**Transcript (part 2 of 4)**

**Externally-Led Patient-Focused Drug Development Meeting on TSC and LAM**

June 21, 2017

tsalliance.org/pfdd

**Morning Session, Panel 2: Current and Future Treatments for TSC**

**James Valentine:** Alright, we're going to go ahead and get started, everyone. So our second topic is on current and the future approaches to treating TSC in infants and children. So here, we're shifting our dialogue from talking about the burdens and impacts on day-to-day life to discussing your approaches to treating and managing the disease. So here we're going to be having a discussion about drug therapies, either those that are approved, could also be off-label, as well as other things that you might do outside of drug therapy to try to improve symptoms and impacts on day-to-day life, which we've already talked about in our first panel discussion. So to kick off our panel two discussion, we have Camila, Tara, Shelly, and Debora. I'll go ahead and pass off the mic to Camila.

**Camila Uribe:** Okay, so good morning everyone. I'm here to talk about and tell you a little more about my daughter, Emma. In 2015, actually, after nine IVFs and a miscarriage, I was finally pregnant. We were absolutely ecstatic. On my 20-week routine examination the doctor saw something on my baby's heart. That day, May 20, 2015, was the first time I heard about tuberous sclerosis complex, and it has been a non-stop emotional roller coaster ever since. Emma was officially diagnosed the day after she was born. An MRI showed she had several rhabdomyomas in her heart, countless nodules in her brain and a few kidney cysts. Of course, we were devastated. We had been researching about this rare genetic disease and we know that she could either be severely affected or live her life without any real symptoms. I remember my call with Kari from the TS Alliance when I was still at the NICU with Emma, two or three days after she was born and what she said. She said as of today you have to be your baby's best advocate. You have to fight for her. Now you have to be on the lookout for any of abnormal activity or infantile spasms and if you see them you have to treat them immediately. With that call I understood the severity and urgency of infantile spasms.

I watch Emma 24/7. Did she have the hiccups or was it a spasm? Was she having acid reflux, or was it a spasm? I filmed everything she did. Not only to keep a souvenir of my first newborn baby, but also to be able to send it to her neurologist as soon as I saw something abnormal. I decided to take two years of work because I needed to be with her all the time. I trusted no one. I felt that in order to identify any odd behavior, I had to be there. In the end it was my responsibility, and if we did not catch her spasms on time the effects could be devastating. I felt it would be my fault if she had any delays, so I never left her side. We were lucky enough to have two great doctors. Dr. Sparagana in Dallas where we live and Dr. Krueger in Cincinnati where we enrolled Emma in the TACERN study. The first time she had an EEG, she was three weeks. Since that moment, we had EEGs every six weeks, alternating between Dallas and Cincinnati. We had to be on the lookout for any abnormal activity. When she was almost three months which she started having some abnormal brain waves. Now I couldn't think about anything else but spasms and when they would appear. A month later she started having some unusual startles and her brain activity, abnormal brain activity increased.

We were then faced with the decision of having to take Sabril in a preventive manner. We had already discussed it several times with my husband, my family. The potential side effects of this medicine were scary. When you go to the website, and you see this warning sign of potential vision loss, it made it even worse. We listened to our doctors. We read testimonials. We debated the pros and cons, but at the end of the day the question remained, should we risk her vision to treat something that really hasn't even occurred? Were the potential risks worth the benefits? It is never easy to have to decide between the lesser of two evils with the health of your newborn baby. However, we were clear that the benefits of Sabril and the consequences of not using it were much more important then its risks. Then we decided to start Emma on Sabril when she was barely five months old, and it was the best decision we had ever made.

Emma, she's 20 months old, she's doing exactly what any 20-month-old should be doing. She does have a little bit of speech delay, but we're a bilingual household, so that was expected. And we're actually starting to wean her off her medicine right now. It is actually a little bit scary, a good type of scary, an optimistic scary. But we were back on watch out mode. Look out mode. Since... Since we learned about Emma's condition, we knew we needed to be proactive and not just wait and see. We started stimulating her as early as we could. We follow up with early intervention since she was a little bit less than two months old and we started her on physical therapy, occupational therapy, speech therapy at 8 months old so that if she was delayed in any type of any area we would be able to treat that immediately. We enrolled her in Play Wisely and Tomatis, which are supposed to be two programs that stimulate brain development. I still take her to all these programs on all the therapies. We gave her medicine even before it was absolutely necessary and we would do everything all over again. We're actually very happy to learn about the PREVeNT trial. We are sure and positive that the results will be amazing.

The most difficult part of this disease is the uncertainty. The uncertainty of how severely it will affect your child and when and which symptoms will occur. If medicine will work. If there will even be medicine available for the symptoms. We might be crossing the bridge of infantile spasms right now. But we are constantly worried about what future complications will come next and will she need to face? What about if she develops AMLs or LAM or SEGAs? Will there be a course of action? What will be the course of action? What will we do in her specific case? We still need so much more research and funds for TSC. We need to understand how to cure it. Sabril was our only option and while it worked for Emma, many families have not been that lucky. We need more options. We need more medicines to treat the many manifestations of TSC because unfortunately today we have many questions, but just a few answers.

**Tara Zimmerman:** Good morning. My name is Tara Zimmerman and I traveled here with my 18-month-old son, Billy, who has TSC. We came from Reno, Nevada. He's in the back of the room, so if you hear a little sound that's him. November 19, 2015 is a day I will never forget. I was, right on cue, I was 32 weeks pregnant. I went in for an ultrasound. The tech spent an unusually long time looking at my son's heart. She was quiet, and she had a look of concern. She left the room. What felt like the twenty longest minutes of my life at that time passed, and eventually the perinatologist came in and gave me the worst news I could imagine. She suspected my son had tuberous sclerosis complex. I didn't hear everything that she said to me in those next few moments, but I did hear this: Epilepsy, tumors, brain, heart, skin, kidneys, developmental delay autism, and incurable. I left the office and started googling cardiac rhabdomyoma, tuberous sclerosis, epilepsy, everything I could think of. I found the TS Alliance website. I found the link to the various clinics, and I found hope. And then that hope left me.

The first 48 hours after his suspected diagnosis were the darkest days of my life. I searched options for terminating my pregnancy. When I saw none, I contemplated ending my own life so that I could protect my son from his. I didn't understand how my body could allow this to happen to my innocent son. Somehow, I continued to push through these feelings and decided then that I had to do everything in my power to advocate for my son and give him the best possible life I could.

I contacted three separate TS clinics on the West Coast and I eventually decided on UCLA. My son was born there on January 5, 2016. Both the best and scariest day of my life. His treatment for TSC started within moments of his birth. I saw him for 30 seconds, and then he was taken away and he was sedated and intubated at just two hours old for the first of many lifelong brain and abdominal MRIs. He was then hooked up to a 24-hour EEG, and every organ was checked for signs of TSC over the next couple of days. I didn't hold him until he was nearly 36 hours old. Thankfully he was seizure free and he was absolutely perfect. After a few days in the NICU we were able to return home.

We drove 15 long hours after a C-section to get home to our house in Northern Nevada and then it started. The waiting game. I watched him. I waited. I felt completely alone and utterly powerless. It quickly became evident to me that this disease is largely a wait-and-see game because of the current drug approvals and treatment plans and that just did not sit well with me.

