Seizing Life, episode 55
Epilepsy Drug Development: Clinical Trials
Guest: Dr. Kelly Knupp
(Transcript)

Kelly Cervantes:	00:00	Hi, I'm Kelly Cervantes, and this is Seizing Life, a bi-weekly podcast produced by Cure Epilepsy.
Kelly Cervantes:	00:17	Today on Seizing Life, we continue our series detailing the drug development process in which we all have a heightened interest with the recent announcement of a vaccine for COVID-19. Today, we talk with Dr. Kelly Knupp about the development process from the IND application, through human clinical studies and the FDA approval process. Dr. Knupp is the associate research director for the Neuroscience Institute and director of the Dravet Program at Children's Hospital of Colorado. She is also a member of the Cure Epilepsy Scientific Advisory Board, and was a founding member of the Pediatric Epilepsy Research Consortium.
Kelly Cervantes:	00:54	Dr. Knupp, thank you so much for joining us today and sharing your insights. So in our first episode about drug trials, we sort of briefly went over the process, but spent a majority of our time focusing on that basic research and preclinical stage. So now I want to dive deeper into the next steps, starting with the INDs. What are they and how long does this process take?
Dr. Kelly Knupp:	01:21	Sure. So first of all, thanks for inviting me to speak about this. I think it's really important for the epilepsy community to understand how research works. So and IND is permission from the FDA to perform research on a study drug, so that's really what an IND is. So anybody who wants to study something in a human needs to obtain an IND from the FDA to have permission to do that. And this process can really be pretty lengthy. So from basic science research to getting a drug into somebody's hands to use on a clinical basis can take sometimes up to 10 years, if not longer. There are lots of steps to the process to ensure safety and efficacy, and so there are lots of steps along the way.
Kelly Cervantes:	02:08	A decade is much longer than the year that it's taken us to get the COVID vaccine. And I keep emphasizing that in these episodes because I don't want people to misunderstand how long this process typically takes versus how long it is currently taking. Thankfully, it's been a much more rapid timeline with COVID. Before we get into the phases of the clinical trials, I want to sort of just cover some basic terms so that we're all on the same page moving forward terminology wise. So a placebo control group and a single masked versus a double masked study.

Dr. Kelly Knupp: 02:50 Yeah. So placebo is often something that looks like the study drug, but doesn't actually have the study drug in it. So one of the things that we do in trials is we give some people the study drug that we're investigating, and then we give people something that looks like study drug so that nobody knows who has it. And that's the best way for us to figure out whether something is effective or not. So placebo is usually a pill that looks like the study drug, but doesn't have the study drug in it, or a liquid that looks like the study drug, but doesn't have an active ingredient in it. So people will sometimes call it a sugar pill. It's not usually sugar, but it's kind of the same idea. It's something that doesn't have an active ingredient in it.

Dr. Kelly Knupp: 03:35 The control group is the group that usually gets the placebo. So in a trial, people usually get randomized or divided into two groups, the study group, which is the group that gets the study drug, and then the control group, which is the group that thinks they're getting the study drug, but actually nothing has changed with them. And that gives us something to compare to so that we can say the group that was in the study group got better, and the group that was in the control group stayed the same. And I think there was one other term.

Kelly Cervantes: 04:06 Single or double masked. Yeah.

Dr. Kelly Knupp: 04:07 So the other terms that we will use is blind, so a single blind or a double blind study. And so most of our studies, our clinical trials are double blind studies, which means that the patients who's getting the study product has no idea whether they're getting placebo or study drug, and the person who's giving it to them, the investigator or the physician at the site, also has no idea who's getting what. And that really is the more formal and best way to investigate something, is to have what's called a double blind or a double masked study so that nobody knows what's going on. And that gives us some of the best data to figure out whether something is efficacious or not.

Kelly Cervantes: 04:49 Okay. So we have the patients obviously that are participating in the study, but who is working on a study on the clinical side? If someone is volunteering for a study, who would they see? And who's working behind the scenes that they may not know?

