Ron: Hello everyone. I'm Ron Bartek, president of the Alliance for a Stronger FDA. I'm joined this morning by Steven Grossman, the Alliance's Executive Director, as well as Mary Dwight, Vice President of the Alliance and Senior Vice President of Policy and Advocacy at the Cystic Fibrosis Foundation.

First, we'd like to give a quick word about the Alliance for a Stronger FDA. We are a multi-stakeholder coalition that advocates for increased appropriated resources for the FDA. We've been an important force in the doubling of the available annual budget authority for the FDA, from $1.6 billion to more than $3.2 billion. And we're the only advocacy organization focused on resources for both food safety and medical products, as well as the other components of the FDA's important mission.

Our members include consumer and patient groups, research advocates, health professional societies, and trade groups, as well as industry. We have about 150 members and always welcome more to further strengthen our advocacy and educational efforts.

Regarding procedures for today's conversation, our speaker has kindly agreed to the format that's worked so well for all of us in our earlier webinars. He will interview himself based on questions the Alliance has already provided him, followed by ample time for him to answer some of your questions. You may submit such questions at any point in this webinar by clicking on the Q&A button at the bottom of your screen. Be sure you click on the Q&A button rather than the chat function.

And now I have the distinct privilege and honor of introducing our esteemed speaker for today's webinar, Dr. Wilson Bryan, director of the Office of Tissues and Advanced Therapies at the FDA's Center for Biologics Evaluation and Research. As most of you probably know, the mission of Dr. Bryan's office is to ensure the safety, potency, and effectiveness of a wide variety of products, including purified and recombinant therapeutic proteins for hematology, cellular therapies, gene therapies, and tissue products for the prevention, diagnosis, and treatment of human diseases – a mission that Dr. Bryan is extremely well-qualified to help accomplish.

Dr. Bryan is a neurologist by training. He graduated from the University of Chicago Pritzker School of Medicine. He served on the neurology faculty of the University of Texas Southwestern Medical School for 13 years. He's been an investigator in clinical

trials in cerebrovascular disease and neuromuscular disorders.

Dr. Bryan joined the FDA in 2000, serving first as a reviewer, then as a team leader, branch chief, division director, and now as director of CBER's Office of Tissues and Advanced Therapies, a position in which he has served from the very beginning of OTAT five years ago. He is responsible in that position for overseeing the regulatory evaluation of the cell and gene therapy programs that are so important and vital to all of us.

Dr. Bryan, thank you so much for your longstanding commitment to advancing leading edge treatments for all of our patients, for your perseverance in maintaining that commitment through the extraordinary additional challenges of the pandemic, and for agreeing to spend some time with us this morning to help us understand how we might best work with you and your colleagues to accomplish the mission we share with you. Dr. Bryan, thank you again, and the floor is yours.

Dr. Bryan: Thank you. And thanks particularly to the Alliance for all that you've done for supporting the FDA. So, I'm happy to be here this morning. And I'm just going to run through the questions that you've given me and just ramble a little bit if that's all right.

So, the first question I got was: Why was the office renamed the Office of Tissues and Advanced Therapies? So, I'll refer to it as OTAT.

OTAT was created back in 2016. And at that time, the Center for Biologics had some hematology applications and hematology expertise in the Office of Blood Research and Review and some hematology expertise and applications in the Office of Cellular Tissue and Gene Therapies, OCTGT. And the thinking was that that was a bit of a duplication of expertise and that we needed to consolidate to be more efficient.

So, the applications for sickle cell, hemophilia, thalassemia, which were being looked at in the Office of Blood sort of combined with the gene therapies for those indications, came together in OTAT, which now regulates cell therapies, gene therapies, as well as plasma-derived products such as immunoglobulins and coagulation factors, all of which have substantial hematology applications. So, it was really a consolidation effort to try to consolidate the hematology expertise.

