairments. For instance, routine visual acuity tests and any mobility training are challenging. Families need to be able to enjoy a childhood just like any other child; doctors' visits are not ideal for a child growing up.

Attaining data quality: iIt takes a lot of effort and resources to gather data in a way that ensures its accuracy, completeness, and efficiency by removing duplication across various registries and any electronic health records. Information on patient treatment and outcomes is gathered by several databases or registries. Yes, we do have those implemented. However, we need to be able to focus on how we can get that data submitted so that when trials do become available, doctors, stakeholders, and everybody are aware of what they need to do, they can have the data, and it's not a challenge for families. All too frequently, these initiatives lacked a lot of initiative; they gathered redundant data and failed to address the research issues that matter the most to stakeholders.

The logistics of things is the post-approval for FDA, which requires tracking a patient for some medications over a 15-year period, which poses logistical challenges for both patients and doctors. Fifteen years is far too long for some people. In the world of rare diseases, time is of the essence, as I stated before, and that's why accelerated approval is important for the rare disease community. Every second matters, and this is a problem that needs to be resolved immediately. Throughout this period, certain health care professionals — nurses, teachers, any other clinical staff — may move, and then a parent will have to start over, and this causes discrepancy.

There's no ongoing feedback loop that allows any information gathered in clinical settings to guide future choices and effectively communicate outcomes. The time providers spend on data-collecting operations is compensated in the clinical trial, but there's concern that providers

won't be charged with that communication.

DR. KUMAR: Cristina, you're running out of time. Can you wrap up and submit your comments to the docket?

MS. VARGAS: I was done; that was my last slide. Thank you for giving me the time. Have a good day, everyone.

DR. KUMAR: Thank you, Cristina. Our next speaker is Ian Bonzani from IQVIA.

DR. IAN BONZANI: Hi there. My name's Ian Bonzani, and I'm a senior principal at IQVIA. I'm part of our global technology function, where we're both developing and deploying a suite of different patient- and site-facing tools and applications to support with various aspects of decentralized research programs particular to real-world data generation. So the topics and themes that we're talking about today are very near and dear to my day-to-day role, both in terms of designing and deploying solutions on studies but also how we're continuing to look at the evolving role and the use of technology on long-term follow-up programs. I have nothing further to disclose on this.

As you look at the real-world data landscape more broadly, we're continuing to see both positive growth and improvement in the accessibility, acceptability, quality, and interoperability of data in all its various forms, which is certainly opening up more and more opportunities for the way that we conduct real-world research studies and specifically long-term follow-up programs. As an example, in the U.S., the combination of the 21st Century Cures Act and the corresponding rules around patients' access to their own data and information, combined with the growing adoption of further interoperability standards, such as FHIR and U.S. Core Data for Interoperability across providers, has created a very unique environment for us to enable truly patient-centric data collection approaches.

As we look at how these environmental factors and enablers get manifested into long follow-up programs for cell and gene therapy, we know it's absolutely critical to think about data in the context of the patient and care journey and how that journey will evolve over time. My colleague Barbara referenced some of the challenges associated with the patient and care journey and thinking about the roles between treating physicians, specialists, and primary care — the challenges associated with how we engage and ensure engagement with pediatric patients and their caregivers and how we think about picking up relevant outcomes between safety, effectiveness, and patient quality of life related to this journey and, importantly, keep participants, patients, and providers engaged throughout the lifetime of the study and the research programs.

One of the pieces we think about a lot is how do we design and operationalize these long-term follow-up studies to enable high-quality data over time but also ensure that they are low-burden, feasible, and cost-effective to implement. As we think about potential sources of data, we absolutely believe that digital health technologies, such as patient-facing apps, portals, connected devices, and wearable technologies in all of their forms, are important to consider for these studies, as they bring data collection closer to the patient, aim to reduce burden, in

support with long-term patient engagement and retention. Of course, they can be heavily personalized to collect unique data about the patient and events that would oftentimes go uncaptured through more traditional modalities.

But we're seeing it's important to also consider some of the lessons learned from some of these experiences, in that technology is not a panacea and it alone cannot solve some of the unique challenges we see with long-term follow-up. You have to think about the appropriate resources and support models that enable certain levels of participant training, as well as important aspects of data quality, validity, and checks put in place, and these things can be adjusted over time. Importantly, from a real-world perspective, you have to think about the accessibility, the usability of technology, and the potential for unintended consequences or biases you may introduce by implementing a certain approach.

The other piece that warrants further and active consideration is how to best leverage existing secondary sources, whether those sources are government datasets, payor and administrative claims and pharmacy claims datasets, existing registries, or other population health databases. These sources could have wide utility to supplement or enrich primary data collection, such as the ability to link to National Death Index information in order to support with loss to follow-up or gain important insights into mortality outcomes or being able to integrate medical and pharmacy claims information on participants to gain wider perspectives on comorbidities, concomitant therapy use, or events that might otherwise go missed through more primary collection approaches. However, as we consider these approaches, it's also important to think about other aspects of how to operationalize that in terms of consent, some of the data privacy preservation and aspects you need to include, data linkage management, and how to do this both in the U.S. and looking at broader geographies. There's certainly a lot of opportunity for value creation here, but there's also a real risk of overpromising what linkage to these existing sources could prove out to be from a design perspective.

Overall, for cell and gene therapy long-term follow-up, we need to continue to look for approaches that leverage these innovations and tap into some of these environmental enablers in order to address the unique needs of these patients and studies over time. Thank you for the time and listening.

DR. KUMAR: Thank you, Ian. Our next speaker is Mantej Chhina from the Alliance for Regenerative Medicine.

MS. MANTEJ (NIMI) CHHINA: Hi, everyone. I am Nimi Chhina, Co-Chair of the U.S. Regulatory Affairs Committee at the Alliance for Regenerative Medicine, or ARM. I am an employee of BioMarin Pharmaceuticals, making comments on behalf of ARM today.

ARM appreciates the opportunity to provide input to FDA on the methods and approaches for capturing post-approval data on cell and gene therapy products, or CGTs, as we support minimizing the burden of post-approval data collection for patients and facilitating efficient data collection processes for health care providers and sponsors while ensuring the safety and efficacy of these therapies. ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients,

health care systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges in policies and practices, and advancing the narrative with data and analysis. As the global voice of the sector, ARM represents more than 475 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

When creating guidance on this topic, we recommend that FDA define the scope of post-approval data to include required confirmatory trials on clinical efficacy for products receiving accelerated approval and required long-term follow-up safety studies with a statement of reporting data on efficacy. Post-traditional approval is at the sponsor's discretion to facilitate consistent application of FDA guidance. Efficacy data from voluntary long-term follow-up studies may be helpful for expanding labeling indications of a therapy. Guidance would be helpful on the requirements of post-approval efficacy data to support label expansion. ARM encourages FDA to provide clarity on the Agency's consideration of input from patients, caregivers, and patient communities when providing guidance on post-approval data collection methods for CGTs.