Dr. Kelly Knupp: 05:07 Yes. Oh, there's so many people that make a trial happen. So, on the front lines, the person that the patient or the study subject interacts with is usually the site investigator, which most often is a physician, but sometimes can be somebody else. But particularly for epilepsy trials, that's usually the epileptologist who is the study investigator. And that's the person who is

officially in charge of the study at the sites, and so they're the ones who review the protocol and make sure they understand how the study is supposed to happen, help recruit the patients and meet with the patient at every study visit. There's also a study coordinator, which is basically the assistant to the investigator. And that may be the person that you have the most interaction with. So that's the person who takes your random phone calls when you're in the study, will help coordinate schedule the visits, make sure that all the study procedures happen.

Dr. Kelly Knupp: 06:00 They may actually do some of the study procedures that don't need to happen, that the investigator doesn't need to do things like drawing blood, or doing an EKG, looking at your seizure diaries, things like that. There may be some extra staff at the study site who help out with some of those procedures. So maybe there's somebody different who comes and does an EKG or somebody different who does an echo, but that's because they have expertise in that. In studies in children, we do a lot of neuropsychological testing, and so many times the neuropsychologists will come and do that neuropsychological testing along with the study procedures, because that's what their expertise is. But behind those scenes that the study subject very rarely sees and may only occasionally hear about, there's a study monitor, that's the person usually at the contract research organization, or something called the CRO, who is helping to coordinate the study.

Dr. Kelly Knupp: 06:56 And so that's who the study staff at the site will talk to. So the site investigator and the coordinator, if they have any questions about the study, will actually reach out to their monitor. The monitor will come and check on the study site usually once a month or so to make sure that everything is being done the way that it should. They go through all of the study documentation to make sure that at every site across the study everybody is doing things the same, because we don't want to have one study site doing something different than another study site. We really want everything to be consistent. And so the monitor is the person who does all of that.

Kelly Cervantes: 07:32 And, so I'm going to stop you here, I want to clarify. The study site is the hospital where the study is taking place, where the patients are going to participate in the study. So it could be they're going to be multiple study sites, multiple epileptologists or hospitals are signing up to be a part of the study, then patients are going to those sites. But the epileptologists are communicating with whoever it is that you're speaking about

now that is actually running the larger study and collecting all of that data.

Dr. Kelly Knupp: 08:03 Yep, exactly. There's also a medical monitor. So we have the study monitor who comes on a regular basis and is the person you would contact on a day-to-day basis about the study, if you have any questions. But if there's a question about a medical decision that needs to be made, then there's a medical monitor, who's almost always a physician, who will help guide the site investigator with any medical decisions that need to be made. So maybe there's a side effect that you're trying to figure out whether it's related to the medication, or maybe somebody is sick and you need to think about doing something different with the study medication, that would be the medical monitor that you would talk to. And that really creates a lot of safety and consistency across the site so there's somebody helping and supervising with all of those decisions so that each individual site doesn't have to make decisions on their own and make different decisions.

Brandon: 08:57 Hi, this is Brandon from Cure Epilepsy. An estimated 3.4 million Americans and 65 million people worldwide currently live with epilepsy. For more than 20 years, Cure Epilepsy has funded cutting edge, patient-focused research. Learn what you can do to support epilepsy research by going to cureepilepsy.org. Now back to Seizing Life.

Kelly Cervantes: 09:20 So sort of diving now into the clinical trial phases, which I don't think most people, I certainly don't understand what these phases mean exactly. I was shocked to learn in preparing for this episode that there's actually sometimes a phase zero.

Dr. Kelly Knupp: 09:39 So phase zero. So in general, people will think about this as four phases. In some studies, some of those phases may be combined because there may not be enough of the study population or we're moving more quickly, such as the vaccine trials, and so we may combine some of these phases. But in general, we go from phase zero to phase four. So phase zero is usually the first time that the drug is used in a person. So up until that point the drugs are studied in labs, chemists look at them and biologists look at them and try to figure out in different models of the disease how the drug might work and whether it might have some benefit. And once they've collected enough information suggesting that it may be helpful in a particular disease population in people, they go to the FDA and get an IND to really start looking at this in people.