The next question is about the projected growth in the workload for OTAT. It was projected that we would have more than 200 INDs per year and further growth in the backlog of more than 800 active cell-based or directly administered gene therapy INDs. Wondering where we stand now?

Well, we stand sort of swamped right now. We've long ago passed that 200 INDs per year. In 2020, we had 354 INDs. In 2021, so far we have 275. I expect we'll over 300 again this year. So, that projection of 200 was a bit of an underestimate. And I expect the numbers that we're seeing now are being held down a little bit by the pandemic and that, as we come out of the pandemic, we'll see an upsurge again.

With regard to the projection of 800 active cell-based or gene therapy INDs, as of last week, we had 1142 active cell therapy INDs and 1201 active gene therapy INDs. So, that projection of 800, again, we're well past that in spite of the pandemic. And I expect that these numbers will increase rapidly as we hopefully get out of this pandemic.

So, that gets to the issue of making projections and predictions as not so easy.

The next question was that FDA, or at least some parties, had projected approval of 10 to 20 cell and gene therapy products a year by 2025. So, what is my thinking on that now?

Well, the pandemic has had an effect, and I don't think we're going to meet that target of 10 to 20 by 2025. Just to give you an idea, if we want to predict how many BLAs we're going to have, we should look at the INDs. And the gene therapy INDs, particularly, increased from 67 in 2016 to 161 by 2019. So, that's a 140% increase in three years.

Well, what happened from 2019 to 2020? There was really no change. It went from 161 to 160. So, we had a 140% increase over three years, and then it plateaued. I don't have the numbers for 2021 yet, but I'm suspecting that we're still going to be in a plateau phase. And the pandemic has really set us back as far as gene therapy is going. So, I think the projections regarding the BLAs and approvals also need to be set back probably by two or three years, depending on how long this pandemic goes on, how long these supply chain issues continue.

I expect that by 2025, we'll be looking at six to eight new cell and gene therapy products, and it won't be until, again, maybe 2027 or 2028 that we're looking at 10 to 20. We'll get there though. It's just the pandemic has slowed us down a little bit.

So, the next question is with all this workload, what changes in the staffing, in other CBER resources do you anticipate will be necessary to deliver on this growth? And there's so many components to this.

Our total INDs, the total number of INDs coming in to OTAT – the first year in 2016, we had 223, and that includes INDs for expanded access or what's sometimes called "compassionate use" as well as INDs for what I think of as being true research, where they're trying to gather evidence of safety and effectiveness to bring a product to market. By 2020, that number had almost tripled up to 666. So, just phenomenal growth. And the Center has been supportive. OTAT has grown. We're now up to approximately 300 employees. But the number of employees and the growth in OTAT has not kept up with the growth in applications.

I mentioned earlier that gene therapy INDs had increased by 140%. Actually, cell therapy INDs increased by a similar amount. We haven't doubled the size of OTAT in three or four years. There's a lot in the press about new **PDUFA** legislation and that that will bring additional resources. I've learned not to count on those things until they're actually in hand.

But just adding employee positions will not be sufficient. We've got to have the ability to recruit effectively and hire effectively. And hiring is a challenge for the FDA. It's challenging partially because our salaries are not competitive with a booming cell and gene therapy industry. The salaries that are offered by industry are so disproportionate.

So, we keep people at FDA because they believe in our mission of public service and because the work is incredibly interesting. There's so much exciting work going on in cell and gene therapy that it's a lot of fun to work in OTAT. But the salary discrepancy can make recruiting and keeping people a challenge at at the FDA.

So, if just having enough people to keep up with the increasing workload isn't going to solve a problem, then we have to think of doing things differently. And one of the things that we have to do differently is we have to be thinking about our organizational

structure. Some of our branches have grown so big that they are difficult to manage. New people coming onboard must get the attention that they need from managers to be appropriately trained. And it's hard for the managers to ensure consistency across all applications, and consistency is very important to us. So, we're looking at trying to restructure our organization in a way that will deal with the increasing workload. And that's a challenge. Restructuring takes a lot of time, but we're thinking about it.