Immediately after we got home from UCLA, I enrolled my son in early intervention. He began receiving occupational therapy and physical therapy at just a month old, and we later added speech therapy due to a speech delay. He also receives eyesight therapy due to his medication, which I'll get into. And he has a developmental specialist who oversees all of his care. Getting him started with these services when I did felt like the only thing that I could do at that time. I had read about Sabril (vigabatrin). I knew it was a miracle drug for so many children with TSC, but like everything else with TSC, vigabatrin was being used to treat after the fact and not as a preventive treatment of what felt like the inevitable.

When my son was just a few weeks old, I reached out to his neurologist at UCLA to see what I could do to change that. I was generally dismissed and told that we could discuss vigabatrin at his next appointment when he was three months old. So I went back to waiting and worrying and wishing for more options, really wishing for any option at that point, and then it happened. We saw his first spasm when he was just nine and a half weeks old. We went to the TSC clinic at Stanford a couple of days later. That was the first one we could get into. We did a 1-hour EEG, and it was confirmed that he had spikes in his EEG that are indicative of the spasms, but we didn't actually capture a spasm episode during that one-hour EEG. Based on what we had described and based on the presence of those spikes, however, his neurologist at Stanford felt it was necessary to start him on the vigabatrin. His neurologist at UCLA did not agree. That didn't sit well with me. I was tired of waiting for the inevitable, so we started him on the vigabatrin and I have not looked back. I have had to fight to keep him on his medication. His neurologist at UCLA wanted us to wean him after just a month of being on it. She wanted us to go back to waiting and seeing yet again if the spasms would come back, and if they did, she wanted us to do a week of having spasms, their chances of having autism goes down. I refused to do the wean and I will never regret doing so.

My son is doing amazingly well today and I absolutely attribute this to his vigabatrin and it preventing him from ever having full-blown spasms again. There's been amazing progress even just since my son was born a year and a half ago. We now have the PREVeNT trial where clinicians are studying whether vigabatrin can prevent the onset of seizures if started prior to clinical onset. Based on my own experience with my son, I think this will absolutely reshape the approach to treatment for kids living with TSC. Parents will no longer have to go through the weeks of agony, anxiety, and unknowns that I experienced. We can finally shift away from playing catch-up to really taking a preventative approach to TSC and epilepsy. Afinitor and the other mTOR inhibitors is another hot topic, as you've heard. People using this medication are seeing profound impacts far beyond what it is currently FDA-approved for. It's currently approved for the treatment of SEGAs in the brain and AMLs in the kidney. My son has neither of those symptoms, but it is also showing huge promise for seizure control, cognition, and overall development. It remains to be seen right now whether my son will need medication for these issues, but I can tell you definitively that this is another drug that I will fight for him if he needs it.

I know how lucky I am that my son is doing as well as he is and I do not take any seizure-free day or any milestone he hits for granted, but my son's journey with TSC is just beginning and things can change for him in an instant. For example, we're starting to see some sensory processing issues and we're working closely with his neurologist and therapist to try to treat them and control them, I suppose. I never let my guard down. Not a day goes by that I don't think about TSC or seizures. Not a day goes by that I that I don't think about the what-ifs with this disease. I have no way of knowing whether more dark days lie ahead, but with the disease like TS it seems more than likely that there will be. I do know that my son is my light and I will never stop fighting for him and all of the others living with this horrible disease. I also know that additional treatment and greater accessibility is needed to ensure that he and all of the others living with TSC can have the best possible chance at a long and independent life. I think we can all agree, all the parents can agree, that that really is ultimately what we want for our children.

**Shelly Meitzler:** Good morning. My name is Shelly Meitzler and I am a mom to three children. Going to share my story. Ashlin is 15 and a half and my son Mason is three and a half living with TSC. In January 2002, my daughter Ashlin experienced her first seizure at four months old. At the local hospital a CT scan was done and spots were found on her brain. I was accused of shaken baby syndrome. In the local medical community there was no other possibility, even though further testing showed no indication of abuse. She was ripped out of my custody, and I demanded a second opinion. I knew something was seriously wrong with my daughter. Fear and downright mistrust for the medical community was all I felt.

Four agonizing weeks later, a second opinion at a children's hospital confirmed with an MRI of the brain that Ashlin had tuberous sclerosis complex. I recall early years and remember medical trauma more than a celebration of my firstborn child. I lived in a reactive state around a disease that I couldn't get one step ahead of. I was defeated as multiple seizures, hospitalizations, life flights, and countless failed medications and endless testing dictated daily life. Status epilepticus, or prolonged seizure, when Ashlin was two-and-a-half years old ripped away a piece of my child forever. She came home after a ten-day hospital stay with right-side paralysis, no vocabulary, the inability to feed herself, sit up, crawl, or walk. Ashlin now 15 years old, sees 10 different specialists, receives in-home therapy three days a week, will require assisted care for the duration of her life and takes 13 doses of six different medications to treat the varying manifestations of TSC. She's prescribed two seizure medications, two medications to help manage behaviors, ADHD, and autism, three supplements daily to counteract side effects of seizure medications, and Afintor to treat the angiomyomas on her kidneys. Ashlin has had positive effects with the Afintor regarding her kidney involvement. The downside to the medication is that any time she encounters a common illness, the medication must be stopped to allow her body the ability to fight off illness due to a weakened immune system. The continued struggle with the increased behavioral manifestations have been the hardest. Significant developmental delays, autism, and language delays cause Ashlin frustration that manifests into self-injurious behaviors and other undesirable disruptive behaviors. As a caregiver this continues to be the biggest symptom of TSC that is not easily remedied.

My son Mason was diagnosed with TSC at seven months old. I immediately enrolled him in early intervention for physical therapy and speech. He was promptly enrolled in a research study at Boston Children's Hospital, and it has been invaluable to Mason's developmental progress. He had a normal EEG at seven months, abnormal at nine months, and his one-year study visit showed subclinical and clinical infantile spasms. The recommended first line of defense, vigabatrin, was started within six days, and we've not seen an infantile spasm since. But that all brought on the need for additional testing. A sedated ERG test to monitor any peripheral vision changes was now needed. After a year and a half on vigabatrin, mild changes were noted with Mason's peripheral vision. It brought an additional medical concern and added additional sedated tests. Mason went into status epilepticus in March 2015. I recognized when the seizure didn't stop with the emergency medication that I always have within arm's reach. He required so much rescue medication, a code blue was called to resuscitate him. I watched as my baby laid lifeless as the seizures ravaged his body, petrified of what the long-term effects would be. He was put on a ventilator and in the PICU for three days. He recovered with no major setbacks. An additional epilepsy medication was added. Despite two seizure medications, Mason still has abnormal EEGs, is high risk for focal and complex seizures, and experienced a breakthrough seizure six months ago. Due to varying symptoms and different insurances, both children are not seen by the same TSC specialists. The travel involved is at least six hours one way and requires outside help and coordination from family members that are capable of medical intervention for either TSC child. I have witnessed over the last 15 years with Ashlin's journey a lot more options available, and I have hope for Mason's future.

My hope for the treatment in the future is additional options to address the different manifestations of TSC. While the TSC community is grateful for the treatment options available, they do not work for everyone. We still have a very large underserved population. The current course of treatment is to monitor and treat as symptoms occur, but the long-term need is to remedy these manifestations before onset. The medication options currently available leave questions of what the long-term effects could be with lifetime use. We have made huge progress with TSC in terms of research and new treatments, but we have more work to be done and more answers to find. Thank you.