Use of registries can be an appropriate approach to collecting long-term follow-up data from trial participants and to conducting registry-based post-approval safety and efficacy studies. The usefulness of existing registries depends on the quality requirements and the data elements collected. Sponsors should be aware that existing registries may not collect all the data points that are required for post-approval studies. FDA development of recommendations and best practices for third-party registries could be helpful to those establishing such registries, as well as to sponsors in being able to assess the quality and reliability of an existing registry for post-approval data collection. When finalizing the draft guidance on assessing registries as real-world data, we suggest FDA provide key examples of how real-world data from registries have been successfully or unsuccessfully used in the post-approval market setting for CGTs.

Decentralized studies can enable real-world data collection that facilitates assessment of meaningful aspects of health in real-life studies. These studies are best facilitated using deployment of electronic data capture involving careful implementation of electronic clinical outcome assessments, or eCOAs, and digital health technologies, or DHTs. eCOA and DHT data are often integrated in concert with analysis of electronic health records to understand clinical benefit and changes in clinical status over time. ARM supports the use of fit-for-purpose digital collection of real-world data to reduce post-approval data collection burden for patients, health care providers, and sponsors. These approaches may contribute to improved patient access, diversity, and retention in trials and reduce participant burden over the course of a study, especially in longer observation periods. DHTs that are used outside of a clinical setting, such as variable sensors, are particularly convenient for patients and have additional benefits like being able to capture data over a longer period of time than single-point-in-time measurement collection in research or clinical settings. DHTs help assess concepts that are reliably observable in real-world settings and increase data efficiency and integrity over long observation periods. While ARM recognizes that some endpoints cannot be adequately replaced solely with eCOA and DHT data, we recommend identifying circumstances in which

these data could serve as a sole source of safety and/or efficacy data.

Sponsors should continue to monitor for signs of tumorigenicity in the post-approval setting if there are relevant translatable signals in the preclinical data that warrant such monitoring. Oncogenicity is a theoretical risk of treatment with AAV gene therapy in humans that can be monitored over time through post-approval patient registries. Sponsors should employ standard pharmacovigilance measures in the post-approval setting in line with the AAV-specific recommendations in FDA's 2020 final guidance on *Long-Term Follow-Up After Administration of Human Gene Therapy Products*. ARM does not recommend surgical biopsies as a standard procedure for post-approval monitoring, given the risk, discomfort, and burden for patients associated with the procedure. Routine monitoring approaches as appropriate for the disease area and product should be considered. ARM encourages and supports development of noninvasive methods for monitoring, including liquid biopsies and other markers. Thank you.

DR. KUMAR: Thank you, Nimi. Our next speaker is Tito Roccia from Janssen.

MR. TITO ROCCIA: Good afternoon, everyone, and thank you for the opportunity to speak at this event. I don't have slides, and I promise to stay within my 5 minutes. My name is Tito Roccia. I'm the Senior Global Medical Affairs Lead here at Janssen, so that's my conflict of interest, and I work on a CAR T therapy for patients with multiple myeloma.

The topic I chose to cover was that of real-world data collected in clinical settings through either one or a combination of a number of available technologies. I will not discuss specific solutions today but rather my proposed approach to creating solutions. The opinions discussed today are my own and do not necessarily reflect Janssen's position.

Before we discuss opportunities offered by real-world data, including registries, I would like to reflect for a moment on what I believe is the role of real-world evidence, highlighting both the strengths and what I believe are the areas of opportunities that real-world data may offer. I would like to start by saying that, for me, well-designed either existing or de novo registries remain a key tool to collect outcomes in the post-approval setting. The main reason for that is that they allow for very robust definition of variables of interest for both safety and efficacy.

However, there's only a limited number really of existing registries that are widespread enough to cover the majority of cellular or gene therapy treatment centers across the United States. To ensure coverage of the majority of your centers while focusing on specific variables of interest for specific products to a specific company, one company may decide to design a de novo registry. But by doing so, they will likely increase the workload at investigational sites, which would have to enter data for the same patients in multiple — both existing and de novo — registries or have multiple registries associated to different drug products. In addition to this, we have to consider that multiple registries may be required to fulfill post-approval requirements coming from different regulatory authorities — namely FDA, EMA, and others.

Lastly, the focus of registries on specific adverse events of interest for cellular or gene therapies may affect their ability to detect and expect safety signals. As has already been mentioned throughout the discussion today, patients in registries may be lost to follow-up once

they are discharged back to sites.

So, I believe there's a real opportunity for both standardization and collaboration; I think you have heard that a few times today. In particular, for me, agreement on the specific criteria requirements for long-term safety data collection may really be beneficial, because it would offer (1) a standard approach to safety data collection for cellular and gene therapies that avoid intercompany variability and (2) a model for safety data collection that may actually inform best practice and address requirements across different regulatory agencies — in other words, create something as a best standard.

Now, there are obvious risks with centralization. For me, one of them is that safety and efficacy requirements relating to a specific drug product or therapy area may be difficult to include in a common registry. However, this risk, I think, can be mitigated with the creation of a consistent core of required variables, complemented by add-on modules for product-specific or therapy-specific variables of interest. For example, a registry for CAR T therapies would obviously include, among other things, the collection of detailed information on cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome, or ICANS, and other modules could be integrated for specific products which may have additional adverse events of interest — for example, additional neurotoxicities.

This really brings me to the role of real-world data systems, which I think have the potential to address some of the gaps affecting real-world evidence, including registries, which we have discussed throughout today. The biggest opportunity, I believe, resides in the possibility of tokenization of individual patients. In that context, adverse events and toxicities which may not be captured for any reason in the registry may be collected from, as an example, electronic health records. In addition, a consenting patient may never be lost to follow-up, because their safety data may continue to feed into the registry from additional data sources.

However, in order for this scenario to be realized, once again, an effort of standardization could be beneficial. If there's only one or a limited number of such models that existed, an incentive would be present for the creation of a robust real-world dataset that could first be more well-adopted and second be designed to continuously feed into a standard registry. In other words, the opposite scenario — where there is a hyper-fragmentation of solutions and individual companies create their own registry or use different existing registries and use their own choice of an additional real-world dataset — is not necessarily a favorable environment for robustness, replicability, and longevity.

I conclude by saying that I would like all of us to consider an opportunity to work together in an effort for standardization that could ultimately translate into a solution that further improves on the current efforts to collect long-term safety data. Thank you very much.

DR. KUMAR: Thank you, Tito. Our next speaker is Megan Freed from Parent Project Muscular Dystrophy.

MS. MEGAN FREED: Hello, everyone. My name is Megan Freed. I am the Director of Data and Technology Strategy for Parent Project Muscular Dystrophy. We're a nonprofit advocacy

organization. I don't have any financial disclosures. I'm going to focus my remarks today on my organization's work over the last years to create the most robust natural history database for Duchenne and Becker muscular dystrophy.

