Welcome to PKD Chronicles, navigating life with polycystic kidney disease.

A podcast by the PKD Foundation presented generously by Otsuka Pharmaceuticals.

This podcast is all about helping you live your best life with PKD. In each

episode, we'll explore the stories, science, and support and resources for families

impacted by PKD. And here's your host, Alyssa Ealy.

>> Hi everyone, and welcome back to another episode. Today we have a very special

guest, Dr. Nira Dahl, to talk to us about clinical trials. Dr. Dahl, since you know

yourself better than anyone, would you like to introduce yourself to our listeners?

>> Sure. My name is Nira Dahl and I am a professor of medicine at the Mayo Clinic in

Rochester. And here I'm the director of the Center of Excellence for PKD and also

the associate director of our Translational PKD program. And in terms of clinical

trials I think a lot of us started doing clinical trials in PKD when the Tolvaptan

studies were ongoing and that's certainly true for me so that was back in 2007 and

basically the Tolvaptan studies took about 10 years so they started the the big

phase 3 study started in 2007 went to 2018 and then after that we built a clinical

trials program for PKD.

>> Excellent. So definitely a good person to have on board with

us today talking about this topic. Definitely the pro. So just to kind of start

with the basics, can you explain what exactly a clinical trial is and how it's used

for the population with PKD? Is it specifically only for treatments or is it for

any therapy? Kind of explain to everybody what that trial process is and why it's so

important for this patient population.

- Yeah, so I'd love to. So we use the word trial pretty liberally,

I guess I would say. It could be that we're looking at a therapy that we're

looking at whether a drug will be effective or not in PKD, But it could also be

that we're looking at something else, we're looking at two different imaging

techniques or we're looking at whether a biomarker lines up with a disease state.

So some of the big clinical trials that have been done in PKD, one was called,

is really an observational study and that was the CRISP study.

And they were looking to see how total kidney volume changed and how kidney function

changed over time, and basically followed a group of patients for years to just see

what the natural history of that disease was. So that kind of clinical trial is

very easy, right? It's just looking at outcomes and then coming back to give us

clinical data at certain points versus being in a drug study where you're either

then getting a drug, an investigational drug or you're getting placebo and we're

looking to see what the difference is in the two groups after that point.

>> Excellent and so you mentioned earlier you use the term phase three. So could you kind of

walk our listeners through what the process is of completing your trial?

>> So if you have a drug that you think is going to be effective in PKD,

the first thing to think about is whether that compound is already on the market.

So if the drug already has FDA approval, you may not need to do as much

preclinical work with it, but if it's a brand new compound that is not already on

the market in some other way, then usually there's some animal studies or if not

animal studies, some studies done in some kind of human tissue that shows that

there's a benefit of that drug in PKD. And then once those preclinical studies are

done, so either in animals or in animal human systems and human tissues, then that

study moves to phase one. And phase one is really all about safety. So sometimes

the drug is then given to healthy volunteers, sometimes at different doses, to see

is the drug safe. And there's nothing about what the effect of the drug is, it's

really just, is it safe? And then that phase two trial, you may have picked your

dose in the phase one if you haven't, then you pick it in the phase two. So you

may have multiple doses in the phase two, and it's sort of like a pilot study.

You're getting more safety data. You're now looking at patients that have the

condition, so patients with PKD, and you're looking at safety, but also looking at

starting to look at outcomes with the different doses. And then once you've sorted

all of that out, you know, the dose you're going to use, you know, the thing that

you're going to use to study the outcome. So in PKD, that would either be kidney

function or total kidney volume. Then you can do your phase three study.

And the phase three study would be the very big study where they would have two

groups of people, one getting placebo, one getting the drug, both the investigator

would be blinded to who's getting which arm of the study, the patient would be

blinded, meaning that they don't know which arm they're in, and everyone involved.

So that's usually called placebo -controlled double -blind clinical trial.

And in the PKD space, a good example of that is the Tempo 3 /4 trial,

which led to the initial excitement about tolvaptan being a drug for PKD.

And then they did another big phase -3 trial called the Repre Study, where they then

showed again that there was benefit in terms of kidney function, preservation of

kidney function with tolvaptan. And so those were the big phase three studies for

tolvaptan, for example.