**Debora Moritz:** Good morning. I'm Debora Moritz. I have a 19-year-old son, Griffin, with TSC. He really should be here speaking for himself, however, the world does not yet accommodate his somewhat unorthodox communication. Griffin's story began at 5 months of age when he was hit with catastrophic infantile spasms, combined with complex partial and tonic-clonic seizures. Controlling his epilepsy became our early treatment focus because infantile spasms can be an early indicator of particularly negative outcomes. Early onset is bad. Difficulty to control is bad. Simultaneous multi seizure types is bad. Risk of status seizures and SUDEP is higher and Griffin was scoring So aggressive treatment was in order. Our first treatment choice was to go out of country to obtain vigabatrin, which at that time was not FDA-approved. But that miracle drug for so many did nothing to stop Griffin's seizures and we had to resort to a course of ACTH injections, which ultimately stopped the infantile spasms, but we spent the next decade trying new AEDs in endless combinations and doses. Considering the VNS implant and surgical resections, modifying his diet, getting him a helmet, and always keeping rescue medication in hand. intervention was our "good place" in terms of seizure control. And during that time he began to develop just about every other negative manifestation that TSC has to offer. His SENs needed regular imaging every six months in case they began to grow. His facial angiofibromas bled readily and he was sent home from preschool until such time as a two-stage laser surgery could be completed to treat them. A treatment that had to be repeated again two years later because of aggressive regrowth.

He takes an array of OTC supplements and additional prescription medications to either offset or treat side effects of his AEDs. He was diagnosed with osteoporosis when he was only 12 years old, a side effect of a heavy AED burden. And so he takes his supplements to help build his immune system, to help build his brain health, to support his kidney function and bone health, and to try and help him sleep. His autism, his intense sensory needs, and his apraxia of speech added the burden of up to 40 hours a week of therapies. We weren't making much progress with his seizures, but we could at least work on behavior and communication. A sensory diet and ABA therapies helped him self-regulate and have evolved as he has matured and learned to express his needs. Behavioral interventions have increased his self-help skills and reduced negative or self-injurious behaviors. AMLs in his kidneys were growing at an astonishing rate, but ultrasound imaging and radiologists unfamiliar with TSC manifestations missed the softball-sized AML in one kidney while mistakenly suggesting he had renal cell carcinoma. That almost sent us on a detour into kidney surgery.

We were trying to be proactive, but nothing was working. Trial and error, and wait and see, were not stopping TSC's relentless assault on my son. I've often described the recurrent nightmare I have of walking down a railroad track, being unable to step off that track, being unable to take the detours and the side switches on a sideline and always knowing there was a freight train approaching me from behind. That freight train is TSC. Then the routine monitoring of his SENs showed that he had an explosion into full-blown SEGAs that were bilateral and multinodular and already causing hydrocephalus and life-threatening. But at that time the treatment for SEGAs was surgery. The freight train had picked up its pace. SEGA treatment became the new focus. Kidneys, face, autism, and communication would have to wait.

And so, I took my nonverbal autistic child with uncontrolled seizures, a bleeding face, and questionable kidneys across the country to enroll him as patient number 25 in a tiny Phase II clinical trial for an mTOR inhibitor that might treat his SEGAs enough to make surgery more feasible. But it didn't do that. It made surgery unnecessary. His response was phenomenal. In fact, the images of his brain were so impressive, they were published with the article in the New England Journal of Medicine. Always an overachiever. His SEGAs shrank, the hydrocephalus was relieved, and we started to see other side effects. But this time they were good ones. Facial angiofibromas receded, eliminating the need for another laser surgery. His kidneys stabilized. AMLs shrank. He became more responsive and in the moment. Communication improved, autistic behaviors lessened, and slowly his seizures began to decrease in both frequency and intensity, until for the first time in a decade he became seizure free.

Griffin's "Cinderfella" stories continues today. He's improving the longer he stays on drug. He is still autistic and still nonverbal. Needing extensive communication and sensory supports in order for him to demonstrate just what a little smartypants he is. Seizure control is tenuous for someone who's had so many years of intractable epilepsy, but still, it's good. But what if the clock strikes midnight and he must come off mTOR inhibitor, and will all the gains he has made be lost? Current treatment has definitely bought him some time and helped keep the manifestations of TSC at bay. But as he enters young adulthood, will neuropsychiatric manifestations become our next focus? Will the side-effects of years of AED treatment finally overwhelm him? What will be the long-term effect of the chronic drug therapy of an mTOR inhibitor? And will he ever sleep well? mTOR inhibitors are an incomplete answer and truly long-term impact is still unknown. But compared to the known long-term impacts of uncontrolled tumor growth, uncontrolled seizures, we're willing to take on that unknown. But where we need to go is to discover why the variable response? Why one miracle drug is that miracle for some patients with TSC and ineffective against another? Why some people like my son have phenomenal response and continuing response to mTOR inhibitors and others struggle with uncontrolled side effects? And finally, Griffin had to have a say. In this I talked too much for him, and so he asked me to share with you a quote from one of his most favorite philosophers, Buzz Lightyear. "Never give up and never surrender." Thank you.

**James Valentine:** Thank you to all of our panelists for sharing your stories. We're now going to move into our second set, or it's really our third set of polling questions for you today. Focused on the same topic of approaches to treatment of TSC. So go ahead and get your clickers ready. All right, so our first question for you is, which drugs for TSC have you or your child tried? Select all that apply. So we have Just as it was getting good. Alright, so it looks like we actually have a very wide spread of experience with different drugs that you used to treat your you or your child with TSC. Those that have been used, the one that has been used the most is vigabatrin. Followed closely by rapamycin or sirolimus or other seizure drugs. So we'll want to hear about those when we move into the discussion. We also have experience with all of the other products. Only a few with CBD and only a few with doxycycline. And we have quite a few other drugs that are not listed at all. So for those of you that said other, I hope you'll raise your hand and share with us what you've what you've tried.

So our second question for you is what are the downsides of the treatments that you or your child have tried? And again, select all that apply. 1) No positive benefit or the benefit was lost over time 2) Weight gain or weight loss So it looks like the most common downside of treatments that you've tried has been that there's been no positive benefit, or that the benefit was lost over time. I think it would be a very important point for our discussion to understand where there was no benefit in which products and how if it was instead lost over time what that looked like. The other was other so we definitely with such a good or a high number of people that have put that response down want to explore that. It looks like we have about in the 9-11% range for responses 2, or pain. Actually a repeat question, sorry about that.

So now we're going to move into our audience discussion. So building on the discussion by the panel and the polling questions you just responded to, we have some things that we'd like you to respond to help us understand your current approaches to treatment as well as your preferences about what you would like to see from future treatment. So our first question is, what are you currently doing to help treat the condition or its symptoms? And we want to know how well is your current treatment regimen that treats the most significant symptoms of the condition? How well is that working? Part of that is to let us know how that is affecting specific activities that are important to you or your child. We'd also like to know again, What are the most significant downsides to current treatments and how they affect your life? Downsides could be things like adverse events related to the drugs, but also just the burdens of taking drugs or up doing other types of approaches to managing the disease. We want to know what specific things you would look for. Basically, short of a cure, what you would look for in an ideal treatment for you, or your child's conditions? Also, what factors do you or your child take into account when making decisions about selecting a course of treatment? So we want to know what information on benefits is important for you to decide on what information about risks? And how do you weigh those benefits and risks when making treatment decisions?

