Vanessa: Perfect five o'clock on the dot. Well, I just want to welcome everybody in this evening. We're so excited to have you all join us for this awesome session. My name is Vanessa, and I will be the hospitality host for this evening. I am a Research Specialist with the foundation. So, I'm really happy to see you all in attendance. So, you have joined us for the disease management for children session with Dr. Lisa Guay Woodford, before we get started, if you have any questions during the session, please type them into the chat box. And I'll do my best to address as many questions as possible during the Q&A session. And we ask that you please keep your microphone muted throughout the session to ensure that we have good quality, audio quality for everyone. And I am very pleased to turn the presentation over to Dr. Lisa Woodford.

Lisa Woodford: Thanks very much. Thanks very much, Vanessa. So, I have the pleasure of speaking with you tonight about the basics of clinical care for children with ADPKD and ARPKD. So, let's jump right in. I've organized this presentation in three parts. First, I'll give you a brief overview about what PKD is, and then dive into the issues with ADPKD. Specifically, the key issues in children current treatment strategies and the promise of targeted therapies and then do the same sort of considerations for ARPKD. So, to begin to understand PKD, we have to first understand the normal kidney and the normal liver, as well as understand the fundamental principles of genetics. So, let me start with the kidney. The kidney really is they look like kidney beans.

They're a pair of reddish-brown organs that are located on either side of the spine just below the diaphragm behind the liver and stomach. And they're about the size of one's fist if you have no structural problems with your kidneys, the primary function of the kidneys to remove waste from the body through the production of urine. They also help to regulate blood pressure, blood volume and the chemical or electrolyte composition of the blood. And how can these do this? Well, they remove waste and fluid from your body through the production of urine. They continuously regulate the body's fluids and chemical composition. So, sodium, potassium, phosphorus and calcium.

They remove drugs and toxins from your body. And they produce and release in a very regulated way hormones into your blood.

So, for example, erythropoietin which is the hormone that stimulates the bone marrow to make red blood cells renin, which regulates blood pressure, and kalsa trial, which is a form of vitamin D that helps the intestine to absorb calcium from the diet and thereby maintain healthy bones. When we think about the kidney handling salted water, it's really quiet a heroic feat. The Kill to the kidney, filters the blood at the structure called the glomerulus. And at the level of the glomerulus. What is filtered on a daily basis in the typical adult kidney is about 1500 grams of salt. So, to put that in more tractable terms, that's about 50 ounces of salt, and that salt is contained in about 200 quarts or 200 liters 50 gallons of fluid.

The kidney works its magic, the fluid travels along the course of this nephron fluids are reabsorbed salts are reabsorbed or not depending on the balance in the body. And at the end, what is excreted here at the end of this collecting duct is urine. And in that urine in the typical American adults was eating the typical American diet. Nope, the French fries and hamburger. We excrete about six grams of salt which is about a teaspoon, and that's contained in about two quarts or two liters. So, a remarkable task that the kitten can accomplish. In terms of the liver. It's one of the largest and most complex organs in the body. It weighs about a pound. It's made of a spongy mass of which shaped loaves and it sits right underneath the right side of the ribcage is many functions that are necessary for life in the website. In the reddish tissue here, the brick red tissue.

This is kind of the factory of the liver, and it helps process carbohydrates, fats and proteins that are absorbed from food in the intestine and turns them into materials that the body needs for life. The materials that are sort of the building blocks of structures that the body needs in these structures called bile ducts. Bile is secreted to help with the digestion of fats. The red structure in the liver also makes factors that are needed for clotting. It stores vitamins, and most importantly, in terms of thinking about, about the drugs that we take, it's very important in breaking down toxins and drugs that we take in

the course of our daily lives. Now, if we switch from the normal kidney and the normal liver to think about the principles of genetics, we have as humans about 20,000 genes they come is, is paired structures, each one is called an allele.