Now, we're also thinking about if you can't actually keep up with all the workload, then you've got to do things differently. And we have a reputation, I think, of providing individual attention for all the IND sponsors that come in. And I think that in the years ahead, there's going to be less individual attention for sponsors. And we've got to find ways to communicate with our sponsors, particularly academic sponsors and small drug companies, so that they don't require as much individual attention.

We're going to look at what we think of as group communication. So, we're actively updating our websites to focus on meetings – how to prepare for meetings, the type of questions to ask at meetings. So, you'll see within the next year an update on our website focused on meetings with the FDA, meetings with OTAT. We also have a webinar series called OTAT Learn that has probably about a dozen webinars there. We're going to add to that, and that will be coming out within the next six months, a few additional webinars. We think that we need to have more webinars in general with our stakeholders in order to communicate. And of course, we have to be thinking of how to put out more guidances.

One thing that we've seen in the pandemic is the FDA putting out brief guidances related to the pandemic. Some of those guidances take the form of bulleted guidances. They're relatively short, very focused on a specific topic guidance. And that paradigm we think may be useful going forward to allow us to communicate more quickly and more deftly with our stakeholders.

So, what about the effect of the pandemic and the Warp Speed efforts on the development of vaccines and treatments? How has that impacted the work of OTAT?

We've had to prioritize a lot during the pandemic. We received many applications for products for treatment of COVID-19, cell therapy products. I mentioned that the gene therapy applications sort of plateaued with the pandemic. Cell therapy products, in

contrast, we had 63 new INDs in 2016, 91 new INDs in 2019. That was a 44% increase in three years. From 2019 to 2020, we had a 66% increase in one year. So, cell therapies kind of took off, and it took off because there're a lot of sponsors who think that cell therapies or cellular-derived products might have anti-inflammatory activity that could be useful in the treatment of COVID-19.

We also saw an upsurge in applications for immunoglobulin products, immunoglobulin products particularly proposed to treat COVID-19. Now, because of this, we've had to prioritize the applications for COVID-19 therapeutics. We've had to delay some meetings. If we think you need a meeting, you get a meeting, but maybe not as quickly as you had hoped and we had hoped.

And along with all of this, I think everyone recognizes the huge burden that has been put on our Office of Vaccines during the pandemic. The work they've done has been absolutely heroic. And whenever we have an opportunity to assist the Office of Vaccines, we have, such as consulting on the topic of myocarditis as an adverse event seen with vaccines. The Office of Blood also has pitched in, and they've helped us with some reviews, such as reviewing INDs for immunoglobulin products.

So, in CBER, the different offices, we help each other. And with CBER being so busy during the pandemic, we're all sort of sharing the workload as much as we can. Now, you can't take a cell and gene therapy reviewer and just turn them into a vaccine reviewer. It doesn't work that way. But we do help out in the little ways that we can.

The next question. How many FDA approvals of cell and gene therapies have been issued to date? And what lessons learned or helpful paradigms might be drawn from them?

We've only got a few products actually, but there's so many lessons learned. And I'm going to start with talking about gene therapy approvals. Now, we have seven gene therapy approvals right now. Five of them are these chimeric antigen receptor, or CAR-T, products that are lifesaving products. They are all indicated for various hematologic malignancies. These represent, in my mind, just the culmination of advancing science.

The scientific basis for these products is exquisite – and they're lifesaving products. They work. They all got approved based on

single-arm studies because they had large effect sizes. And that's one of the things that's been proven in the gene therapy approvals, is that, if there's a large effect size, the clinical trials don't need to be big. And we can do clinical trials in small populations.