- It's really amazing when you think about how much data was

collected on the back end before you even started using tolvaptan in patients. So I

don't think a lot of people understand just how many years of research it takes for

something to go from thought to actually treating patients in everyday clinical

practice. So if you had to guess, how long do you think that all takes? You

mentioned Tolvaptan took about 10 years to get to patients and get approval to be

used as a treatment. But when did that all start? You said you got involved in

2007. Tolvaptan was already a drug on the market. So even was that with the

speeding up or was that?

- So Tolvaptan was a drug on the market,

but it was a drug on the market for treatment of hyponatremia because tolvaptan

blocks the effect of vasopressin. And so the drug was first being developed as a

treatment for hyponatremia. And that's when the sodium level in the blood is low and

it's low because there's too much water in the system. And so this gets rid of

excess water, so it's a great treatment for that. And so those studies, they were

looking at people who are prone to getting hyponatremia, which would be people with

heart failure or people with liver disease. And it was actually the insight of one

of the physicians here, Dr. Torres, who realized that oh, vasopressin is also

stimulates cyclic AMP and cyclic AMP drives cyst growth and cyst proliferation,

the cell proliferation. So when he was seeing this data on hyponatremia, he said,

"Hey, I have an idea," and they started doing the mouse data. And you're at Yale,

so you'll like the story. That mouse data was done with a mouse that Dr.

Somlow, who used to be the division chief at Yale, developed.

And so this is a mouse that gets cystic kidney disease due to a PKD2 variant,

a human PKD2 variant. And in those mice, they showed that if you gave a compound

that was the precursor to Tolvaptan, then you would get less cyst growth and better

preservation of kidney function in those mice. And so they were very, very excited

about that and then that led to going to the FDA and developing these clinical

trials. For short -term clinical trials, for safety studies, then the short -term phase

two trials to see what are the the hemodynamic effects of the drug and then ready

they got ready to launch the big phase three clinical trial in 2007. So that's when

it started.

- It is very exciting. I will say clinical trials are really the only

time I'm ever excited to talk about mice. So not usually my favorite subject,

but it's always really interesting when you think about the journey that a medication

takes to get to practice. So what do you think is the biggest challenge to

developing clinical trials for PKD specifically?

>> The challenge in PKD specifically has been that it is a very slowly progressive

disease so people develop kidney failure you know the people who are progressing very

rapidly it may be in their late 40s to 50s but the people who are progressing more

slowly it may be in their 60s to 70s and so then the question becomes how if

you're the one doing the clinical trial, how do you design the trial so the trial

isn't taking two years or three years to do, but can be done in a shorter period

of time because clinical trials are very, very expensive to run and patients move

and things happen and so to follow a patient in a clinical trial for three years

or four years takes a lot of effort and coordination. And so that was a big issue.

So particularly if you think about PKD, early on in PKD,

the kidneys are growing, but there's still preservation of kidney function. And so

one of the sort of brilliant ideas that changed how we think about PKD is,

well, could we use that first marker, that kidney growth marker, as a marker of

progression and not wait for the change in kidney function. Because the kidney

function is going to be slow, it's going to be difficult to measure. We know there

are a lot of problems following serial creatinine measurements, so creatinine is that

what tests we use to follow kidney function. And it can vary for a lot of

different reasons. So you wanna make sure that if you're seeing a change in

creatinine that it's truly reflecting something that the drug did and not that,

you know, the patient took an Advil the day before they came in or they were

really dehydrated or they had a big steak dinner or something like that. So it's a

complicated marker to follow. And one of the reasons that the FDA sort of changed

the process and the Tolvaptan trials took so long is initially, Tempo 3 4 was written

to show that the primary outcome was total kidney volume, and then there was a

second composite outcome of change in kidney function. But the FDA first had thought

that they would use total kidney volume as an endpoint for this study, and then

said, "No, we really need to see the GFR change." And so in tempo 3 -4,

they showed both, but part of the reason for doing the second study was to then

show the GFR change in particular. So I think one of the things that sort of came

from that big struggle with should total kidney volume be a good marker in PKD,

was then the researchers who think about clinical trials in PKD pooled all of their

data together and had a big consortium called the PK doc, an outcomes consortium,

and showed that over time total kidney volume changes, and that people who have the

biggest kidneys at the younger age were at highest risk of progression.