And in the course of reproduction, you inherit one allele from your father and one allele from your mother in an entirely random fashion, in the dominant form of polycystic kidney disease, shown here in this upper squared, part of the diagram, the father is carrying an abnormal version of a PKD gene, and entirely by random transmits it to his son who now becomes his affected son. Whereas the father, transmit transmits the normal allele shown here in blue, to his daughter, and so she is unaffected. This is dominant transmission. In the recessive form of the disease, each parent is carrying an abnormal copy of the gene. And again, entirely by random, they can transmit either an effective copy or an unaffected copy to offspring, there's a 25% chance that both the mother and the father will transmit their abnormal copies to a child and then therefore that child would be affected.

So, why with this kind of primer as the backdrop what is polycystic kidney disease and what goes wrong? Well in the kidney, this nephron's structure, can have cysts form either as sort of soap bubble or bubble gum like budding out of the continuity of the nephron or delimitation of this last part of the nephron called the collecting duct. In the liver, the reddish tissue, which is about 95% of the mass of the liver, is really typically unaffected. The problem in PKD really involves these bile duct structures, as we'll talk about in just a minute. And when we think about polycystic kidney disease, you've heard terms like adult polycystic kidney disease and infantile polycystic kidney disease. Typically, adult polycystic kidney disease refers to the dominant form of PKD.

But it really isn't the right way to describe it. Because in point of fact, while most symptomatic patients have clinically significant issues, early in adulthood, there is a subset of children that come to medical attention because they too have problems related to their ADPKD. Similarly, but in kind of in a reverse way, while ARPKD is largely a disorder that comes to medical

attention in the first few years of life. There is a clinically significant smaller, but clinically significant subset of adolescents and young adults that come to medical attention for the first time, later in in their life course. So, if we think about ADPKD, let's drill into the key issues in children. So, the dominant form of polycystic kidney disease has a prevalence in the population of about one and 800 to one and 1000.

In terms of the molecular genetics, there are principally two genes that are involved PKD-1 and PKD-2. GANAD, which has been the subject of conversations here at PKD connect over the years accounts for probably less than 1% of the cases. And in addition, there are a few even rarer disease-causing genes that are involved in ADPKD. But primarily ADPKD is a disorder caused by one of these two genes. And as a consequence of the DID effect in one of these two genes, you can see the development of the soap bubble like cysts anywhere along the course of this nephron although by and large, it's primarily at the latter half of the nephron. As a result, the kidneys can be very, very large in in size, or the kidneys can be normal in size with just a few soap bubbles, depending on the severity of the disease and quite frankly, the age of the patient.

What is important to note is that this soap bubble kind of abnormality only affects about one to 2% of the nephrons, and so they really become kind of bullies in the applecart causing problems not only for the nephron structures that are adjacent to them, but also triggering a processes of inflammation and fibrosis. And together that probably is what causes for some patients a decline in kidney function. Other associations in the dominant form of polycystic kidney disease you here in the course of PKD connect can be biliary cysts and pancreatic cysts, vascular aneurysms, hernias and male infertility. But by and large, these are not clinically significant problems for children in children. ADPKD is largely a kidney disease. And when we think about the age-related manifestations of ADPKD, it really can be kind of subsisted into three groups.

There are a subset of children who have very early onset disease, they present in the prenatal period or in the first year of life. They have a very high

frequency of high blood pressure, and about 25% of them can go on to end stage renal disease to develop end stage kidney disease. With by the time, they're on the threshold of becoming adults, the lion's share of patients with ADPKD clinically significant ADPKD are diagnosed in childhood. And they've diagnosed in childhood because they have blood in their urine, protein in their urine, high blood pressure, rarely kidney stones. These children when you look at them from an imaging perspective, particularly with sensitive imaging, like MRI, you can see liver cysts. But again, these are unusual.

It is unusual for these liver cysts to be clinically symptomatic. When we think about the management of ADPKD. This table is a compilation of, of information and data from a variety of adult studies. So, hypertension, we know what kinds of treatments we should use this first line therapy, abdominal pain and flank pain. We know the different sorts of causes for either acute or chronic pain and how to manage that cyst, hemorrhage and gross he material or blood that is visible in the urine, kidney stones, cyst infection, progression to end stage kidney disease is a very low risk of renal cell cancer. And we have markers to identify when that might be a problem.