So we'll go ahead and move into the audience discussion. So we have our first volunteer. I think you know one of the things that I'd like to start out with is talking about your approaches to managing the epilepsy, the seizures. We heard a number of strategies, both drug therapy as well as some different kind of lifestyle modifications, that were needed to accommodate the seizures. Have you had similar experiences to what we heard from the panel? I think that's important for FDA to hear as well as if you've tried other drugs or other approaches that we haven't yet talked about. Yes, Shannon. And before Shannon starts, I'll take the opportunity just to remind everyone please state your name before you comment. We do have note takers that are keeping notes for the report that will go to the FDA. And also please only use your hand if you are a patient or caregiver either living with TSC or a caregiver of a child with TSC.

**Shannon Grandia:** My name is Shannon. I just wanted to talk about a little bit about Luke with his battle with the seizures. At one point we had him on six antiepileptic drugs and we couldn't tell you which was doing what or if any were even helpful. And that came from neurologists just continue to add because we couldn't get the seizures to stop. He was pretty comatose. He just lay there. He couldn't do a whole lot. He was so drugged up and the seizures were so bad and it was really difficult. Then we had the ACTH shot and his body swelled and that just added more complications. It wasn't until we got with a neurologist that basically said we need to get him off some drugs. And then we started just trial and error, just weaning. And we started the modified Atkins diet. That was really life-changing for him. We didn't go all the way with the ketogenic just because with having two other kids with TSC, monitoring the ketogenic we thought would be a little bit too difficult and keeping the strictness that needed to go with it. Thankfully the modified Atkins was enough for him. It took him, at the time he was having between 30 to 40 seizures a day down to 10, just by the diet. Then over time that has really been the game changer for him along with, he's now on three antiepileptic meds with the diet. That has currently got us the best control.

**James Valentine:** What medicines is he currently on?

**Shannon Grandia:** He's on Trileptal, zonisamide, and Onfi.

**James Valentine:** Thank you. Others like to share their approaches to treating and managing seizures associated with TSC? Pass the mic down.

**Ary Agami:** My name is Ary and Larissa, my daughter, she was treatment with the vigabatrin. It was very effective. Seems he just started the treatment and it stopped the seizures. She had been eight years. That's fantastic. Could you tell us since vigabatrin has worked, were there other things that you had tried prior to vigabatrin that didn't work? What led you to that? Yes, we try a lot. We tried different kind of drugs and until we go to Cincinnati and we met Dr. Franz. They just put vigabatrin in the treatment and since that time is a different girl.

**James Valentine:** Great. That's wonderful to hear. Thank you.

**Micaela Rosenberg:** Hi, Micaela from Portugal. For me the last question would have made sense if you would ask, even though with all the side effects would you still continue to give the medication? And I'm sure that the answers are...

**James Valentine:** Right so one of the considerations is what side effects are you in your benefit-risk decision as a parent? What are your consideration? Are there certain common side effects that you're willing to tolerate? Are there also even severe, but maybe rare side effects that you'd be willing to tolerate in exchange for what benefits are you thinking? Is there... Do you need a complete stop of seizures or is a reduction in seizures? So part of what we're exploring is what benefits have you already been experienced from therapies, those that are approved or not yet approved. Or maybe even things that aren't drugs. But also, then when you're looking to what's left, so not everyone is going to be as lucky to have complete seizure control. You know what would be meaningful to you as a parent of a child with TSC and what would you consider when making that decision for that benefit? So do you have thoughts on that?

**Micaela Rosenberg:** Yeah, I think every parent before gives a medication, that's a meaningful decision to take. But I think most of us will take the risk of giving a medication because we're talking about a disorder that is life-threatening.

**James Valentine:** So the point being that there's a high risk tolerance for side effects.

**James Valentine:** Yes. Debora.

**Debora Moritz:** Speaking on behalf of someone who had severe and chronic epilepsy. Very difficult to control. One of the challenges that comes about is when you get to a point of polypharmacy, you've got three or four medications, and maybe the seizures are controlled, but side effects begin to mount. When my son experienced osteoporosis and the question was all right now, can we back any of them down or which one can we back down and how do we go about it? And you look at side effects, if you read all the package inserts provided by the FDA. They're pretty scary stuff if you go through each one. Most of them ending in risk of death as one of the possibles. Griffin's Felbatol indicated high risk of aplastic anemia. Yet it was one of the most effective, but now you know he's at seizure control and I've got three things to guess about. Could we reduce them in order to reduce the side effects? At what point... because you don't want to give up what took so long to gain. And yet you want to give him the best quality of life in the least complex way. And then just I'm going to kind of blend into another question going on. After you've been on long term but new drugs are coming out and you go okay, I've got all the old ones in my regimen here, but maybe one new one could do it. Is there any way to facilitate the ability to transition or predict a transition for that in order to advance it? The one thing I have in mind right now is something like CBD, which is showing some effect with seizures. But the metabolism thing comes in, it metabolizes down the same route as mTOR inhibitor, and what will go wacky when I add that to the mix if I try it. Is it worth it? And top it off with having a young adult who's beginning to have his own opinion about what should go on. Gets challenging.

**James Valentine:** Sure. So it sounds like there's a couple of things that you're considering when thinking about future treatment. One of them being potentially drug-drug interaction or not only some side effects, but potentially, in terms of reducing side effects from any one individual drug, picking that which will be most effective. And that's hard to do when you've got multiple things in the system. So if there were... So you talked about CBD and it being potentially beneficial. Is there some benefit that you would look for that would trump using current treatments? Then eliminate that aspect of having to worry about the side effects of those treatments, or drug-drug interaction.

**Debora Moritz:** Well, like in Griffin's case and the success ultimately came with the addition of the Afinitor, an mTOR inhibitor. It acts very, very differently in the body than any of his other seizure meds had. And so I guess piecing that out is something that benefits him as a whole. His whole TSC experience versus focusing on the one symptom of epilepsy has been good. You know that like in terms of choosing therapies, I would go with the Epilepsy Foundation or the autism groups and find therapies they had, but what I had was a kid with TSC who had complex issues. And so when you talk about selecting something, does it address the complexity of his disorder and maybe help me in a multi-symptom format versus only the current problem of seizures. In my story there were always current problems to address, but yeah. So the treatment that would address on the whole would be great, or perfect, be preventative.

**James Valentine:** That's really informative. Thank you. Thank you, Debora. Other comments from the audience.

**Ary Agami:** Ary again. I just want to add important information that in 2006 when Larissa first got vigabatrin, it was prohibited here in the United States and it was available in Mexico. So the other doctor. I was in El Paso, Texas. He knew about vigabatrin but he want just to look at the risk for the symptoms or for the other symptoms that can she had so that's.