In 2007, PPMD launched the Duchenne Registry, a patient report registry for boys with Duchenne and Becker muscular dystrophy. Over the last 15 years, we've collected data on approximately 6,000 patients and carriers through the administration of web-based and, most recently, app-based surveys that assess both function and quality of life. As the implementation of the 21st Century Cures Act began to take effect a couple of years ago, PPMD authored and launched a complementary study to gather clinician-reported outcome data or real-world data through the extraction of electronic health records.

Our overall intent is to reduce burden on patients, caregivers, and clinicians who are really overwhelmed by data collection and survey administration and to break down silos that exist across the Duchenne and Becker muscular dystrophy space. As part of this effort, we also built the Duchenne Outcomes Research Interchange, a data warehouse designed to ingest and combine disparate types of data and house a robust natural history database.

Along with several peer organizations in the rare disease space, we have experienced firsthand both the benefits of implementing an EHR extraction study and the significant challenges. I'd like to now highlight them for you. Clearly, obtaining electronic health records through an automated push of data allows near-immediate access to a patient's most recent functional outcome measures. Gone are the days when caregivers had to lug around binders full of medical records and copy and fax information to organizations like ours to be input into patient registries. The sophistication of data warehouses, along with federal legislation on data interoperability, allows for combining and mapping data from different sources. This is so very important when we think about the best source for various types of information. For example, from our experience, patients may not recall the results of their most recent ejection fraction, but they or their caregivers can very accurately pinpoint — to the minute, sometimes — the day that their loves ones lost ambulation. By working with information technology experts at medical centers, we're able to automate the sharing of this patient data, thereby reducing the amount of manual input we ask of clinicians, research staff, patients, and caregivers.

Yet there are significant challenges to efficiently implementing an EHR extraction study nationwide. Not only must you get the buy-in and support of your principal investigators — which, for us, are neuromuscular, pulmonary, and cardiac specialists — but you need the institution's IT department to understand the strategy and prioritize the implementation of the study's requirements. There are various levels of compliance above and beyond institutional review boards, including security reviews for any technology or study component that will "touch" the medical records system. And of course, we're competing with many other needs and requests of the IT department's time. From our experience, most IT staff have no experience with EHR extraction studies and, like us, are learning as they go; this, in and of itself, creates multiple speed bumps along the road. While we've designed our study grant to support and compensate for IT time, we've found that there's really no mechanism at most institutions for a portion of the grant money to flow directly to IT.

I just wanted to thank you for the opportunity to share PPMD's experience launching and implementing an EHR extraction study. Selecting real-world data to prove efficacy and safety of cell and gene therapies is critically important; no one argues against that. But we need to place equal importance on the process to obtain these data. As we approach two potential approvals for gene therapy in Duchenne this year, we strongly support any additional guidance and recommendations that FDA and other regulatory bodies can produce to help guide the implementation of this work in a more efficient way. Thank you.

DR. KUMAR: Thank you, Megan. Thank you to all of this session's speakers for sharing your perspectives on this topic. I will now open it up to the FDA panel to ask any clarifying or follow-up questions.

FDA Questions

DR. LAPTEVA: I would like to thank all of the speakers in this session for sharing their perspectives and experiences. I have a question for Dr. Bonzani, who spoke about leveraging digital health technologies and the data that come from wearables, telehealth visits, and other tools and ensuring that when we use those data, particularly in a real-world setting, they do translate and translate accurately the parameters that are measured or outcomes that we're looking for through these technologies. I recognize that this may be a difficult question, but any perspective that you could share, I would appreciate. Are you aware of any approaches or efforts to, in fact, ensure data reliability when data are collected through newer technologies and maybe some efforts to compare what is measured directly with what is measured by the digital health technologies? Because obviously when these measurements are not performed accurately or in a standardized and uniform manner, we end up with biased data or data that do not provide valid results. We've had discussions here at FDA about this problem, so if you could, provide your perspective. Thank you.

DR. BONZANI: Thank you. Yes, absolutely, it is a critical facet to consider as part of your up-front design, as well as the selection of the devices and/or wearables you're looking to utilize on the study. I think a critical piece of it is the selection of a device. That the device has been already clinically validated to collect a certain measure or metric of interest, of course, could be a critical feature that you'd want to prioritize as part of that selection. But as we continue to see more and more accessibility to consumer devices and/or other devices, I think putting in place a robust plan and strategy to ensure that the measures you are going to test and validate to ensure that the data that's going to come from those devices is certainly valid and high quality is important.

Importantly, you need a measurement strategy that also makes sense for the participants, particularly for participants that might not have access to the Internet at all times or might not be wearing their watch or be tracking sleep constantly. Having a measurement strategy that makes sense for participants and their daily lives is also a critical facet to consider to ensure the reliability and quality of data on the back end. But I think we need a more robust framework for how we do that validation in the real-world setting, considering the differences

that we're seeing with some of the clinical trial validation exercises that happen.

DR. LAPTEVA: Thank you.

DR. KUMAR: Several of you had very good comments in the chat; please submit them to the docket. With this, we will wrap up Session 3, and we will be taking a 5-minute break, because we are slightly ahead of schedule.

Session 4: Determination of specific safety or efficacy outcomes

DR. KUMAR: Welcome back, everyone. Our fourth and final session of the day is on determination of specific safety or efficacy outcomes for which collection of post-approval safety or efficacy data may be necessary for cell or gene therapies.

We have eight speakers for this session, and each speaker will have 5 minutes. We will give you a 30-second notice before your time is up so that you can then wrap up your presentation. For those speakers who have submitted slides, we will advance the slides on your behalf; please just say, "Next slide." All speakers in Session 4 should now have access to their microphones and cameras; if not, please use the chat function to alert us. I would like to remind our speakers to stay online after you speak and for the duration of your session in the event FDA panelists have questions for you at the end of the session.

Our first speaker is James Nickas from BioMarin Pharmaceutical Inc.

DR. JAMES NICKAS: Good afternoon. My name is James Nickas, and I'm the Global Head of Pharmacovigilance at BioMarin, which is a global biotech company in California dedicated to transforming lives through genetic discovery. Among our portfolio of investigational products in the United States are targeted gene therapies for persons living with rare monogenic diseases that are often incurable. One example is our investigational liver-directed AAV vector-based gene therapy for the treatment of persons with severe hemophilia A.

As has been stated earlier, while there has been tremendous progress in gene therapy over the past decade, with a number of transformative product approvals in the United States, there are still important knowledge gaps and uncertainties concerning the long-term safety of gene therapy products and of the variability and durability of their effectiveness. On behalf of BioMarin, I do appreciate the opportunity to provide input to FDA on methods and approaches for capturing post-approval data on cell and gene therapy products, which will be essential to increase our understanding of treatment outcomes with these products and their benefit-risk profile over time.