And in more recent years, we've really learned how to monitor the progressive increase in size of the kidneys by monitoring system growth using a classification that was developed by investigators at the Mayo Clinic. But I would point out to you, these data apply to adults, they're derived from adults, and they apply to adults. And we at this point, tend to extrapolate these adult findings into children so that we can think about their management in in sort of the most comprehensive way. But these are not childhood data. Recognizing that limitation, there has been a recent report of an international consensus statement about the diagnosis and management of ADPKD in children and young people. And essentially the key.

The three key takeaways from this really lovely report is the children with a positive family history should be monitored for hypertension, and for protein in the urine, that if they develop hypertension, or proteinuria, or hyperfiltration, that finding based on laboratory studies that the kidneys are

working especially on that this is the class of drugs that can be most effective. ADPKD children as all children should be encouraged to achieve a relatively low dietary salt intake. In the United States, our diet by and large is too heavy on terms of the salt that we eat. So, this is not a particular reference for ADPKD children, but just to say that all children should have a relatively low dietary salt intake. And we can talk about that in the question answer if people have questions.

Now, when we think about PKD biology, we've learned over the years starting in animal models and extending to clinical trials, that that that this cell signaling diagram has several if you will druggable targets. The first of these is the production of cyclic ANP. And that is generated by the vasopressin two receptor. And that vasopressin two receptor can be blocked by drug by the drug that is called generic and as initially it's generic name is tolvaptan. M-TOR activators. This is a pathway here that's also involved in tuber sclerosis and drugs like enviroximes at least in animal studies, can block the activity of M-TOR and therefore, decrease the cell's ability to replicate itself in a somewhat uncontrolled way.

And then more recently, there have been there has been studies looking at this misplaced receptor on the urine facing surface of the cell and blocking the signaling from that receptor, again, based on animal studies, and there have been some very preliminary studies in humans. Now when we think about actually, let me just stop here. When we think about children, there has been a recent study, in fact, we have just submitted for publication, looking at this drug, generic or tolvaptan. It's a study that was done in Europe, about 90 children 65, or 66 of them were between 12 and 17 years of age, and the remainder were between four and 11 years of age, it was a relatively small study. But what we can say is tolvaptan, in the doses that were used in that study is physiologically active.

And so that we know that it binds to the V2 receptor and has a physiologic effect. We also know that again, limited number of patients, not a big study, relatively small study, but that the increase in size of the kidneys of those children who took tolvaptan tended to be blunted, they didn't increase the size

of their kidneys, as rapidly as the children who receive placebo. And then finally, that one of the big side effects that I'm sure all of you have heard about with tolvaptan, is that it really causes you to pee like a bandit, if you will. It's called aqua, Risa says a tremendous operatic effect. That's part of how the pathway that it targets. That's part of how that pathway works. And one of the concerns was how well will children tolerate that operatic side effect.

And it turns out that it was reasonable, it was reasonably well tolerated. And there were very few children that dropped out of the study, because of their issues with Aqua Rhesus. So, this is very promising for future larger scale studies to look at children with, with ADPKD. But I think by and large, the current recommendation is that this kind of drug because it does have side effects should really be reserved for children who have really rapidly progressive ADPKD. There are children, I certainly take care of them where they can be treated off label, because in the United States, tolvaptan is not yet approved for use in patients less than 18 years of age, but they really should be selected carefully for rapidly progressive disease. There is no consensus about the use of statins.

For those of you who are parents of children with ADPKD, who have ADPKD yourself, statins is probably part of your therapeutic armamentarium. And despite the very encouraging data from animal studies, there aren't good data in in adult humans to say that M-TOR inhibitors, or somatic statin analogs, we didn't really talk about this, but they're not recommended for even using them off label in children. And I want to just bring to your attention the use of tolvaptan in very early onset disease. And this is a little cherub that was reported from the UK, who was born with not one but two abnormal copies of the PKD one gene, and she had massive renal enlargement, hypertension, hyponatremia respiratory compromise, and she was treated with tolvaptan from one month of age to 12 months of age, and essentially tolerated it well and got better.