**James Valentine:** Thank you. Shannon, did you have a comment?

**Shannon Grandia:** I just want to add to the choosing whether to try the drug or not, like we're really debating on doing Afinitor for Luke. He does have a SEGA, it has not been growing, and then we're monitoring it and our biggest concern is he has already has broken immune system. He's had chronic pneumonia his whole life and so we've been going back and forth with our neurologist, is it worth the effort to try it and see if it helps with the additional seizures and possibly helps that SEGA to shrink or do we keep going the path we're going right now where it's okay? And for us having lived through he would had when he was on the Depakote. That's what caused the liver damage which caused the kidney damage and for us one to two seizures a day is already life-changing. We can already see his personality we can allow him to develop. So that's kind of in our back pocket, but not something we're pushing for. Because thinking of a quality of life, do I want to risk him going back into the hospital with more pneumonias and more illness and then the seizures increasing and the aspiration increasing, or are we okay with what we're doing right now? So it's exciting to know that Afinitor is out there, and it's kind of our, in our deck of cards, so when we get to that point where the seizures are increasing again because we anticipate it and we're not in a denial that it's not going to possibly get worse. He's only ten. We still got a long life and that Afinitor and the upcoming drugs are kind of just in our pocket, like, okay, we know we can have something that we can try when this fails. So I just wanted to kind of elaborate on that because it's awesome what Afinitor is, but for us with what we have to pick and choose and what he's been through, a couple seizures day is nothing compared to where we've been or where we could go if it didn't have the right side effects.

**James Valentine:** That's useful. Rebecca.

**Rebecca Anhang Price:** This is Rebecca. So building off of what Debora said and I think what Sarah mentioned on the earlier panel. It seems that there's little to no evidence base with which neurologists and patients can and families can think about what the next drug should be and what the next drug should be weaned off, as Debora mentioned, so I think many of the families who've spoken have family members who are on multiple drugs at the same time, and in order to make room for a new one you hopefully get rid of an old one and who knows how to do that, and it's very challenging. It's stressful, but it also potentially places the individual at risk of losing the seizure control they had in the, in the hopes of gaining better control over time. That's the first piece and the second is that, again, given that this is a really complex condition with a lot of commonly co-occurring conditions, it would be really helpful to have treatments that address multiple of them at the same time, which is why I think mTORs have been so exciting for those who for whom they've been successful. I mean, it would be nice given, you know I have a child with epilepsy so he's on three epilepsy meds. Have we really pursued his full-blown case of ADHD medically? Not so much because it's one more neurological medicine to tinker with over time and it would be really nice to be addressing that more fully, but there are sort of trade-offs in our ability to do that, and so I think moving towards treatments that address root causes more I think is really the future here.

**James Valentine:** Sure. And can I ask a follow-up question? On your first point, getting back to kind of more of the incremental addition of medicine, for you, what is, because there is a difficulty of having to wean one and then potential interactions. What is your decision making for deciding when it's finally appropriate to try to add something or swap something out?

**Rebecca Anhang Price:** So our approach has been to maintain a current regimen as long as it's working and then only adjust it when seizures become out of control. The challenge of that is you never know which thing you should wean down to make room for another, because, again, as I mentioned earlier, the latitude for making a mistake is not there. I mean, in my son's nine-year history of taking antiepileptic medicine, we once forgot one dose of the two medicines he was taking at the time and he had 87 seizures that day. I mean we can't sort of make a mistake in trying to wean him off one to make room for another and so we basically do our best by using Seizure Tracker to try to figure out what the effectiveness of different meds have been over time for him to pick which one we might wean down, but we're really stuck with a fuller regimen than even potentially he needs because we're too scared to back off on anything while things are going well, and who knows what the side effects are of any of those meds because he's been on them for so long?

**James Valentine:** And what level you mentioned if seizures got out of control, so kind of breakthrough, you know seizures what is out of control to you? Can you define that for us?

**Rebecca Anhang Price:** So in our case, we've been fortunate that out of control means any seizures, and the reason we have that threshold is that we had an experience early in his life or when he started to have just one seizure every day or two, he shortly thereafter had status epilepticus, so a status seizure, and that was so scary that we basically have a zero tolerance threshold for him, and we've been very fortunate to largely be able to achieve it over time.

**James Valentine:** Other comments on.... We've one in the front and then we'll go to the back of the room next.

**Seth Fritts:** My name is Seth again, and first of all I just want to thank all of the caregivers. It's really remarkable what you all have gone through, and I look back at what my mother had to deal with, dealing with my situation, which, again was relatively small comparative, and it's just as I think about this some of the things that I wonder if it would help with the caregivers is creating some type of decision matrix, some way to actually, because you start to look at what does drugs are going to work or whatever, and it's like, you start with this and you move through that and all that and maybe creating some type of tooling or something that would allow people to make these decisions more effectively, and I know you have to kind of take, there's a lot of things that are going to work for some that work for others, but as you can kind of create some kind of mechanism or a tool that allows people to start thinking about, like, here's how we're going to progress with this because, again, given the uncertainty of the disorder, haven't really seen anything that's been great for that.

**James Valentine:** Comment in the back.

**Rob Moss:** Rob Moss.

**James Valentine:** Hi, Rob.

**Rob Moss:** If I can build on Debora and Rebecca's comments a little bit, I think personally we've observed that there's a very additive theory for medications in treating epilepsy which if you're thinking about quality of life and the impacts of the side effects of those medications that impact the cognitive, the next highest importance on our, as a patient, so I think it's a it would be really interesting to look at the epilepsy community and say why are why do we have an additive philosophy on medications and not a subtractive philosophy? So our son has been on 14 medications at times. He's been on four medications simultaneously. Most of those medications have been pushed up to the highest dose possible without toxicity, so never, it's been rare that we've been approached by our physician and said and say well, maybe We need to look at this differently and say let's start taking off medications, get back to baseline and there's a danger in that obviously but the approach and maybe through the FDA we can look at drug-drug interaction more, but this philosophy of subtractive therapies in an environment that we rely on these medications as an additive therapy just seems counterproductive in a lot of situations, so one thing we can look at, too, is a lot of the epilepsies have different side effects given the medication, so if we look at sodium channel epilepsies a lot of the medications are detrimental, and we don't know that necessarily until we can manipulate the medications and say, well, we know this medication is having different side effects than another medication is having, so there's a much larger issue here. I think the polytherapy issue in epilepsy, specifically, has a lot of impact on neural cognition and a really, misinterpretation or the lack of ability to interpret the efficacy of those medications.

**James Valentine:** Do you have any experiences in your child's treatment history that could inform what your decision making is for subtracting therapies? I know you mentioned at one point your, I don't know if he or she was on 14, and now he or she's on four, is that..

**Rob Moss:** Not 14 at one time but we've been on four medications at one time and all of those medications were pushed up to their max dosage.

**James Valentine:** Sure.

**Rob Moss:** So I guess what a good example might be, or one of the, what's problematic, let's say as we were on Onfi and we had pushed that up to the major dose that we could get to and to move on to another medication knowing how that metabolizes it took us two years to get off of that medication successfully without very detrimental side effects of withdrawal so that medication probably didn't have a real good effect on seizure control and had a lot of cognitive issues associated with it. And we pushed it all the way up and in hindsight, knowing that, we probably would have never gone on that medication knowing the issues that of getting him off and our history with medications and knowing that this was probably not going to be a successful treatment, that the and then the side-effects that would happen as we try to withdraw him from that treatment would have negated us ever going on it in the first place. Yeah, so that's one example there. Yeah, there's a few others that I'm sure people can contribute to that. So I would, I personally and I would hope that I represent a larger epilepsy and TSC combined community but I would like to see exploration and a subtractive therapy theory over an additive therapy theory.