And so then the FDA said, okay, we get that now. So we'll use TKV in the studies

going forward as a surrogate biomarker. So you still have to show the EGFR,

but you can change how you do the studies now so they can be shorter,

smaller studies with EGR as an outcome.

>> Awesome. So it sounds like there's really a lot of movement to accelerate this

whole process, which is so important for this population because there's such urgency

for access to new treatments and there's really just not much treatment option at

this point in time. So do you anticipate this accelerated model will dramatically

change that outcome that we'll see more therapies in years to come? What do you

think that looks like? 10 years, 20 years?

>> Yeah, so I think that's a great

question, right? And particularly if you're thinking about participating in a clinical

trial, you want to make sure that the benefit is going to be something that you

can take part in as well, right? That your kidney function is still good enough

that you can you can benefit from the drug. drug. So, what's happened?

So, you know, I think Tolvaptan is a good case study of how you do the preclinical

work and then the phase one studies and then the phase two studies and then these

two very large phase three studies. The new model is you have the preclinical data,

you get some safety data, the phase one data and then the FDA has really moved to

accelerated clinical trials, particularly for rare diseases. And so if I step away

from PKD for a minute and you think about something like IgA nephropathy, so in

that disease people have protein in the urine and protein in the urine is a

surrogate marker for then what they have to show, which is improvement in GFR. So

if you do, you have a first outcome measure and say,

oh, these patients were on drug for four months and look the amount of protein in

the urine is lower, then you would continue on and do the rest of the study and

show, okay, now over two years, there's an improvement in GFR. And So in PKD,

what that looks like is now when they do a study, it's almost always or will

likely be a combined phase two, phase three study. So in the first part of it,

you say, hey, look at a year or at 18 months, I'm showing you that there's an

improvement in total kidney volume, that the kidneys are smaller. And if you meet

that outcome, then the FDA says great, go ahead and they will give approval at that

point, at the point of the TKV showing a benefit. That approval is contingent on

meeting the second metric of having the EGFR improvement as well.

So it's conditional approval, pending full approval.

But that's the accelerated approval pathway for PKD, and we're pretty excited to have

something like that because it really slows down, probably cuts,

you know, three to five years off of what would otherwise be a pretty long journey

of getting the drug approved into the patient.

>> Yeah, I think that's something that

patients will really benefit from hearing. I know in my own experience with having

conversations with patients about this, they're so anxious for something new to come

out and be available. And I think this new accelerated model will really, really

help with that. And maybe even just ease some of the anxiety of knowing that there

are solutions that people are working towards. And it may not take 10 to 15 years

to get it out to the patient at the bedside?

- Yeah, I think that's true. And I

think what's also really exciting in the PKD space is for a while we didn't have,

Tolvaptan got approved, that was in 2018, but it's 2024. And people are like,

"Hey, what's happening?" And then what happened was there were a lot of ideas for

potential drugs that just didn't pan out, which happens, right? Sometimes a drug

doesn't meet an improvement in GFR, or doesn't meet an improvement in TKV,

and so it doesn't progress, which is appropriate. And I think now that we're

starting to move into 2025, there will be some of these combined phase two,

phase three studies coming out, looking at different ways of trying to hit other

targets in PKD besides vasopressin -mediated growth.

So that's pretty exciting. I think for anyone who has PKD,

I would say keep your ear to the grapevine somehow either by checking in with your

physician and asking what are the new clinical trials that are starting or by

checking in with the PKD Foundation because they often list what are those new

trials that are starting. And there's a lot of interest, you know,

we're talking about drug studies but there's a lot of interest in looking at dietary

modification and improvement in outcomes in PKD. So I think those trials are ongoing

or whether weight loss helps with slowing the progression of PKD. So there's some

interesting trial data I think that will be coming in the next couple of years.

>> Yeah, there's definitely so many interesting things coming down the pipeline it seems.

So you kind of started to touch on this, but let's say that I was a patient with

PKD and I was interested in enrolling in a clinical trial, you kind of started to

mention some of the different ways that people can get involved starting with asking

their provider. Are there any other ways that people can get involved? Because I

think about some of those people who may not be near a center where they have

trial participation. What other resources are there out there for students or sorry,

for patients who are interested in joining or participating.