That's an important case, both for treating children who have ADPKD with tolvaptan. And because she had such severe disease, you'll see in just a

moment, it is part of the basis that allowed us to develop a protocol for a clinical trial in the recessive form of polycystic kidney disease. So, we're already with clinical trials. Well, as of this month, there are 22 trials that are either open and enrolling or have recently closed, most of them involve on studies of tolvaptan but there are studies looking at Curcumin, privatestatin, Docselone, and fluid therapy, just fluid therapy by itself as well as an herbal medicine being investigated in in China. So, there's clinical trial activity in ADPKD in children. And there's a registry, there's a worldwide registry that has been established by Jelala Makely in Belgium, she has to date recruited almost 1500 patients, we are a site in North America, we to date, I've recruited almost 40 patients.

And with the help of the foundation, we're recruiting more patients and the idea is to gather these patients and their clinical information so that we can sort through what is going on with these kiddos in terms of their clinical features, their imaging features, their laboratory features, and can we subset those patients that are likely to go on and develop more severe disease from those patients that will have milder disease. So, clinical databases are really, really important for us to really understand the course of this disease. Let's switch gears at this point and we'll pick that team up about registries in just a moment. But talk about ARPKD. So, the recessive form of the disease much less common than the dominant form. The molecular genetics point largely to one major gene being involved, there are two genes that are responsible for rarer cases of ARPKD.

The renal disease is quite different than in the dominant form of the disease. There's delimitation of this collecting that so not so prophylaxis, and other associations pretty much are restricted to the liver. And what I mean by that is, this is the normal nephron. This is the normal collecting tubule. Here's the delimitation of the collecting tool that can lead to massively enlarged kidneys. In the liver, there is a problem in the development of these bile ducts that are associated with a portal vein. And that's the bile duct complex that I spoke about before. That whole process of patterning goes awry, such that it

leads to this chaotic bile duct formation and a pattern that we as clinicians recognize as congenital hepatic fibrosis.

Scarring around this bile duct complex causes the flow of blood from the intestines into the liver, sometimes to back up and can back up into the spleen, causing the spleen to be big, it can back up into the veins around the esophagus, putting some of those dilated structures at risk for bleeding. And there will be a talk tomorrow by in terms of managing congenital hepatic fibrosis, particularly as it relates to ARPKD. The last couple of years we've done a study trying to ask the question, well, how common is ARPKD and using the electronic health record, we were able to determine that the incidents that is how many babies with ARPKD are born in the United States per year, about one in 26,000 live births.

And that sort of translates into about 120 new babies a year with ARPKD, we're also able to dig a little further and really address the question that there are all sorts of numbers that float out there on Google about and how many of those babies actually die in the newborn period as a complication of their poor lung development due to their kidney disease. And we asked we calculate that the perinatal mortality rate is about 21%. And then finally, to ask the question, well, how many patients does that mean, are alive in the United States with ARPKD, between say, zero and 29 years of age? At the time we did this analysis, we estimate that there are about 1500 patients with ARPKD living in the US in terms of patient's survival.

I use this diagram from some rather older studies to simply make the point that ARPKD is a disorder that if patients die, they tend to die very early in life. And this, although it's a small number really makes the point that after perinatal mortality, the next major lethal events in ARPKD patients is well into adulthood. When we think about the features of ARPKD, we really have to subset them into two groups, newborns, these kiddos are typically born between 34 and 36-weeks' gestation, because of their massively enlarged kidneys, and the decreased production of amniotic fluid.

Many of them have poor lung development that can cause perinatal mortality and 21% of these babes, the kidney issues, again, low levels of sodium in the blood, that's a delusional effect, not that they're losing too much sodium, decreased kidneys, function, very enlarged kidneys, you can see this cherub's belly is really quite small, and even in very young children, hypertension, when children get older, chronic lung disease you would think would be a major problem for these kiddos for reasons we don't really understand even those that are on a ventilator, that not really something that we that we see a tremendous issue. These kiddos though, do have hypertension, and they are at risk for declining kidney function. They can have liver disease, we talked about this portal hypertension that can lead to vertical bleeding.