Today I'm providing input on this session's topic, which is determination of specific safety or efficacy outcomes for which collection of post-approval safety or efficacy data may be necessary for cell or gene therapies. For the forthcoming guidance that FDA is developing, I think it'll be helpful to convey a clear objective for the guidance, such as to optimize post-approval data collection to address knowledge gaps and uncertainties concerning important

safety and effectiveness outcomes with cell or gene therapies to inform ongoing benefit-risk evaluations and to ensure that their benefits continue to outweigh risks.

One general principle to consider when developing the new guidance is to adopt risk-proportionate post-approval safety surveillance strategies when determining what safety outcomes require for the data collection. One strategy, for example, is to focus on important identified or potential risks and missing information that could actually have an impact on the benefit-risk evaluations and for which there are safety hypotheses gleaned from findings from either nonclinical or clinical studies and/or community safety concerns.

Another is to adapt safety surveillance approaches to the level of risk. For example, there may be greater risk of delayed adverse drug reactions with use of maybe integrating viruses or viruses capable of latency reactivation and genome-editing products and perhaps lower risk with AAV vector-based gene therapies. There may be other differences as well.

Another general principle to consider in the guidance — and I think it's been stated earlier as well — is to foster and encourage health authority, patient advocacy group, key opinion leader, and sponsor collaboration to identify product class-specific safety and efficacy outcomes that matter and for which post-approval data collection will be critical.

Lastly, as also stated earlier by other speakers, it would be helpful in the guidance to identify mechanisms to access and integrate data sources — such as sentinel electronic health records, insurance claims, and so forth — to conduct pharmacoepidemiologic safety evaluations. One important application of this principle might be to determine the general background risk of cancer in target populations to contextualize malignancies that could emerge in patients treated with cell or gene therapies. An example is to contextualize the theoretical risk of cancer in persons treated with liver-directed AAV vector-based gene therapies.

I'd now like to convey four specific recommendations to consider for the new guidance:

1. Product-specific safety outcomes for which post-approval data collection may be necessary should be addressed in the guidance and include, but are probably not limited to the following: new malignancies, which have been discussed already; liver toxicity, or hepatotoxicity; new incidence or exacerbation of a preexisting neurologic disorder, like dorsal root ganglion inflammation; new incidence or exacerbation of prior rheumatologic or autoimmune disorders; new incidence of a hematologic disorder, such as thrombocytopenia and thrombotic microangiopathy, which have emerged with some treatments already; new incidence of infection that is potentially related to a product; cardiac events; and germline integration. With respect to that area, in the guidance that emerges, I'd like to see clarification on what FDA is meaning, in the example, by effects on fertility, which could be challenging to evaluate in the post-approval setting. Any clarity on that in the guidance would be very helpful.

2. When relevant, it would be very helpful for the new guidance to provide clarity on how best to monitor for off-target effects that are considered possible safety concerns.

3. It would also be helpful to establish term definitions for prespecified safety outcomes,

which will help with ascertainment and reporting and comparison across data sources.

4. Lastly, defining core datasets for important product safety and efficacy outcomes would be helpful to facilitate standardized data collection and enable integration of data sources.

Thank you, and I appreciate the opportunity.

DR. KUMAR: Thank you, James. Our next speaker is Jhil Amitbhai Patel.

MS. JHIL AMITBHAI PATEL: Hello. Originally, actually, I was supposed to be speaking on determination of specific safety or efficacy outcomes, but there was a misunderstanding, so I'm going to be presenting around the real-world evidence topic. My name is Jhil Patel. I'm doing a master of the science in regulatory affairs from Northeastern University. I have a background and experience in the domain of biotechnology.

We all know that gene and cell therapy products are high risk, high reward. Of the many risks, I would like to highlight the two main risks: First, gene and cell therapy products are extremely expensive to manufacture, and they are also technologically difficult to manufacture, discover, and launch. Number two, the patients in treatment who can turn for gene and cell therapy products are much fewer, so the variety of data that we can generate is also much less. This amount of data and this variation of data are okay for partial FDA approval, but when a manufacturer goes to do a full-blown FDA approval for cell and gene therapy, this data pool is not enough. So this is when real-world evidence and real-world data come into the picture. With the help of real-world data, we can actually address the issue of the patient approval in the clinical trial, and we can also address those problems that are there for the post-marketing commitments that the manufacturer has given to a patient.

What FDA actually needs to highlight in its guidance is how to create a robust [audio issues] strategy in such a way that all this data from product registries, regional registries, and state registries are included. Some in-depth information on this topic would help manufacturers build a strong foundation for real-world evidence and real-world data problems. Also, I think it would be good if guidance specifically mentions how to scale and plan the IRB plan in such a way that the perfect combination of a patient pool is taken into consideration to meet the safety and efficacy requirements for patients, for clinicians, and for a lot of people.

One more suggestion that I would like to put here is that guidance on how to reduce site patient burden in order to increase the long-term follow-up should also be explicitly mentioned in the new FDA guidance.

Also, right now, since a manufacturer would be making an IRB plan, it will also create reimbursement policies. In-depth information about what sort of reimbursement policies would be able to attract more patients and henceforth increase the variation and the quantity of data should also be mentioned. Thank you.

DR. KUMAR: Thank you, Jhil. Our next speaker is Heather Smith from SCID Angels for Life Foundation.

MS. HEATHER SMITH: Good afternoon. I'd like to disclose that SCID Angels is a paid consultant for Mustang Bio. My name is Heather Smith, and I'm President and Founder of SCID Angels for Life Foundation, which I started 15 years ago. More importantly, I am the mother of two children born with severe combined immunodeficiency, or SCID. SCID is the most severe form of primary immune deficiency, and in lay terms, these babies are born without a functioning immune system, leaving them vulnerable to infections as simple as a common cold.

This is what happened to my first child. Born before the era of SCID newborn screening, at the age of 6 months, he came down with what we thought was his first cold. But it developed into something much more serious: a rare form of pneumonia which is primarily seen in patients with SCID and should have been a red flag. Unfortunately, the doctors didn't recognize this in time, and 4 weeks later, he passed away.

In 1994, when I became pregnant for the second time with another SCID baby, we researched our options and learned the standard-of-care treatment for X-linked SCID (X-SCID) at the time was a bone marrow transplant. We also discovered that being treated at a hospital with expertise in SCID would require us to travel out of state. We weren't crazy about that idea, but we were willing to do anything to better the health of our unborn child. During that visit with the medical experts, we learned about an experimental treatment therapy that was successful in an animal model but had not yet been done in humans. After reviewing the research papers and much discussion with our family, we opted for the experimental treatment, and in 1995, my son Taylor was the first in the world to successfully undergo a bone marrow transplant in utero while I was still pregnant.