**James Valentine:** Thank you. So we've talked a lot about focusing and mitigating the epilepsy, the seizures, I was wondering if in addition to what we've already talked about there's been approaches to treating some of the behavioral or cognitive issues that have been talked about in our first topic in addition to what is being used that might directly be related to reducing seizures, and then hopefully over time reducing the burden on the behavioral and cognitive issues, but how have you, what have you, been your approaches to kind of managing those once they've arisen with it with your children? And this can be drug treatments as well as other types of things.

**Clare Stuart:** My name is Clare, my sister had tuberous sclerosis so I'm speaking about that experience, but I also have the experiences that I assist with of whole community of people with tuberous sclerosis in Australia. I think when we think about TAND, as we call it in the TSC community now, because otherwise you divide it into so many pieces and so many different ways that we don't have any consistency and epilepsy kind of trumps it at the post as Petrus highlighted, but you know TAND is a whole lot of things, but we think about the non-drug treatments for TAND I think, the stories today have highlighted the huge hours and hours let alone money spent on all those different therapies, and I think, you think about the whole family impact of that, I mean, I have great memories of playing with shaving cream as a four or five year old because that's what my sister's OT was doing at home with her as a toddler, but beyond that, you know, the invasion of those therapists into the home we go, oh, I had home treatment is great, but that changes the dynamic and then families are weighing up how much should they be doing. How much is enough? If I don't do this, am I making developmental delay worse? Is my child keeping up? And I think it's a little bit unsatisfying when all we have in the research at the moment is well Let's treat these TAND aspects of TSC as if this person didn't have TSC, but that approach of let's just engage the speech here, let's engage the physio and the OT and everything else in the ABA and find a good school for them. I think that's unsatisfactory.

We don't have the research that shows which of these is actually beneficial and all that allied health intervention and the burden of that it might not be the same sort of very measurable burden that we have with drug therapy, but that impact on time and costs whether that's borne by the family or some sort of insurance or state reimbursement is major and we're not good at measuring it and without a drug manufacturer out there motivated to research this, there isn't funding available for us as a TSC community to go and look at what are these interventions are the most effective? Is there a combined intervention approach that is more effective in TSC? And I think beyond the early intervention years that flows right through to the mood and anxiety disorders, the challenging behaviors all those things that flow through into later in life, and it's the best answer our psychiatrist can tell us now is get that screening, get that diagnosis, treat as if you didn't have TSC. But TSC is so complicated that leads to a really high treatment burden and I don't know that those answers are good enough.

**James Valentine:** Do you see a role, or did you see a role in your sister's experience for occupational therapy and for kind of, one-on-one kind of interactions with occupational therapists, other types of your therapist, I don't know what your sister's experience was..

**Clare Stuart:** Yeah, look absolutely, and I see it's hard knowing that this is an FDA meeting, I don't necessarily think the Australian experience correlates really well, but one of the other things that bothers me is yes, a lot of those therapies have huge improvements, and make acquiring those life skills or improving speech go much faster than they would have, but it's sort of like pushing a heavy car up a hill. Can we go a little bit further? I hope that metaphor resonates, I just thought of it then. So maybe there is some breakthrough, and maybe the breakthrough will be a medicine and certainly those therapies help. We don't have huge evidence on a TSC-specific population, but the other thing that bothers me in the Australian context and I believe it would be the case in the US as well is the inequity of access to those treatments or therapies and we can have drug policy that fixes the drug aspects, but what are our social policies? And not only equity of access but the burden that places on the parent to fight for access, and we've had situations in Australia where there's some access program but you can only access it if you get the diagnosis of autism and if your child doesn't quite meet the criteria even the people that you're talking to say well, obviously they need early intervention, we know they benefit, but sorry you can't access that pot of money. And I imagine the States is probably a different rule in every state so even for the advocacy organization to have the resources to help people in every situation in all of your huge country that's a real challenge as well.

**James Valentine:** Sure yeah. Other strategies?

**Shannon Grandia:** Shannon again, and I just want to elaborate on that so for Jake, three is when he started regressing. It wasn't until ten that we got the autism diagnosis and were able to start ABA therapy, so it was a seven-year battle and I mean battle with the school district, with the neurologist, they want to keep trying different behavior medications. They kept saying it's not your stereotypical autistic child, we can't give him, he would make eye contact walking across the room, so he couldn't be autistic, and so if we had had our early intervention, because I know the growth we've made in just the last three years has been tremendous with him. How we communicate with him, how we deal with him, how he's learning to communicate with us and his siblings, and it's been night and day and so if we had had that intervention, that access, earlier, who knows where my boy would be today? And that what if seems very difficult to parents because what if, what if I had fought harder for that diagnosis? What if, and you can kind of beat yourself up with any of these with the epilepsy, the autism, but just to put that intervention is key, and getting access to that intervention without having to fight tooth and nail, and I will say for us it might have been a little more difficult because we were battling Luke's epilepsy, so Jake got kind of put in the back burner because we're in the hospital a lot. And so maybe that is what kind of made it spiral as much as it did when it did, but it was not easy. Everything was a fight. We had to fight the school district. We had to fight the neurologist. We had to fight everybody to get him the services he needed, and I can say 100%, the ABA therapy and getting in a school that could support him has made a huge difference to where now, at 13, I can do more stuff with him now, even though he's taller than me, than I could do with him when he was five or six, because at five or six he would completely melt down and hurt me. Now I have faith I can take him even though now he could take me out easily. I feel more confident taking him places because I'm able to communicate with him better because the therapies have been happening.

**James Valentine:** Sure, so I know that the access issues are a little bit outside of the scope. I'm sure if FDA could help with that, they would, but I think it was useful to know, and I want to follow up on what you're talking about in terms of the benefit that was seen from that kind of intervention. Could you paint the picture of, that night and day difference, okay? What can you, whether that be an example, or how would you describe that?

**Shannon Grandia:** Well it used to be he would not, he knows how to speak, he doesn't know how to communicate. So he's never had speech delay per se, but he's never been able to fully communicate with us. So what he would want if he wanted let's say, for example, and say he used to hurt me when I changed the TV if I didn't realize he was watching a show and I changed it, He couldn't say, "Hey, mom, I was watching that." He couldn't even point to the changer. He just come over and start biting me and scratching me, and it was an immediate result and that was how he would communicate. That's how he would get his point across. His brother snagged his toy, it wasn't a "Hey, give that back," it was a bop across the head and he grabbed it from you. And now we've gotten to a point where he can now say, "Hey, mom, watch that," or "Mom, don't change it," and it's gotten to the point where he can actually kind of give us, it's still it's still hit or miss, but his first reaction is no longer I'm going to physically hurt you to get my point across, it's even if it's a one word or even if we have non verbals now, we have if he's frustrated we do eye raises, we do our eyebrows, and that was that him telling us, okay, something's going on and learning those nonverbals has been huge because we're able to interpret and figure out, it was like he wanted us to read his mind and we couldn't because he couldn't tell us anything, and now we have cues and strategies that came from ABA and came from support from school that we are able to communicate with him now, and now he's starting to talk more, and it's kind of progressing the positive versus the negative.