Those dilated bile ducts are set up for infection. Some of these children can develop colon Janus because of the massive increase in their kidney size, feeding issues can lead to poor growth. And Dr. Arum Hartron at the Children's Hospital of Philadelphia and other investigators in Europe have reported a handful less than a handful of patients who have intracranial aneurysms with the gene mutation that causes ARPKD. Is that causal? Is there a mechanism that a defective gene causes intracranial aneurysms? Or is this sort of true and unrelated? The numbers are very small, and we don't know the answer to that question at this point, when we think about clinical management, we have to manage the low sodium manage the high blood pressure, these cherubs are at increased risk for reasons we don't understand to develop urinary tract infection.

A sorry about that, a fair portion of them develop chronic kidney disease in childhood, and a subset even go on to end stage kidney disease in childhood growth as an issue, portal hypertension, as we talked about. When we think about the biology, there are remarkable similarities in terms of the cell signaling diagram and what goes wrong in ARPKD as compared to what goes wrong in ADPKD. So many of these same agents potentially theoretically, could be useful in managing children with ARPKD. The problem is right now there are only three current clinical trials, and soon there will be five clinical trials in ARPKD in the entire world. So, what's the problem?

If we have related disease mechanisms in ADPKD and ARPKD, can't there be the potential that ADPKD therapies could be effective in ARPKD? Well, the issues for ARPKD have been the disease onset This is a disease that develops in utero typically causes massively enlarged kidneys by birth. Kidney volume doesn't inextricably go up as a child ages. It is really very big in the first two to four years of age, sometimes with exponential growth in that time period, then the growth slows to secondary scarring and a loss of nephrons. So, we don't have easy imaging markers to follow the trajectory of the disease, kidney function is variable and not well correlated with disease severity. And until very recently, we just didn't have predictive markers of disease progression.

So, how do we get around that research ready patient cohorts? I noticed as we were coming to this session, that the PKD foundation is really emphasizing the importance of having registries of patients so that we can understand the natural history of these diseases AD and ARPKD. Biologic insights, what's common to PKD? And what specific for ARPKD and I know that there are a numbers of folks including some in the audience today who are working on specific path of biologic insights in terms of ARPKD, looking for biomarkers of disease progression, clinical biochemical genetic and imaging, and then thinking about therapeutics, both repurposing drugs that we know how to use and thinking about novel agents, particularly for these specific targets that are involved in ARPKD, specific pathobiology.

Here's a kind of a summary of the databases the European ARPKD database that is led by Max Liebau in Cologne. These are data from 2021. I know Max has more than 700 patients currently enrolled our database here in the US, we now have 183 patients enrolled and there is a registry also in the UK. And what I want to point out is that these databases are yielding information. And so, a lovely study from Max Liebau’s group talks about the fact that looking at the data from there, then about 300 patients with ARPKD, they were able to determine that a child was born with all ago or anhydrous embryos, either low or absent, amniotic fluid, enlarged kidneys and renal cysts had a 32%

risk of needing dialysis by 12 months of age, and an almost 35% risk of needing dialysis by 36 months of age.

So, these are the kinds of insights the databases I can provide for us up sorry, one other thing I wanted to say maybe this is the slide that would be better to do it on. When we think about the sort of pathobiology there is a as I said information that that that the V2 receptor is an important target in ARPKD pathobiology. And in the next month or two, we are going to open two clinical trials, one for children between 28 days and less than 12 weeks of age and one between children who are 28 days and less than 18 years of age using tolvaptan. In the first group, it will be safety and tolerability and some initial information about efficacy because those children are in the steep rise in terms of renal function for that period in their life and for the older children really looking at safety and tolerability.

And so, this is the beginning for clinical trials now not just in ADPKD but in ARPKD as well So let me sort of bring this talk to a close by saying PKD is a clinically significant disorder not just in adults, but also in children. And in children, it's a clinically significant disorder in childhood because these children do not uniformly die in the newborn period. Despite what the deep recesses of the internet sets, while Polycystic Kidney Diseases are clinically distinct, there are many disease manifestations that are common. Current therapy focuses right now on supportive management. But we need more clinical data to know that we're doing this supportive management in a way that is really targeted to the disease as it exists as it progresses in children. clinical trial design for therapeutic targets, has until recently been hampered by the lack of prognostic and predictive markers. With the development of databases, we're having more information about prognostic and predictive markers.