Taylor led a healthy and productive life, but during the spring semester of his junior year in college, we learned his immune system was waning, and it was only a matter of time before he'd have to seek additional treatment. Again, we did our research and weighed the risks and benefited associated with each option, but when your options are limited like they are with SCID, you must make a decision based on the potential benefits foremost. That's exactly what Taylor did when he decided to enroll in the NIH lentivector gene therapy trial. Seven months following graduation from college, Taylor was an inpatient at NIH receiving his gene-corrected cells shown here in this slide.

As someone who has personally helped pioneer an experimental therapy and then gone on to assist her adult child in the decision-making process surrounding gene therapy, I've been through it and have a pretty good understanding of what the issues are when it comes to the methods and approaches for capturing post-approval safety and efficacy data on cell and gene therapy products. Five minutes isn't enough time to go through all the issues I've seen firsthand and feel need to be addressed, but I will take a moment to discuss one that I feel is the most important: The manner in which cell therapy participants are notified of an adverse event that has affected at least one participant under the protocol and triggered the suspension of a gene therapy trial is alarming.

During a previous FDA public listening meeting held last November, I briefly spoke of this problem and asked for something to be written within the protocol guidelines stating that if a

safety rule was triggered, immediate notification to enrolled study participants would be made surrounding the circumstances before updating the ClinicalTrials.gov website. This was because of an actual incident that happened to enrolled participants within the adult X-SCID NIH lentivector gene therapy trial. In the summer of 2022, the SCID Angels private Facebook group received a post from a SCID parent saying, "It's been seen on the ClinicalTrials.gov website that the trial has been suspended, and the reason in parentheses states, 'Clones representing 10% or more of the subject's patient myeloid lineage have been detected or evidence of malignancy found.'" You become alarmed. It is my understanding that safety rules were written in the protocol prior to starting the study, and if one of those safety rules is triggered by a certain percentage of study participants, enrollment is stopped and the trial is suspended, which is what happened in the trial my son was in. Fortunately, there's no evidence in any of the study participants that there is an increased risk of cancer or any abnormalities in blood and immune cell formation or function at this time.

Ironically, the gene therapy trial LVXSCID-ND for newly diagnosed infants, sponsored by St. Jude and using the same vector as the NIH trial, recently paused enrollment and was put on a voluntary hold at the beginning of April of this year for the same reason as the NIH trial that my son is enrolled in. This time around, the families were all notified by the PI *before* it was posted on the ClinicalTrials.gov website as being suspended. I don't know if this was a result of my previous testimony or not, but I do know that participants, for the most part, were pleased by the written letter that was received and informational fact sheets that were included.

However, there are still improvements that can be made when something like this happens. The participants in the St. Jude trial are not being made aware of who the patients are that are showing clonal expansion, like we did in the NIH trial. This is extremely unnerving for most of the families, as they feel they have a right to know if their child is one of the three who have recently been uncovered.

Finding the viral vector within the HMGA2 gene was first reported over 10 years ago and to date, no patients with circulating cells containing an insertion into HMGA2 have developed any type of blood cancer. My point is, transparency is crucial, and in all circumstances to come, unless you can promise that the blood cancer can't happen after the current 15-year-long follow-up study period has been completed, and unless follow-up studies turn into lifelong ones, we must be vigilant of those patients, especially those who are currently showing clonal expansion. Please consider the way study participants are made aware of these types of suspensions. Thank you for your time.

DR. KUMAR: Thank you, Heather. We understand that 5 minutes might not be sufficient time to share your perspective. We encourage all participants to submit their detailed comments to the docket. Our next speaker is Diego Correa from IQVIA.

DR. DIEGO CORREA: Good afternoon, everyone. My name is Diego Correa. I'm the Interim Global Head and Medical Strategy Lead of the Cell and Gene Therapy Center of Excellence here at IQVIA. I'm a physician scientist with more than 18 years of experience covering preclinical and clinical research, as well as trial operationalization in cell and gene therapy. I do not have any financial relationships to disclose, and you can find my contact information

here on this slide.

To provide some background on the topic, currently marketed cell and gene therapies receive approval despite limited evidence of their long-term safety, efficacy, and durability profiles. But it's important to know that, at the time of the launch, the clinical needs significantly outweigh the potential risks associated with the various risks and uncertainties. Consequently, it is critical to generate more robust evidence based on long-term follow-up data that supports comprehensive safety and efficacy profiles of these products required by all stakeholders, including regulators, clinicians, payors, and certainly patients and families, as we just heard from Heather just minutes ago.

To do that, a different framework than the one established for the hypothesis-based trials during clinical development is needed, with more flexible or pragmatic protocols to capture long-term safety and efficacy data under real-world conditions. And of course, this requires rethinking endpoints and outcomes to reflect both a wider and more heterogeneous population and the real-world clinical practice environments where these therapies are and will be used in the future. Given the complexity of these tasks and the limited time available today, I just wanted to provide for discussion more of a diagnostics perspective with suggestions around the elements that we think need to be considered to determine such outcomes.

To start, as my colleague Barbara Arone described earlier today, each and every cell and gene therapy platform is different, with specificities and commonalities among platforms, especially on their mechanism of action, intended activity, durability, and safety profiles. Similarly, there are significant differences in the types of clinical assessments and access to sampling among these different tissues and organs that could be targeted with cell and gene therapies. Therefore, more tailored guidelines — perhaps distinguished by type of therapy and the tissue or tissues involved — may provide more specificity regarding the data that can be obtained.

Now, continuing with the use of therapies outside of clinical development, various elements in the real world may have an impact on durability and safety in the long term. Let me just give you a couple of examples. For instance, factors like structural changes in the organ due to growth and the variability of the therapies in terms of transduction efficiency influence the therapy threshold, or what we call the minimum expression level, to generate an effect with AAV-driven gene therapies, potentially requiring multidose schemes. On the other hand, patients in the real world do have comorbidities that may impact the quantity and quality of the raw material necessary to generate the product, as is the case in the autologous model for gene-modified CAR T-cell therapies, requiring the use of suboptimal products and/or doses, of course determined by clinical judgment.

In terms of outcomes, a few concepts are worth mentioning. In agreement with James, who just spoke minutes ago, there is a need for incorporating approaches that help contextualize adverse events after the therapy, as the real-world population has other long-term risks associated with existing comorbidities, parallel treatments, and disease prevalence — for instance, cancer and cardiovascular disease — and may confound the relatedness of the therapy with those particular events. A growing debate involves the introduction of patient-originated outcomes, defined by the patients themselves and based on their own criteria of importance — for

instance, the impact of the therapies on quality of life and productivity. Of course, it is important to be mindful that these patient-centered perspectives need to be balanced with the high degree of subjectivity that these outcomes may have among distinct populations.