And we have two gene therapies approved that are not CAR-T products. One is Luxturna, a treatment for a rare form of retinal dystrophy, a rare form of blindness. And the other is Zolgensma, the treatment for a rare neuromuscular disorder, spinal muscular atrophy, a fatal disease in infants. So, Zolgensma is a lifesaving product. And Luxturna lets blind people see. I mean, these products are just wonderful.

Zolgensma and Luxturna, each of these products, their clinical development program had just two trials, two trials for each one. And the total number of patients who were enrolled into the Luxturna gene therapy program in the two trials was 36. And the same 36, the same number of patients, for the Zolgensma. So, it doesn't take huge numbers. And Zolgensma used natural history controls. When you have good natural history data and you have a huge effect size, then natural history controls in small studies are feasible. We need more natural history studies, and we need to design clinical trials for these rare diseases. And the science has advanced to the point where, as mentioned, we get huge effects.

Now, the implication, what follows from this, is that the first in-human studies of these products need to be randomized. Folks need to be thinking about whether the very first study could provide the evidence of effectiveness to support a marketing application. We need to stop thinking about doing phase one, then phase two, then phase three studies. In rare disease, there simply aren't enough patients for that paradigm.

Because of the huge unmet need, people can't wait. Drug development takes too long. And because the science has advanced so much, that particularly with gene therapies, we can see huge effect sizes in phase one so that we can have phase one studies that provide evidence of effectiveness.

Now, it's not just what we've learned from our approvals, we ought to be talking too about what we've learned from things that don't get approved. The public doesn't get to see this so much, but we do here at the FDA. And what's holding up approvals in many cases are CMC and manufacturing issues. And they're holding up development, and they're holding up approvals. We really need for

sponsors to start working on CMC issues early. Potency assays are a particular challenge. You've got to understand your product. You've got to figure out its mechanism of action and develop a good potency assay as early as possible in development.

We do have cell therapies coming along as well. I should mention that this year we've approved two gene therapies, Breyanzi and Abecma. And we've approved two cell therapies, Stratagraft for partial thickness burns and Rethymic for a rare immune disorder, DiGeorge syndrome. These again, are lifechanging and lifesaving products. So, we're very excited about what's going on in gene therapy and cell therapy with regard to having a real impact on rare diseases.

I want to also mention that three of these products, Breyanzi, Stratagraft, and Rethymic, are our first approvals for products that have Regenerative Medicine Advanced Therapy Designation. That designation came into existence in 2016, and so it's been around for about five years. And we've got our first three products through the system that have RMAT designation. OTAT now has approximately 92 products that have either RMAT designation or breakthrough designation.

What follows from that, what RMAT designation and breakthrough designation get you is more attention from the FDA. Well, if we've got over 1100 cell therapy active INDs and over 1200 gene therapy active INDs - and that doesn't count all the INDs that we have that are for xenotransplantation, or immunoglobulin products, or convalescent plasma – I'm sorry, convalescent plasma's in Office of Blood – I mean plasma-derived products. If you don't count those – we've got just probably in the neighborhood of 2500 active INDs. That's just a huge number. If some products that have breakthrough and RMAT designation get extra attention, then that leaves less attention for everybody else.

And it comes back to the idea that we can't keep doing business the same as we always have. I think breakthrough and RMAT designations are very valuable because they allow us to focus on products that have provided preliminary evidence that they truly have an effect for patients. But we're going to have to communicate differently for all the other products in order to serve all the patients and bring as many things forward as we can.

So, the next question from the Alliance: How would you characterize progress being made on challenges facing cell and

gene therapy and particularly a development of efficient delivery vehicles such as viral vectors?

So, there's going to come a day when we have hundreds, maybe thousands, of gene therapies on the market. And we'll have decades of experience with these products. And we'll know which vectors do what. And we're not there yet. We've got seven products on the market, seven gene therapy products on the market. Two administered using AAV, adeno-associated virus. The other five, the CAR T products using ex vivo gene modification. We've got so much to learn. And one of the things we're learning is about safety issues.