And we have started clinical trials, trials that will look at not just the safety and the tolerability, but the efficacy of these directed agents in slowing the disease progression. Right now, we're just focused on the kidney, but the liver, particularly in ARPKD will follow along. And so, I think that that's very encouraging, and that our research ready cohorts are part of the reason

that this landscape is changing. So, let me acknowledge my colleagues at the University of Alabama at Birmingham and Children's National who've been integral for this work. My collaborators in Europe and in the United States, our ARPKD and ADPKD, database collaborators, and of course, our funding sources. This is my contact information, copy to field questions now. And after PKD connect concludes, and I would be happy to have Vanessa, send me questions.

Vanessa: Awesome. Thank you so much for that presentation. It was really wonderful. So, right now we're going to start the Q&A. So, if anyone has any questions, please continue to stay muted, and send them over to me in the chat. And we can go ahead and get that started for the next 15 minutes. But in the meantime, while we wait for some folks to think of a few questions, Dr. Woodford, is there anything else you would like to say before this session is over?

Lisa Woodford: Sure. So, I'd like to just talk about the clinical trials, because you know, I've come to that I've had the pleasure of coming to a PKD connect annual meeting for a long time. And that clinical trials in children has always sort of been the Holy Grail. I think that the successful conclusion of the trial in Europe, with children who have ADPKD is probably in the not-too-distant future going to translate into clinical trials, that are global clinical trials, and our children in the United States will be able to participate.

And that will be really, really important, not just look at looking at tolvaptan as a targeted therapy, because remember, that's really going to be appropriate for a subset of children with rapidly progressive disease, but having large numbers of children so we really understand how do we most effectively treat and manage blood pressure is there a threshold to which we should be targeting blood pressure control, thinking about the use of statins, thinking about other agents that can slow disease progression. And then of course, for the recessive form of polycystic kidney disease, that it's very exciting that we're going to start these trials, the two trials that I mentioned, each one enroll, probably no more than 20 patients internationally.

So, we're not going to have a large number of patients from any one country or any one region of the world, because again, it's the first foray into safety and efficacy. But sort of keeping your radar tuned to the PKD foundation will be a wonderful way to understand what's coming in the near term.

Vanessa: Yeah, clinical trials are extremely important, especially to the understanding of the disease, but also to hopefully finding some therapeutics, we have gotten a question in the chat. So, someone asks, if there are if you have any thoughts on accessing optimal care, such as finding a picky expert, because this can be tough, especially for people who do not live close to a large academic center.

Lisa Woodford: Right. So, I would ask us all to sort of think about what the Covid-19 pandemic has taught us. It's taught us we can do effective communication, effective education using these electronic platforms like some two or three years ago it was no, we can never do that. It's just it's too hard. We really need to be in person. This this just really won't work but we know we can do it now. I think that that that one of the things that when you have a relatively rare disease, and you don't have a distributed network of experts for that disease, we again have to think in in creative ways. So, for example, there are numbers of folks in the United States who are interested in inherited disorders of the kidney, we have in Washington, and inherited and polycystic kidney disorders program, we see kids from all over the country.

But I feel very strongly that those kids to have root to be really well cared for need to have a local provider. And so there are times that I work with their local pediatric nephrologist in New Orleans, in Salt Lake City, in other in Wichita, Kansas, in other parts of the country, and they come to see me once a year, or maybe once every two years, or maybe they just come once. I've also worked with pediatricians. And when I was at the University of Alabama at Birmingham, some of my most collegial and effective partners were family practitioners. And so, what I think what, what you want is, if you have a child with a rare disease, the idea that you need to build a care team, hopefully you have some resources that you might be able to see an expert at least once and sort of begin to engage that person in your care team for your specific

situation, because we can do these talks, but it's not specific to any one child. But I think that that is an important way for us to deal with rare disorders.

Vanessa: Yeah, so do you know of any specific networks that families can turn to or resource this that they may be able to learn of different experts, especially for children? And sometimes that can be tougher.