- So I think one way

that's available by the web, it's not a trial, but it's a registry, which is

through the PKD Foundation. And this is a way for patients who may not ever be

able to get to a site that does trials to share some of what their experience has

been, what complications they've had, what outcomes they've had. For those who feel

comfortable you can also share some of your electronic medical records and it gives

us a way to start to comprehensively build information about PKD. PKD at the end of

the day is still considered a rare disease and you know it's not very common.

It's the most common cause of genetic kidney disease but still it’s one in 500 to

one in a thousand and so people may not have a lot of exposure to it so if we

can build a database within this registry of a lot of patients and see what

problems they're running into and also what their imaging looks like and what their

genetics looks like then all of a sudden we start to learn more about the natural

history of the disease which is really, really helpful. So that's one way anybody can

get involved. There are some centers where what they're looking for is what we call

a genotype -phenotype correlation where they're looking to see okay you have PKD and

we see on the images what that PKD looks like. So let's go back and figure out

which gene is causing that. So we know that most PKD is caused by PKD1 or PKD2,

but there are a lot of other minor genes that cause things that look like PKD.

And those people who have PKD caused by those other genes may have a very different

outcome than the people who have PKD1 or PKD2. And so that genotype,

phenotype correlation study is going on at a couple of places. So it's something

we're doing here at Mayo, and it's something that, for example, Whitney is doing.

She was, Whitney Bessie, who's at Yale, was very interested in looking, still is

interested in looking at the, what causes liver cysts to happen, which can be a big

part of PKD. And there's a very interesting study that Terry Wattnick is running out

of the University of Maryland where they're looking for people with PKD who have had

aneurysms to understand what is it about those patients who develop aneurysms that's

different. Is there a different modifier gene that they all have? Or is there like

another thing that happens that causes those aneurysms to form so that that's an

easy those are easy studies to get involved with because it's basically just reaching

out to the coordinator and they mail you a kit and you do the kit at home and

send it back in.

>>Wow super easy

>> super easy, Yeah

>> Anything that comes in a kit to my door step I will be able to do very easily. My Amazon delivery driver knows this about me. So there really are a lot of options for people,

even if they're not necessarily engaged in that large center, you don't even

necessarily need your provider to be up to date on all current trials, because you

can find a lot of this information through PKD Foundation and through some of these

other avenues.

>> Yeah. And then, you know, I think for those people who are able to

to give us the time and to come to the centers; There's value also in being a

trial patient in that often for these clinical trials we're measuring total kidney

volume so that's information that goes back to the patient. We're measuring kidney

function very frequently. We're measuring you know, blood pressures,

we're doing all of that sort of routine care at the same time that we have the

patient enrolled in the study. And so it's a it's a nice way for those who can to

actually learn more about the condition and make sure the condition is being well

monitored. With a downside, right, you have to come and spend the time in the

center and that can often be limiting for a lot of people.

>> So for some of theseclinic visits they could be pretty timely then for the patient as well.

>> Oh so typically, it depends on the study of course not every study is exactly the same and

I think that the people who design the clinical trials are very aware of this idea

that you know PKD affects people who or working or they're going to school or they

have lives outside of being in clinical trials. And so they really try to streamline

the study procedures so that there aren't as many visits that mean coming back into

the center. It depends on the kind of study you're enrolled in. So phase one or

phase two study may be much longer because they're doing something called PK

measurements or pharmacokinetic measurements. They want to see how quickly the drug is

metabolized so they might ask you to stay there for a few hours so they can get

that final time point of blood to see how much blood is in the bloodstream at that

point in time or they may say great everything looks great come back in tomorrow

morning and let us draw blood again so we can see how much drug is clear. And so

those studies can be those phase two PK studies can be very long studies for

patients, sometimes that they require coming in overnight and staying in our clinical

research units. But then there are other studies where once you've done sort of the

initial work and have the first you know maybe three or four hour long visit for

the first study, then maybe you're only coming back once a month for an injection

or an infusion. And that goes a little bit faster. And usually most of the studies,

especially those that are sponsored by a drug company, there's an understanding that

the study is taking time out of somebody's busy day. And so there's usually some

compensation for that, either in the form of travel compensation or something else so

that it doesn't feel so overwhelming to miss work,

for example.