We had an advisory committee meeting in September talking about the safety issues that we're seeing with AAV. Now, people had been talking about safety issues with vectors such as insertional mutagenesis **[inaudible] [00:30:43]** and hepatotoxicity. We've been talking about those for a long time. But now we're seeing other safety issues, like microangiopathy and neurologic problems such as dorsal root ganglion problems and **[inaudible]** MRI findings. We weren't talking about these things decades ago. And over the years to come, we're going to see more and more safety issues, and we're going to figure out which vectors have which safety issues. And that's what lies ahead of us. There's a lot of learnings to be done.

The next question was about anticipating and responding to immunogenicity. Immunogenicity is a huge issue. It limits safety and effectiveness. And I'm very optimistic that we will work out the issues of immunogenicity. And this is very important because we know that for some gene therapies, their effectiveness wears off.

And if, for example, you're treating a patient with a very – a child with a fatal disease, a very bad disease, and you give them a gene therapy, you need to monitor that child to see if that's wearing off. And probably, it will start to wear off long before we realize that it's wearing off, and we need mechanisms to repeat administration or give a second dose. That's something we're going to have to work out. I'm confident we will. There's so many products and there's so much science around the immune system these days that we're going to work that one out.

Now, I was also asked to comment about early inclusion of pediatric patients in clinical trials, and it's important to remember

that children are a vulnerable population. They can't give true informed consent for clinical trials. And so, we're getting to ethical issues with enrolling patients into trials who can't give true informed consent. And so, the regulations provide special protections for children.

So, what the regulations specify is that we need to have evidence of a prospect of direct benefit to the child that participates in the study. This is not required for studies in adults. Do a study in adult, there doesn't have to be any prospect of benefit for that study subject. But in kids, there does need to be a prospect of benefit, and we get evidence of a prospect of benefit either from nonclinical studies or from human experience in adults.

That human experience in adults, how much we require depends on the specific situation. And in some cases, adult studies are not ethical or feasible; it depends on the specific disorder of interest. But in other cases, we do ask for safety and/or efficacy studies in adults before studying kids. So, it's really very much a case-by-case basis.

I was asked to also comment about gene and vector manufacturing. And the pandemic, again, has really set back manufacturing, particularly for gene therapy that supply chain issues have a problem. People can't get – early in the pandemic, the labs were closed. People weren't going to their labs to do the research. I think labs are opening up these days. But vector manufacturing was being diverted to the pandemic, as it should. But we're now seeing vector manufacturing going back to gene therapy, so it's picking up again.

We're involved in a couple of public-private partnerships that are focused on trying to improve manufacturing. These include the Advanced Regenerative Manufacturing Institute, or ARMI, which is interested in advanced manufacturing for cell and gene therapy products. And we're also involved in NIIMBL, the National Institute for Innovation in Manufacturing Biopharmaceuticals.

Now, NIIMBL works with all types of products, not just cell and gene therapies, but also small molecules, and monoclonal antibodies, and those sorts of things. But they're interested in cell and gene therapy too. So, both of those organizations have been public-private partnerships that we're working on and we think are very helpful in trying to move manufacturing forward. Because as I mentioned earlier, manufacturing issues really have been a big

stumbling block for development of cell and gene therapies.

So, I'm going to stop there and turn it back over to the moderators to see if there are other questions that are coming in.

Mary: Thank you so much, Dr. Bryan. That was wonderful, and it was really excellent to hear that just the sheer volume is staggering. I know we all hear about it, but to hear you go through the tallies and just realizing the resourcing challenges you all are facing, kudos to all that you are doing.

So, I wanna just make a flag for those. I know we have a few questions already in the Q&A section. If you have questions for Dr. Bryan, please do put them in that Q&A box, not the chat box. Put your questions in the Q&A box, and we'll try to get to as many as we can. We know we've got several coming in already.