A few considerations regarding all the assessments involved. First, the inclusion of patient, site, and physician burden and disease prognosis to calculate frequency and duration of the clinical and lab assessment during long-term follow-ups, as patients with some of these conditions are susceptible to be treated with cell and gene therapies may not be able to reach such extended periods of time. Second, define the risk and benefit of potentially invasive methods of sampling — like tissue biopsies, when feasible — to have more direct evidence of durability — for instance, change in gene expression levels or chimerism level over time — to complement noninvasive methods like imaging when biomarkers weren't existent.

Regarding the data sources, my colleague Ian Bonzani discussed this earlier in the forum. Here I just wanted to emphasize the importance of the data quality from sources like standard of care in the real world and the ongoing long-term follow-up studies, which need to be designed differently from the hypothesis-based pre-marketing trials.

Finally, just a growing area that focuses on the identification and validation of analog or surrogate data to infer durability in cases where proper outcomes either do not exist or are difficult to obtain. In this area, ongoing efforts focus right now on establishing the biological validity based on the elements with the underlying disease, the functional characteristics of the therapy, the targeted tissue, and the overall biological mechanism. With that, I'd like to thank FDA for the invitation.

DR. KUMAR: Thank you, Diego. Our next speaker is Mecide Gharibo.

DR. MECIDE GHARIBO: Thank you, Dr. Kumar, for the opportunity to speak here this afternoon. I'd like to speak in regard to the challenges with existing methods of post-marketing access to nonconformed products and data collection. My name is Mecide Gharibo, and I'm part of Bristol Myers Squibb (BMS), the U.S. medical hematology organization. I also oversee the expanded access protocols for nonconformed products released in the post-marketing requirement.

All current autologous CAR T products that are intended for commercial manufacturing are associated with a subset of products being out of spec to commercial release and considered investigational. For cell therapies, the commercial drug product specifications are typically more stringent and based on clinical trials with limited sample size and by applying tight tolerance intervals. This approach poses a significant challenge for the cell therapy field in general, with higher out-of-spec rates in the commercial setting compared with the clinical trial setting.

Out-of-spec products can only be released via single-patient IND application (sIND) or manufacturer-expanded access programs (EAPs). Out-of-spec products are eligible for access programs that have stringent quality specifications for these EAPs based on indication, as well as release criteria. These products are in general consistent with clinical-grade products that

are eligible for these protocols. In addition, these EAP studies also mandate a period of follow-up within the EAPs with regard to data capture of safety and efficacy outcomes, which also adds to duplication of data collection for many of these patients that are in parallel enrolled in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry.

Based on BMS's experience with two approved autologous CAR T products, the majority of the out-of-spec products meet the clinical-grade specifications. The vast majority only narrowly miss the commercial drug product specification that results in being out of spec, and these products would have met the same specifications in the clinical trials that were the basis for regulatory approval with an established benefit and risk profile.

Patients enrolled in access program protocols are in parallel enrolled in registries such as the CIBMTR to meet the 15-year post-marketing long-term follow-up requirement for safety and effectiveness outcomes. This is consistent with the methods of data capture for patients who receive a commercial-grade product. This results in duplicative effort with data collection for patients who are enrolled in these expanded protocols for the duration of their participation and added burden to sites of care with cost and resource challenges. If an alternative mechanism for release of out-of-spec products would be considered, instead of mandated access protocols, prospective data collection via CIBMTR could still occur and capture FDA required data for out-of-spec products without duplication. Published data to date from such registries have demonstrated similar safety and clinical meaningful benefit outcomes observed in patients administered out-of-spec products.

The current process of sIND and access protocols for release of out-of-spec products is complex and burdensome, with significant resource challenges to sites of care and patients with potential delays to treatment, and not optimal for patients that with life-threatening, aggressive hematologic malignancies for which current CAR T products are approved. For each new CAR T product and/or label expansion of approved CAR T products, additional protocols and/or amendments are required, which add burden to sites of care and resources and will not be sustainable as the field of cell therapy expands to broader patient populations and disease areas.

There is experience with other country health authorities, such as the EMA, for which the mechanism of release of post-marketing out-of-spec products does not require access protocols or sIND application and simplify the process for the physician and the patient.

In response to having the potential speaker today, we would like to propose to FDA to consider an alternative mechanism for release of nonconformed products that meet clinical-grade specifications and implementation of a process such as manufacturing outcomes mitigation strategy with risk-based assessment for clinical-grade non-conformed products, in lieu of access programs. Similar to the risk evaluation and mitigation strategy, this would simplify and standardize the notification and process of release of such products for physicians and patients, meanwhile maintaining data capture for safety and efficacy consistent with commercial-grade products via the CIBMTR prospective data method.

If access programs must remain a key mechanism for release of out-of-spec products, then

consider implementing guidance for manufacturers with a platform study approach that would enable access of a manufacturers' out-of-spec CAR T products in the post-marketing setting within one program and eliminate the need for multiple access protocols, thereby leveraging efficiencies, significantly decreasing burden for sites of care and physicians as well as the patients, and ultimately ensuring cell therapy to be more sustainable for the broader patient population as this field continues to expand. Thank you very much for the opportunity to present today and for your consideration.

DR. KUMAR: Thank you, Mecide. Our next speaker is Fyodor Urnov from the Innovative Genomics Institute at the University of California, Berkeley.

DR. FYODOR URNOV: Thank you, sir. Folks, my name is Fyodor Urnov. I'm a professor of molecular therapeutics at the University of California, Berkeley, and a scientific director at its Innovative Genomics Institute, which was founded by Dr. Jennifer Doudna, winner of the Nobel Prize for inventing CRISPR-Cas genome editing. I'm honored to present an overview of the genomic therapies work group, a joint effort between the IGI and the ASH Research Collaborative on behalf of my co-chair, Dr. Donna Neuberg, and all the group members. On this slide are my disclosures.

I will provide a brief summary of the work and output of our initiative. You can find more details about the initiative and the full copy of our working group report at this URL.

Our work brought together experts across academia, industry, and government, including researchers, clinicians, regulators, experts in dating standardization, and members of the sickle cell disease community. We aimed for and attained comprehensive cross-functional expertise. We held stakeholder roundtables to present our impact report and presented at the American Society of Hematology annual meeting and more recently to a broad group at CBER and CDER of FDA.

This is a table from our report. It showcases the fact that we live in a period of absolutely unprecedented scale of clinical deployment of genomic therapies for sickle cell disease. We believe that there is a unique opportunity to leverage this extraordinary variety to better understand and improve the technology. Specifically, the two swim plots you see on the left are data from two separate clinical trials. One's from gene therapy; the other's from genome editing. This showed that such genomic therapies can have sustained, robust disease-modifying activity. The questions our group asked: "Are there identifiable factors that can predict or modulate the robustness and stability of the anti-sickling mechanism that has been employed? Do different therapeutic strategies vary? How do the different delivery mechanisms, viral or nonviral, contribute to overall robustness and persistence of the therapy? How durable are the modified clones contributing to hematopoiesis post-infusion?" By broad strokes, the group identified many assays and types of data they would want to generate to build a full picture of the drivers of robustness and persistence over time.