**James Valentine:** Thank you. That's very useful. So in our last couple of minutes we talked a lot about approaches to the treatment and embedded in that you share a lot with what kind of the still remaining unmet need for treatment, what that is, but I'd like to open it up, if there's any final thoughts on what, basically, short of a complete cure of TSC, based off of what you currently have, what is it that you would look for in that next therapy? That could be a whole wide range of things. That could be some particular benefit that you don't currently have in your armamentarium or it could be something to help you replace what you already have which we've heard a lot about. If you have any thoughts about that, since that is one of our questions, I wanted to give you an opportunity to discuss that before we wrap up. So we are just looking for patient perspective, want to give them a chance before you run out of time there? Debora?

**Debora Moritz:** I would just say, I mean, I would look for something that looks at Griffin as a whole person so that it would be a system-wide benefit and something that could be more personalized, that if there could be a genetic analysis of him to say he's more responsive to A, B, C and D based on his mutation, therefore avoiding the guessing game of application. I know that's a ways out, but I believe that's possible and that whole respect for him as a whole person and not symptomatic treatment, but getting to the root cause of his disorder, and I know we didn't spend much time talking about complementary and alternative approaches to treatments as well, but other than pharmacy those are some ways to boost, I'll throw in my plug for some yoga and some neurologic music therapy has been some of the most enduring things that have benefitted Griffin, and I think we can build forward from that.

**James Valentine:** Great. Thank you, Debora. Any final comments? Okay Thank you panel. You are free to go. So now we're moving into the, we've completed the kind of portion of our agenda, with getting your input on both living with TSC as well as your current approaches to treatment and some thoughts about future approaches to treatment, I now have the honor of inviting up our FDA representative, who's going to be giving a summary of the morning session

So it's my privilege to introduce Dr. Jonathan Goldsmith, who is the Associate Director of the Rare Diseases Program in CDER's Office of New Drugs. He earned his medical degree from NYU and received his postgraduate training in internal medicine at Vanderbilt and has completed specialty training in hematology at UNC. He has an extensive career in academia as a tenured professor =and in regulated industry in focusing on clinical drug development and with rare disease foundations, so join me in welcoming Dr. Goldsmith.

**Jonathan Goldsmith:** Okay, thank you very much. I'm standing between you and lunch, as I understand it. This the least desirable place to be, you know, on an agenda, But it's really an honor to be invited here to say what I heard this morning and to try and give you some feedback about what somebody who has kind of a broad experience in drug development as well as medicine and rare diseases. So I want to thank the organizers, the patients and families, members of regulated industry, academia and government. As you we're just told my background is that of a hematologist, an expert in blood diseases, and it's a discipline really of rare diseases, so even though we didn't talk about rare diseases as kind of an entity at least when I was being trained many decades ago, that's what I was doing, and those kind of skills that you learn along the way, things like listening to what the patient's saying. It's really helpful.

Those are skills that we use now all the time in terms of how we think about rare diseases, and we think about things of trying to do drug development in a very small platform. That we have very limited number of patients who are available to participate in trials, what I think of as human capital, that we just don't have a lot of people to do these studies, so we have to plan them really well in advance. If you want to get some of the developments you want in the coming years, you have to do this planning work and it's painful sometimes because you say well, we know that works, it's a great animal model, but we don't really know what it will do in humans. So we have to be very careful about the planning, and I think that's important as you go forward because you have so many things in, so many irons are in the fire right now you have to think about which are the ones that make the most sense and so on. How do we have the best background information? Do we do we have information that can be useful? Have we actually done a natural history study, for instance? Do we have good data? Or is it international data where there's no uniform medical language, and when it goes to our reviewers they can't make sense of the data? Even if it's translated into English, it doesn't translate very well, so think about that as you go forward. I know you're very well put together organization so I think it'd be important to kind of focus on this.

Okay, so now back to the main theme, so we're now at an active transition from our Patient-Focused Drug Development meetings that we've done at FDA for close to five years, and that to try and move out this process to the so-called Externally-led Patient-Focused Drug Development meetings which you are holding today. The Patient-Focused Drug Development meetings, there will be a total of 24 performed. Dr. Woodcock mentioned we were funded to do 20, but they were really a good exercise so we wanted it to go on further. About 40% of those were devoted to rare diseases and the remainder to more common disorders, and but that's actually part of what we do in government is we try to focus on where the drug development is so we can respond to it. We've tried to put together these meetings in the first place to get a systematic scientific approach to the methodologies and analyses that were being performed. A lot of the things that we hear about as regulators are things that are personal opinion, or well, you know what we might call anecdote and that's fine. That's okay. You're entitled to your opinion, but we need to see that there's scientific evidence that that confirms that this particular agent is safe and effective. That's actually the law. We have to follow the law. You can do anything you want, you can travel around the world and try anything you like, but that won't necessarily lead to an assessment of the safety and efficacy of that particular therapeutic and make it licensable in the United States.

Well, you know we've learned from these Patient-Focused Drug Development meetings a great deal, things that I think as the physician are kind of at least from the practice that I had for a long time are kind of just the way I always did it, but I think that I think was important to have greater learning amongst the regulatory community. And you know we've learned, as Dr. Woodcock said this morning, that patients and families are uniquely positioned to inform the FDA about their disease and what the impact is on them and their families. There are current mechanisms that were in place before this process started to obtain patient input, but FDA was really limited to using these based on just the presence of a single application, but not about, let's say, a whole disease process like we're talking about here. This is a much more generalized, broader, and I think at the end of the day a much more effective approach.

Patient-Focused Drug Development meetings, the ones that deal with rare diseases, are very important if you look at the new molecular entities that were approved at CDER over the last, let's say, three years. Way more than 40% were for treatment of rare diseases and orphan indications. So it's a big part of the business that we do and we have to pay special attention to it. And I think that the Patient-Focused Drug Development meetings have confirmed the value of the Voice of the Patients report, that you're contemplating preparing for this meeting. These are useful to reviewers, the people actually read the documents that come in as well as the reviewers, talk to the sponsors of new drug applications to make sure that they have a good understanding about this as well. So I think these are important changes that are going on. So now just a few comments about what I heard this morning.

So tuberous sclerosis is a serious disease, there are unmet medical needs. The manifestations of the disease are really almost protean, you know, ranging from neurologic, manifested by epilepsy, intellectual disabilities. There are non-malignant tumors, cystic disease of the lung, and it's probably one of the frustrations from the drug manufacturing side about what are they really going to target on? What are they going to really approach? And I think from this morning session on children and infants the things I heard is that they should work on the seizure manifestations, that this was really a big deal and that we needed better therapeutics for it. So this is a very well attended meeting, I should say, and a very articulate audience. You should know all that. We really appreciate and heard very well the commitment and love you have for your children and your family members, and your courage and determination to try and move this whole field forward comes through quite well, it's quite meaningful. We've also heard about the heavy burden of the disease for patients and families, and we heard about the uncertainty because that's what you all live with every day. I heard that again and again and again from all of you. So here we are, but I don't know what will happen tomorrow or in a month, and that's that's really one of the greatest burdens of all and if you have a therapeutic that would reduce some of that uncertainty besides psychotropic medicines, that that would be very useful.