Again, it's impressive to see the breadth of your work and also to hear about the resource challenges that that puts on OTAT. I want to talk about process. And hearing you think about some of the organizational and process questions that you're really grappling with as you shift to address this volume.

Can you speak about some of the efficiencies of collaboration that your contemplating? So, whether you're a patient group or a smaller company and thinking about how to approach OTAT, can you help us better understand the requirements for developing a trial or opportunities in the disease area and really how we, your constituency, can be best prepared to interface with you all for the most efficient process?

Dr. Bryan: Right. So, thank you for that question because one of the challenges that we have is receiving applications, IND applications, or meeting requests that really are so grossly deficient that we can't communicate effectively with the stakeholder. And that ends up taking a lot of our time that is not productive and is not really helping the sponsor much either. It's in the best interest of everyone if the sponsor can submit a meeting package, or an IND application, and questions that have the material there that we need to answer the questions and have questions that we can understand. So, that's how to make the whole process more efficient.

As I mentioned, we're in the process of revising our website. And you'll see a revised website within the next year, I'm hoping within

the next six months, that will focus on meetings – the different types of meetings, the INTERACT meeting that comes very early in development, the pre-IND meeting, as well as our usual end-of-phase meetings, pre-BLA meetings, and Type C meetings. So, we need to do a better job of communicating to our stakeholders so that they can submit INDs and meeting packages that are more effective now.

Now, we have a lot of guidances out that talk about various topics. But for a small drug company – now we're seeing big drug companies – they can learn our guidances and learn their lessons. The academician, the scientists at a university, they don't have the time and the resources to become an expert in regulations. And we need to keep that in mind. And again, I'm hoping that our website and our webinars that we'll be putting out will be useful to the academicians who've been driving the science in so much of cell and gene therapy.

Ron: Thank you so much, Dr. Bryan, for the overall presentation and for answering that first question. You mentioned that there were some multiple-stakeholder, public-private partnerships ongoing with your office and CBER generally. I want to highlight one of them that you and I have talked about before, and that is the Bespoke Cell and Gene Therapy collaboration, which seems to us to be quite exciting.

Can you comment briefly on that effort with the friends of the NIH, and NCATs, and some of our sponsors, and NORD and all that and how it might lead to early publication of data that would be made readily available to all parties in sort of a precompetitive space?

Dr. Bryan: Well, this is one of my favorite projects. What the Human Genome Project did back in 2003 was it identified all these genes, and scientists in labs, thousands, tens of thousands of labs all over the world, started looking at these individual genes and figuring out what the individual gene did, and what happened when that gene was mutated, and what diseases we saw, and started thinking about how we're going to fix them.

And so many of these diseases are bad diseases. These are the kinds of diseases that your kid, your three-year-old kid or your six-year-old kid starts not doing something right, and something's not quite going right. And you take them to a doctor, and the doctor says – well, it used to be the doctor said, "I don't know what this is,

and I can't do anything about it." But now with genome sequencing, they figure out what it is, and they tell you what the gene is and was mutated. And still the answer is, "I don't have an answer for you." Well, that's going to change, and we're going to fix those diseases. I don't know how long it's going to take, but we're going to a fix them.

And the question is, how do we get there? And the Bespoke Gene Therapy Consortium is, in my mind, a sort of no-patient-left-behind initiative. These were people who sort of felt abandoned by the pharmaceutical industry because the diseases are so rare that there's no money in it. And that's not okay. We've got to figure out a way to fix every one of these for every patient. And I realize that's a huge challenge. But the Bespoke Gene Therapy Consortium is stepping to the plate.

I think they've got a budget of about $59 million for the next five years. And the idea is to use the consortium framework and a common set of procedures in a precompetitive environment to promote access to individualized gene therapies. And as you mentioned, it's multiple NIH institutes. It's FDA. It's certainly NCATS, the National Center for Advancing Translational Sciences, led with particularly their rare diseases group, NCATS' rare diseases group, including PJ Brooks and Anne Pariser who have been extremely active in this. And it includes industry organizations, academic investigators, advocacy groups, everybody working together because this is so important.