Lisa Woodford: So, I think that you have a couple of experts about childhood PKD talking here at PKD connect. So, I'm more than happy to say as I said, I've done this for years to see kids from all over the country see sometimes kids from Canada and sometimes kids from other international destinations. The Children's Hospital of Philadelphia, Dr. Aaron Hartung, we believe is here this weekend, also has a strong interest in in PKD.

Dr. Catherine Dell in Cleveland has a strong interest in PKD. Dr. Asha Gulati, who's here this weekend is one of my partners at Children's National Dr. Laura Willock. At Children's Mercy in Kansas City. So, there are numbers of folks. The other thing is most of us are willing to field an email or a phone call, and to help you find folks. So, there isn't necessarily a network that you can do what you do when you shop on Amazon at two in the morning, you don't need anybody else, you just do click, click and find it. That probably doesn't exist the way that it will, perhaps in the next five to 10 years. But any of us and I think I can speak for all of us, any of us would be willing to field an email field a phone call and help direct you. And if we do see your child work with your local providers, so your child has the best possible care.

Vanessa: Wonderful, I know, just from my experience of working with a lot of the different physicians. Yes, everyone is really willing to help each other out. So, definitely take her up on that offer. We do have another question in the chat. This one is saying clinical studies. So, if you would mind explaining the difference?

Lisa Woodford: Chris, this is a great question. You've picked up on what seems to be something somewhat a lot illogical. We have two small studies, and we're

going to compete for these children between 28 days and 12 weeks of age. Part of the reason is because it's Sukkah advisory committee that I happen to sit on water and really to target this therapy, or this trial to children between 28 days, so well out of the neonatal period 28 days, but still very young. So that's why 12 Weeks was decided upon the EMA said, that's fine. But you have to also do a study in the whole range of childhood. And so, there is a regulatory reason that these two trials are being offered. They will also have a somewhat different perspective.

So, we're really looking for efficacy, even a signal that suggests efficacy in that first group the what's called the tool for trial that we're going to look for a signal to see does it can we slow the rate of increase in the kidneys because as I mentioned at that very young age, there's they are many of these children's still have an exponential increase in their kidney size that only flattens out later. In childhood, for the older group, it's safety and tolerability. What can these kids tolerate in different age groups? So, that really, it's not there's not a biologic reason, it really is a regulatory risk rationale. Yes, that's right.

Vanessa: Perfect. We have a few minutes remaining. Does anyone else have any last questions?

Lisa Woodford: Yeah. So, Michelle asked what sites are doing those trials. So, there are 35 sites globally, we are one of them. What is really cool is that its sukkah is doing so I see kids from all over the countries, for example, there's a family that I follow in Chicago, and I would wager they will be interested for the older children at sukkah is providing sort of traveling nurse support. So that if you are enrolled, say with me in Washington, with Erin Hart tongue, in cheek chop, because I know Philadelphia is doing it with Katherine Dell, in Cleveland, and you live hundreds of miles away, you can still participate in that study. So, it's not like the clinical trials of old where you had to figure out how you were going to get back and forth to the study site to be part of that clinical trial.

And I think that's something that we worked very hard with sukkah, to try to bring to reality because I think that's important for a rare disease, again, without a network that is geographically distributed across the country.

Vanessa: I also like to add that we do have just set the foundation for the website, clinical trials finder, and we try to keep that pretty up to date, I actually update that every quarter. So, when those sites and are ready to be sign up for, we'll make sure we have that on there.

Lisa Woodford: Great, wonderful. Again, there are numbers of us here who are interested in childhood PKD. I will speak here just for myself. If I can help you, please don't hesitate to reach out. And I want to thank the foundation for giving me the opportunity to participate in this year's PKD Connect.

Vanessa: Thank you so much, Dr. Guay Woodford. This was a really amazing presentation. And I really appreciate it also for the participants in your questions. So, don't forget to answer the survey on your way out, that'd be really helpful for us. And also, just knowing how it went and also for planning PKD connect next year. Excuse me, but again, thank you, everyone, we appreciate you all taking the time to be here. And I hope you enjoy the keynote speaker earlier tonight. And the rest of PKD occurring tomorrow.

Lisa Woodford: Thanks.

Vanessa: Thank you.

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