- Yeah, absolutely. And I want to come back to one thing that you've

kind of mentioned a few times. You've talked about total kidney volume or the TKV

in a couple of different sections of the talk. You also very briefly mentioned

genetic testing and looking for different markers that could be contributing to PKD.

Are these things required for any patient with PKD who's interested in enrolling in

a study or will it change their ability to participate if they don't have a certain

genetic mutation or they don't have a certain size kidneys?

>> Yeah, that's a great question. So what you're asking is what we on the clinical research side call

an inclusion criteria. So these are what are those things who are the patients

we're looking for. And often we use total kidney volume as a way of selecting

patients. So there's something the height and age adjusted total kidney volume is

called the male imaging classification, and that male imaging classification we know

that the high -risk patients are male 1C, 1D, and 1E, and those patients are usually

the patients that the companies want to be recruited into their clinical trials. So

if you don't have that imaging classification, you may not be eligible to be in the

clinical trial. And then usually there's a GFR restriction too. So we're looking for

people with, you know, maybe a little bit of loss of kidney function, but still

preserved enough that they can go for another two years or three years until the

trial completes. So they're usually in any study, total kidney volume and GFR

criteria. But then, You know, the question you asked is, should there be a genetic

criteria, right? Should it be only available for people of a specific genotype? I

think we're going to see that start to be part of some of the studies coming up

in the future. But it hasn't been a big part of the studies we've done to date.

To date, it's really been what's the male imaging class and what's the GFR.

>> Okay. Excellent. We will have an entire segment on MRI imaging and the TKV for

those who are interested in that. And we also have a whole talk on genetic

mutations in PKD. So this is kind of the perfect blend of all of these pieces of

care. So do you have any final things that you think patients with PKD need to

know? Anything that their family members should know about clinical trials?

>> Yeah,

so what I would say is the clinical trial and the drug discovery can't happen

without patient participation. So we're always so thankful and so grateful when

patients decide to participate in a clinical trial and often patients feel that it's

very rewarding as well because they there's a sense of ownership in that you're

driving the you're accelerating discovery and accelerating new therapies and

patients who have been in trials before have said you know it's really so rewarding

for me to do this right? Like I don't mind coming here and doing this because it's

how I'm paying back and I think that needs to be balanced with the time commitment

of the trials and sort of how how do you do that right a clinical trial may not

be for everybody and that's okay but if you can do it and you're interested in it

you know we would love to have more conversations about that because I think that

the time is right like we're in this era of really starting to understand how to

treat genetic diseases by treating the genetic defect that's causing that disease and

to study those different drugs and those different ideas for how to approach that

problem, we will need, you know, this very committed group of patients to say yes,

you know, sign me up, I'm ready. So I think that would be my last word, just

really consider participating.

>> I will say in my experience patients who have

participated in trials have loved it and for those of you who don't know Dr. Dahl

and I worked together for many years and so all the patients that were in the

trial that she worked on still tell me about how Dr. Dahl got them involved in

this trial and it was a great experience and I will say it definitely is helpful

for patient empowerment. I think when you better understand the process that goes into

management and you understand the disease a little bit better, there's a lot more

like control that you kind of get over how you exist with this disease.

And I think that's really something powerful that comes out of this concept of

clinical trials and just really being a part of the change that we wanna see for

management.

- I think that all of that is true, right? Like if nothing else, when

you come in once a month, you see us and we talk about PKD for 10 or 15 minutes,

and so there's some value to that too.

- Excellent. Well, thank you so much for

being here with us today. It has definitely been very informative, and I hope

everybody will consider participating in a clinical trial, or at least checking out

the PKD Foundation Registry, 'cause even just data will be helpful in helping us

move closer to a cure.

- Well, thank you so much for having me, Alyssa. It's always

a pleasure talking to you

>> Anytime. Always a pleasure.

Thank you for listening to this episode of PKD Chronicles, navigating life with

polycystic kidney disease, a podcast by the PKD Foundation, generously presented by

Otsuka Pharmaceuticals. The PKD Foundation is the only organization in the U.S.

solely dedicated to finding treatments and a cure for polycystic kidney disease, PKD.

The Foundation funds research, education, advocacy, support, and awareness on a

national and local level and is the largest private funder of PKD research. For more

information, resources, or to donate to the PKD Foundation, please visit pkdcure.org

and connect with us on social media.