When we talk about rare diseases, we talk about diseases that have less than 200,000 people in the United States. Well, if you've got 10,000 patients in the United States, you can do a trial of several hundred patients. But what about the diseases that have 20 patients in the United States or 50 patients in the United States? That's what this consortium is focusing on. I think the numbers that they're using are from zero to 100 patients. I guess zero doesn't count. But up to 100 patients in the United States is the group that they're focusing on.

And the idea is to gather these data and processes in a precompetitive space that is going to be a sort of public learning process so that what we learn as we go through this will be available to everyone to really move the field forward. So much of what's done in drug development is proprietary and not made public. And that really is unfortunate. And the Bespoke Gene Therapy Consortium is bringing so many stakeholders together to

try to learn together and share that learning. So, we're excited about the process, and we're very happy to be part of it.

Ron: Thanks –

Mary: I think with two rare disease advocates asking you questions, we share your enthusiasm and are really excited about it. Thank you for sharing. In the CF world, we say, "Share seamlessly and shamelessly," and it sounds like that's very much what the Bespoke Consortium is designed to do. So, it's wonderful.

Let me go back to resourcing. A lot of questions in the Q&A are coming through about staffing. You talked about that in your early remarks and really just the breadth between capacity and just sheer volume coming through. Can you talk a little bit about your strategies?

Obviously, resourcing is a key piece, but also how you're thinking about hiring, the numbers you'd like to reach. Do you have a target of how many new scientists and new FDA staff you need to be able to handle this volume? And also, any particular strategies around recruiting or training? I'm lumping in a lot of questions that are coming through. And hopefully, you can just speak a little bit about your thinking on staffing.

Dr. Bryan: So, there's a lot there. First of all, as I mentioned, we've got to grow. Particularly, cell and gene therapy are growing so rapidly and are going to continue to grow so rapidly that we have to increase in size. We've got approximately 300 – I think it's actually just over 300 positions available in OTAT. Probably, I think we've got about 40 openings.

And particular, we've had challenges in recruiting physicians. Particularly, hematologists have been – and we've got so much exciting work being done in hematology that that's a challenge for us, recruiting physicians and hematologists. And it's a challenge particularly because our salaries are not competitive in many ways. And we have to recruit people who obviously are committed to the mission.

I expect that over the next five years or so we will grow to 400 to 500, something in that range in size. And that's good. We'll need to do that. It won't be as fast as the cell and gene therapy fields grow, if things go well. We want cell and gene therapy to grow quickly. But we will hopefully increase our number in order to deal with the

workload, but it's going to be a challenge.

And I mentioned earlier we're going to have to change our structure, I think. We're talking about that. We're not sure how to do it, but we have to think about changing our structure in order to have an environment that is welcoming for new people to come on and stay with us.

In looking at training, we're looking about partnering with industry, the pharmaceutical industry in training of new folks. So, that too will be a – that would be something new for us if we can work that out.

The recruiting. We've been reaching out more and more through social media. And I would name the different social media applications that are being used, except that I'm not all that familiar with them. And our recruiting folks come in, and they say we're advertising on this, this, this, and this. And they're things that I never heard of because I'm not so media savvy. But that's obviously important to do. And we've also been reaching out to individual universities, and it's just – I can't overstate how much of a challenge hiring has been for us.

Ron: Thank you. Dr. Bryan, we'd like to in the interest of time – we have only about five minutes remaining in your busy schedule. So, we'd like to shift to sort of a lightening round of questions and answers if we could. And the first question in that regard is based on the excellent comments you made earlier about the need to change the way we operate because there's just not enough time to provide the individual attention as you have in the past. And as badly as that is needed, there's just – I mean, if you look at the thousands of submissions, there's just not enough time. So, we'd like to explore that just briefly.