The overarching driver behind our effort is definitive proof of the 13-year history of gene therapy that only human clinical trial data can inform on safety risk and efficacy modifiers. The first of many examples is 20 years ago: A gene therapy trial for bubble boy disease was

associated with multiple serious adverse effects (SAEs). The vector was redesigned, and a well-tolerated curative gene therapy now exists. Ten years ago, Emily Whitehead, a pediatric subject on a CAR T trial, was within 24 hours of death before the treating physician's skill saved her by the administration of tocilizumab. That medicine is now part of the approach to administer CAR T safely, with 20,000 subjects dosed. The general point: These and other SAEs could not have been predicted from any preclinical data at the time; they emerged in the clinic. This argues strongly that sponsors of distinct approaches to genomic therapies for sickle benefit from participation in a harmonized framework for gathering and analyzing evidence pre- and post-dosing, because this creates an opportunity for all to understand and address any drivers for genomic outcomes of concern that allows for robust cause mitigation and addresses potential future regulatory concerns proactively. As Dr. Daniel Bauer of Children's Boston, member of our group, said, "We have to act from knowledge."

What are our high-level recommendations? We recommend that sponsors openly share data about successes and failure and that data are recorded associated with every subject dosed. We argue for a biorepository, which is essential to support research. We argue for the regular collection of samples to place into the biorepository. We request that the Agency supplement its current guidance document and develop a guidance that supports understanding of data needs and collection of real-world data for long-term study of genomic therapies.

Let me focus on the biorepository component. A logical frame to adopt is that of the patient journey, as an individual living with sickle cell disease is considering a genomic therapy and is then brought into the hospital for the harvesting of cells. As the cell product is manufactured and released, the subject returns to have the drug product administered, and then there is follow-up. We argue that the best way to learn from the experience of each patient is to gather specific biospecimens shown on this slide, and we believe that these specific biospecimens should be placed into a biorepository.

We propose the creation of a Genomic Therapy Biorepository in which peripheral blood samples and samples of critical reagents can be put. We believe it is essential to support research to guide future regulatory action and to enable studies on modifications that contribute to outcomes, both positive and negative, across approaches. Finally, if connected with data from a resource such as the ASH RC, we believe that this could be the proverbial rising tide that lifts all boats.

In conclusion, thank you to the Agency for giving me an opportunity to speak with you and to all the working group members who have made it a success.

DR. KUMAR: Thank you, Fyodor. Our next speaker is Gerald Downey from bluebird bio.

MR. GERALD DOWNEY: Thank you, Vijay. Hello, my name's Gerry Downey. I'm a statistician, and I serve as the Lead Stats Consultant across the bluebird bio product-based registries. I will speak about considerations for balancing the need for robust data collection and monitoring for patient safety with patient caregiver burden to support minimizing patient attrition in the post-approval setting. This presentation is based on bluebird bio's interactions during two biologics license applications in 2022 and also our recent experiences in

implementing post-marketing requirements for one of our pre-approved therapies.

Post-marketing studies for gene therapy will need to strike a balance between appropriately monitoring for early development of malignancies in the post-marketing setting and the associated data collection while keeping the patient and caregiver burden in mind to minimize patient attrition. Registry studies of gene therapy products needs to be efficient with the gains from enrolling, balanced with the participation burden for patients, caregivers, and their physicians.

This slide presents selected routine safety assessments using one of our programs, SKYSONA, as an example. SKYSONA has a boxed warning for hematologic malignancy, including life-threatening cases of myelodysplastic syndrome, which has occurred in SKYSONA-treated patients. Therefore, much of the monitoring in the post-approval registry study in pediatric patients is related to early detection of malignancies by requiring frequent bloodwork and early bone marrow biopsies. Routine and protocol-driven complete blood counts are monthly in the first year. Many of these can be done locally. Essential readings are required by the regulatory agencies for the peripheral blood smear, and central labs are necessary for the gene therapy tests, which means local lab use is much more difficult logistically. These central lab tests are required every 4 months in Years 2 through 10 and then every 6 months for 15 years after treatment. In addition, there are protocol mandates triggered for more frequent testing, which are not shown on this slide. Given the risk of hematologic malignancy with SKYSONA, the post-marketing study requires frequent assessments to ensure adequate monitoring for hematologic malignancy, but we need to also keep some realities about rare diseases in mind.

Gene therapies are frequently aimed to treat rare diseases, which are best treated as specialty centers, which are by definition sparse and therefore not likely to be near where many of the patients live. This frequently involves the need for air travel and hotel accommodations when the patients travel to the study sites. In addition, gene therapy frequently treats pediatric patients, which means that the child will miss school, and also the child's parents or caregiver will miss work, while the lives of the siblings are also interrupted due to the level of routine monitoring. These are real-world logistic issues that the child's families must manage over 15 years, extending from elementary school into adulthood, where they'll be making their own decisions about trips to see a childhood disease specialist.

There is a concern within bluebird bio and other stakeholders that in the drive to gather more granular information through monitoring, we may lose patient, caregiver, and physician support for such assessments, leading to attrition in the post-marketing setting. This may result in obtaining limited or no data for patients versus data that is less frequent but complete. Loss to follow-up in the post-marketing setting is already a concern in the cellular therapy context and is even more critical in the pediatric rare disease nonmalignant setting. Our concerns are supported by data that a recent analysis from the CIBMTR showed risk factors for loss to follow-up in autologous and allogeneic transplant recipients, including younger age at time of treatment, treatment for nonmalignant disease, further distance from the transplant center, and lack of private medical insurance. Follow-up focusing on minimizing patient attrition in this patient population is therefore essential to ensure surveillance for late effects.

As statisticians, we can bring our missing data toolbox to the table to assess the impact of loss to follow-up, to describe the extent of missing data, and to determine if the reasons for loss to follow-up are related to the safety outcome of interest. The best approach statistically to handling missing data is not to have it in the first place.

I would now like to speak to considerations for minimizing patient attrition. What mechanisms can we put in place to strike that balance between appropriately monitoring for the potential development of malignancies and the successful enrollment and retention of study participants? The first approach would be for all stakeholders to seek input and take action from the patient community when designing studies, having a patient community voice at the table. The second approach to enhance patient retention would be for the sponsor to establish a cadence for evaluation of study protocol deviations, noncompliance, patient attrition, and even refusal to enroll with the regulatory agencies. The sponsor in the regulatory agency should then be open to honest evaluations of the impact of the study methods and assessments, develop protocol methods within a realist framework, and be willing to amend the protocol to optimize the balance needed for the patient safety, data collection, and patient retention.

bluebird bio would like to thank the FDA CBER OTP for holding this public listening meeting. It is a prime example of the forum where we can openly share challenges and solutions. Thank you for listening.