We heard about a diagnostic journey today. This is very typical and rare diseases and we've heard about misdiagnoses and terrible things that have happened to people in terms of being accused of abusing their children because the doctor didn't stop and think for a second. You know that should be the last thing you think of, but you should think of it, But think about what could be going on. We heard about the impact of intractable seizures. Hundreds of seizures a day, seizures that go on for hours and you end up in the ICU. We've heard about the transgenerational impact of genetic disease, about the parents and then their children and what happens and some of the variability in each of you, which is I don't think very well understood, from a genetic point of view, but I think it will be one day. We've heard about managing complicated medical care at home. You have lots of difficulties. Talking just the story about the chair in schools to keep the child from flailing out and falling out of the chair, you have to make all these accommodations in your home, But if those things improved, those would be clinically meaningful and could be used as potentially this kind of wild but as an endpoint in a clinical study, were you able to throw out the chair? You know it's subjective and if it worked like that those are some of the things that we look for in terms of regulation. Heard about the impact of frequent and often prolonged hospitalizations and more routine frequent physician visits. I think I heard like 300 times in a year I had to go to see a doctor or had my child in the hospital. Well, obviously it takes over your whole life. That's it. You can't go back to work, you're taking care of your child. There are family impacts of this disorder, of some of these are financial, loss of income, loss of jobs, and that there are losses and potential losses including that of a normal or a near normal life for your child or for yourself. Having independence, or some kind of independence, or no independence. Developmental delays were an important part here, different kinds of behaviors that may be difficult, and we heard about intellectual disabilities. It was also mentioned obviously these non-cancerous, but potentially life-threatening tumors of the brain and the heart and the kidney may not be cancer except for a subset of the renal cell, but it still may be life-threatening. And I heard about lots of discussion about individualized treatment plans. That's a great burden because a lot of the burden falls back on to the family. So many of you said, well the doctor said "Well, what do you want to do?" Which is not a very good answer to be honest, but that's what you are up against. Well the individualization is really, It's critical to do it. This is, it's the epitome of this personalized medicine that's being talked about so much now. Maybe there's a genetic basis for it. Maybe there's a way to figure this out, but I think is a heavy burden for you to bear.

Only a few more words. I heard about some technological benefits that the that your iPhones were used for diagnosis and probably could be used for follow-up somehow, and it could be part of some kind of assessment system that might be put in place for learning whether or not a therapy was a successful therapy. So some of that can be used as objective evidence as you as you move towards drug development. And then a few thoughts. I heard about your views on new treatments, and those under development, regarding possible drug treatment effects and heard a lot about weighing risks and benefits, because you never know where you are in the curve, so when is it worth taking the risk? I've heard different answers from different people, some of you are what we used to call therapeutic enthusiasts and then of course there are therapeutic nihilists who want to wait and see what happens. The woman who went from Nevada who went to Stanford and UCLA, she got totally different opinions, And she picked the one she wanted so, but she wanted to do something and so it should be there. We've heard about early interventions and whether you select them or not. So would you be willing to participate in a clinical trial? That's the way a regulator would look at it. So you're willing to take on the risk of participating in clinical trials? It's something that you can do as individuals and as an organization to try and when drug developers come along and have a product they want to test, well the organization representing it to all of its membership can facilitate this process of enrolling people, making sure they stay in the trial, Making sure, as Dr. Woodcock said, that they'd finish the trial so we get the data. That's really critical for drug development. And then also I heard about the use of ancillary treatment modalities, something other than a pill or a shot and that and that many of you thought these were extremely effective. I don't know how well these have been assessed in the scheme of treatment, but things like that, outcome assessments may be important for some of this as these serve as ancillaries to the other particular drug or biologic that's being developed for treatment.

So let me just close and say that your voice helps FDA as we perform our public health mission to evaluate and improve new drug and biologic applications. If you want to shorten the time to market, I heard actually a lot of comments and Jim was nice enough to deflect that from the FDA. So I'll step in it. Because I think we should say something about it because we want it to be short, too. You know we want to license drugs as soon as we possibly can and the way we can do that is if we have the best data as soon as you can get it to us. That's the way it works. Anecdote is great, but it doesn't it won't lead to licensure. One of the things that there are three things that you probably could do to shorten the time to drug development, besides making sure that you can enroll quickly and retain quickly. You have to use your human capital wisely, human capital means the people who could be in the trials. I'm not using it as a derogatory term, it just it's the facts. You have a rare disease, you have 50,000 people, you're not going to do a trial of 10,000 people, there's no way. You probably do a trial of, lucky, a 100, 200 patients at best. That's probably what it'll boil down to in terms of who meet the inclusion criteria, so you have to choose wisely which means you have to do the right studies from the beginning. There's always enthusiasm, when there's a new theory about how a drug might work or some other repurposed drugs and people want to try it. I understand that, but if you want to get a license what you ought to do is use that human capital wisely and you should randomize from the first person who comes into the trial. It's hard to do, there are ways to reduce the pain of placebos or standard of care arms. And there are ways to minimize the time of staying in that, because you have seizures here on such a I mean it's kind of I oh, it's pretty easy if you have a hundred events a day and I can take it down to two events a day, well, that's a big deal. You know so I think you have some endpoints you can look at that will be helpful, but to just when there's something new and exciting to just kind of give it out and see if it works that that's not a good way to do regulatory drug development.

Also, you've worked on natural history registries, understanding the natural history of the disease, if you have good data it's usable, if it's a rigorous study, prospective study, it can be used as an external control, so there may not have to be a concurrent control for the development of the drug. But it has to be good data. And you know it'll be analyzed by people who look at this stuff all the time. It has to meet their standards and the other thing I heard about today here in terms of trying to shorten the time to market is the use of biomarkers, and you've identified the electroencephalogram as a potential biomarker to find out who's at risk and when they're at risk and you probably have lots of data on that that would be useful and maybe could be used earlier if you're looking at earlier treatments to try and validate that biomarker. Because of the way the EEGs are performed is standardized pretty much or could be standardized at all of your clinical sites. Okay, so I want to thank you for including me and the FDA in an excellent program and fostering a strong sense of collaboration between FDA and the patient community volunteer stakeholder side and I'm looking forward to the afternoon to hear more about the adult perspectives, as well. Thank you very much for letting me talk to you.

**Kari Luther Rosbeck:** So you're wrong, I'm the one who's between lunch. Okay, so just a couple of points, as we said in the beginning The PFDD site will be open for 30 days at www.tsalliance.org/pfdd. We would welcome anyone who is listening at home, here virtually or in the audience to make further comments. We will include a transcript of all of today's proceedings on that site eventually, and of course the recording of this meeting will also be posted there. I want to just thank our families, panelists, everybody who participated, shared your stories. What tremendous courage again that you all took to vocalize your experiences, and we have one of our tag lines at the TS Alliance is "We will give everything. But up." You all demonstrate that beautifully every day.

A little plug for Petrus de Vries, just for the FDA, something we want you to take home with you is the phrase TAND, TSC-Associated Neuropsychiatric Disorders, very very important component of TSC that encompasses all the behavioral aspects, all the things that Dr. de Vries mentioned that come together, that is really a burdensome part of TSC throughout a lifetime, so I just wanted to mention that.

We will take a short lunch break till 1:00 p.m. There'll be boxed lunches. Anybody who is a TSC and/or LAM patient or caregiver that is providing testimony, we'd love to get a picture of you all now before people start going home, so if you could just stay for a few minutes, so we could get your picture. Thank you all very much, and we hope to see you back at 1 p.m.