I think you mentioned listening sessions as a possible way to communicate with individual sponsors. We know that there's this INTERACT program that also might provide some opportunities. There's also just the written response format. So, how would you encourage this audience and those who will read the transcript later to pursue that kind of necessary engagement with you and your office when they're not ready to submit their IND? They need some help pre-IND-wise. So, how would you encourage them to do so?

Dr. Bryan: Well, since these are supposed to be rapid-fire questions, I think

that means I'm not supposed to ramble too much in my answer. I would say participate in our webinars. We're going to be having more webinars. Participate in those because we will – as with this, we will be taking questions from individual sponsors. And what the individual sponsor asks, it almost always is relevant to other people in the room. So, participate in the webinars. And again, watch our website. We will be talking about written responses. And you will be seeing, I think, more and more written responses as the format rather than telecons and face-to-face meetings.

Ron: Thank you so much. Mary.

Mary: Okay. You said in our preparation for today's webinar that you love talking about trial designs. I'm going to try to ask you a high-up trial design question.

A lot of our patients are looking for any opportunity to really have a chance at a cure or significant treatment. Do you have a view or approach on maximizing opportunities for patients to enroll in a additional studies of other therapies if no benefit is shown in a first gene therapy trial? So, in other words, might this conflict with requirements for long-term follow-up or other risks in antibody development? Love to hear your thoughts on that.

Dr. Bryan: Oh, this is a real challenge. And I worry sometimes that patients aren't fully informed that, if you participate in a gene therapy trial, it may limit your access to other investigational therapies. And I think that what needs to happen is that these people need to be eligible for expanded access programs or compassionate programs. I would like to see those programs expanded.

As you know, we at the FDA don't have the authority to mandate that drug companies make their products available under expanded access. But I think that that's very important for these patients who have received a gene therapy and then are not eligible to participate in the next clinical trial.

Ron: Okay. So, with like one minute remaining, I'd like to ask probably what will be the final question, Dr. Bryan. That is, you made some very helpful comments about the preclinical work that's necessary to develop that first in-human clinical trial. Can you expand a little bit on the very important question of how we can ensure, in pediatrics and in adults, that that first in-human dose is potentially beneficial, significantly beneficial? And how to balance that against the safety concerns that always drive the approval process?

Dr. Bryan: Right. So, we're going to develop new methodologies in nonclinical studies. We're going more to *in silico* models. We're going more to cellular models. And the animal models will continue to be useful to identify doses that hopefully will be, from day one, a benefit.

Now, there's no way to be absolutely certain that that first dose is going to be beneficial, and it's unlikely that that first dose will be the optimal dose. If you remember the Zolgensma experience, their initial first in-human study looked at two different dose levels. And that first study I think provided both – both dose levels provided benefit, but the higher dose level provided more benefit.

So, there'll be no way to guarantee, but we'll have to continue to do rigorous preclinical investigation to try to meet that promise of a prospect of benefit for each patient.

Ron: And thank you for that answer. And of course, that will also lead to what you commented on earlier. And that was, it'd be important that we develop the capability for a second dose or multiple doses so we can make sure that that first in-human dosed patient will receive more profoundly beneficial treatment later.

Dr. Bryan: Agreed.

Ron: Okay. So, Mary, did you have any last comment?

Mary: I think we have maxed our time.

Ron: Okay.

Mary: So, I'll hand it over to you to conclude us, Ron. Thank you so much, Dr. Bryan.

Dr. Bryan: Thank you.

Ron: Thank you so much, Dr. Wilson Bryan. You've been very helpful. We deeply appreciate your time with us this morning.

Dr. Bryan: Thank you. I appreciate the opportunity, and I appreciate what you folks are doing.

Ron: Yeah. We'll look forward to working harder and harder in your behalf to get you the resources you need to accomplish these

important missions for our patients. So, thank you very much.

[End of Audio]

Duration: 61 minutes