DR. KUMAR: Thank you, Gerald. Thank you to all of the session's speakers for sharing your perspective on this topic. I will now open it up to FDA to ask any clarifying or follow-up questions.

FDA Questions

DR. ALIMCHANDANI: I had a question for Dr. Diego Correa. You talked about data assessments and data sources. I think it was mentioned in a prior IQVIA presentation as well — leveraging real-world data — population-based data sources. One of the issues with the long-term latency adverse effects with gene therapies is secondary malignancies, as has been spoken several times during these sessions. For that, we need to show analysis and verify causal association with the viral vector, for a really detailed issue analysis. How would we leverage population-based data sources to get that kind of data? Would it be possible to do that?

DR. CORREA: A very important question. As a matter of fact, yes, because one of the things that we think here at IQVIA is that we need to have some of these outcomes and data to contextualize the adverse events and relate them with potential epidemiological prevalences in these patients to have specific adverse events or entities, like cancer. Of course, tumorigenicity is highly prevalent in specific populations. Basically, what we may need to do is just incorporate those analyses from an epidemiological perspective and then contrast with the potential generation of this tumorigenicity by the gene therapy. Actually, we are doing that for a couple of sponsors in which, if the case of a malignancy actually arises during the long-term

follow-up, with specific techniques, you can actually discriminate just to see whether this tumorigenicity was molecularly and genetically associated with your therapy or not and link this information that is more mechanistic with more epidemiological information just to make a true assessment of the relatedness between the therapy and the potential oncogenicity of the therapy itself.

DR. ALIMCHANDANI: Thanks. I also wanted to thank Ms. Heather Smith for her comments and for sharing her personal experiences. I didn't have any questions. I just wanted to say thank you.

DR. KUMAR: Thank you, Dr. Alimchandani. Dr. Lapteva, you have a question?

DR. LAPTEVA: Thank you. I also would like to thank all of the speakers for sharing their perspectives and maybe would like to get some more clarification on the perspective of patient advocates and perhaps have a question to Ms. Smith from the SCID Angels for Life Foundation. Again, since we're speaking in this session about specific safety and efficacy outcomes, from the perspective of the patient and caregiver, are there any specific outcomes that you would like to see measured in the long term with gene therapies? We're talking here about potential life events like development of cancer or effect on fertility or any other outcomes that you would want to see measured long term versus those outcomes that you believe would not be helpful to evaluate.

MS. SMITH: Thank you for the question. This is a great question, and I think the two that you mentioned are probably the two that are most relevant and most talked about in our group of patient advocates when we talk about gene therapy. That would be the risk of cancer, just because of the family's prior fear of what history has shown in the past, although things have changed. But from a family's perspective, of course that's very scary. Going forward, you would want long term.

We would love to see, like other groups have mentioned today, long term to be more than 15 years, especially when it comes to something like cancer or even fertility. Like you said, depending on the age of the patient, long term may not even be when they're at childbearing age. If you're only doing a study that follows them for the first 15 years and they had gene therapy in the first few months of life because they were part of the St. Jude trial, for example, it wouldn't even be in childbearing years yet that that would be following up. Definitely, that's very, very important. Even to those who are of childbearing age when they go through the treatment for gene therapy, they take preservation very seriously for their fertility, beforehand because they would like to make sure that that is an option for them. Thank you for bringing that up. Those are definitely the two most important that I would say we would like to see followed.

DR. LAPTEVA: Thank you. This is helpful.

DR. KUMAR: Thank you. Any additional questions from FDA panelists?

DR. YOGURTCU: I have one question for James Nickas from BioMarin. In your opinion, how can the FDA guidance foster health authority, patient advocacy group, key opinion leader, and

sponsor collaboration to identify product class-specific safety and efficacy outcomes that matter for post-approval monitoring?

DR. NICKAS: Thanks for the question. I think this is a lifecycle management question, and I think it's consistent with FDA's approach to risk management conversations with sponsors and key opinion leaders throughout the drug development process. I would suggest these conversations about what's important to collect not just in clinical trials that would extend to the post-marketing but to actually bring those stakeholders together early when a drug is being developed. Of course, as data accumulates and matures, those views can evolve as well. I think that early and ongoing dialogue incorporated into the milestone type of conversations that occur throughout drug development might be the place where we could improve the precision of how we evaluate safety and effectiveness throughout the product lifecycle.

To the point that was just talked about — the two events of importance of the cancers and fertility — just take cancer, for example. The opportunity there is that that's an event that's likely not missed in recoding in the various claims databases. We probably have all the occurrences of that, so there are opportunities to really link information to put some of these most important events in proper context for the users and the patients who get these treatments to either put to bed that the risk is less than what we thought or identify something that needs to be addressed. I think it's a conversation that has to go out throughout the lifecycle and at the milestone conversations that we have as part of drug development.

DR. YOGURTCU: Thank you. This was helpful.

DR. KUMAR: Thank you, Dr. Yogurtcu. You have another question?

DR. YOGURTCU: I had one question for Dr. Urnov, perhaps a naïve question. Is a genomic therapy biorepository really necessary? Couldn't we fully digitize the information and collect that information in silico? I see potential benefits by specimen digitization, such as ease of access to data and analysis and smaller cost, so perhaps a hybrid approach may be preferable. But I'd like to hear your perspective, of course. Thank you.

DR. URNOV: Dr. Yogurtcu, I really share your framing in the sense that we really have to leverage every type of capability to gather data on subjects' experience in clinical trials and post-approval. One interesting feature of my field of genomic therapy, particularly gene editing, is that new assays in analytics are being developed all the time to assess the consequences both from a benefit and potential risk perspective on the subjects undergoing clinical trials. While I support your vision absolutely, I think that the biorepository for physical specimens would allow us, if you will, to forward-integrate such a biorepository to the fact that, let's say — heaven forbid — 5 years from now, a subject experiences a peculiar SAE. The subject was dosed years prior, and there is now finally an assay that has been developed of some flavor that can be used to assess the causes and consequences of that outcome in a way that currently doesn't exist. The only way to make that happen — sort of future-proof the biorepository — is to actually store living specimens. But I do not disagree with anything you said.

DR. YOGURTCU: Thank you very much.

DR. KUMAR: Thank you. Okay, if there are no more questions, that will wrap up today's listening meeting.

Closing

DR. KUMAR: Thank you for attending today's event, and a special thank-you to our public speakers and FDA panelists. As a reminder, a recording of today's event will be posted on FDA.gov in the next few days. If you have additional comments to share, please add those to the docket, which will be open for public comment until May 26, 2023. To access the docket, type FDA-2023-N-0398 in the search bar on Regulations.gov.

Thank you again for joining. Have a great day.