Dr. Kelly Knupp:	10:35	And so these first trials, the phase zero trials, usually only have a handful of healthy volunteers that participate. By a handful, I mean 5 to 10. And they take the study drug, they know that they're getting study drug. And then their studied to see how this works. Does it change anything in their blood? Does it change anything in their urine? Does it make them feel funny? Does their hair fallout? Is their heart okay? Does it make them too sleepy? All of these kinds of things. So it's usually the first time that we get a sense of, how does a human liver break down this medication? How does a human kidney break down this medication? What does your body do with this? So it's kind of a risky thing for them, these healthy volunteers-
Kelly Cervantes:	11:22	Thank goodness for those brave people out there.
Dr. Kelly Knupp:	11:24	Yes. And they're usually compensated for the risk that they're taking, but it's still a risk because it's an unknown entity at that point.
Kelly Cervantes:	11:33	So we have discussed those phase zero. We've gone through the IND FDA approval to start phase one trials. So what happens in a phase one? What are the goals? How many people are participating now?
Dr. Kelly Knupp:	11:50	Yeah. So phase one just has a few more people, so usually it's 10 to 20 people. And the goal of phase one is to figure out what would be the best dose for the medication. So again, this is almost always healthy volunteers, although sometimes if it's a rare disease, it may be people with the disease who are studied. And basically they start increasing the dose of the medication to see what kind of side effects do you have with a bigger dose? And so, the main goal is to figure out what is a safe dose of the medication and what's a tolerable dose of the medication?
Kelly Cervantes:	12:22	All right. So now we get to phase two. Same thing, concerns, goals, how many people?
Dr. Kelly Knupp:	12:28	Yeah. So this is, again, a few more people. So usually around 30 or 40 people in a phase two trial. And this is to really figure out, in the disease population, is the study doing what we think it's supposed to do? So this is where we start to look still at safety to make sure that we think it's a safe drug, but if this is supposed to treat seizures, does it actually make somebody's seizures go away? So this is where we start to look at how well is this working to do what we want it to do?

Kelly Cervantes: 12:57 Is it the same people who are participating in the phase two trial that were participating in the phase one, or is it an entirely new group of people?

Dr. Kelly Knupp: 13:03 Yeah, it's usually the disease population, whereas in phase zero and phase one it's usually a healthy population. So oftentimes it is not the same population that was in the first two studies, because these are people who have the disease that we're concerned about. I will say there are some caveats to that these days that are important for the epilepsy population to be aware of. So, in some of our very rare diseases, particularly genetic diseases, because there are so few people in who have that disease, we want to make sure that we study everything from the very beginning in that patient population.

Dr. Kelly Knupp: 13:40 And the FDA has really encouraged companies to think about using the disease population from the very beginning. So for some rare diseases, those phase zero and phase one studies, first of all, may be combined into two, so they may be doing both things at the same time, and may be performed in the study population. And we are starting to see that particularly in some of our pediatric epilepsies that are pretty rare and have a genetic underpinnings to it, from the very beginning the disease population is being included in the trials. So I think we will start to see some shift in that.

Kelly Cervantes: 14:18 Okay. Interesting. So what is different about a phase three than a phase two?

Dr. Kelly Knupp: 14:24 Yeah. So a phase three, the main goal is to figure out in a bigger population, does this study drug do what we think it does? And so this is where we really want to figure out, is this doing what we want it to do? Many times up until the phase three trial we are not blinded, so everybody knows they're getting study drugs. So in phase zero and phase one, all of those participants know that they're getting study drug. In phase two, most often we know that you're getting study drug and we're just watching to see, how does this work in our specific population we want to study?

Dr. Kelly Knupp: 15:01 But phase three is when we really start to see randomization into two or three groups, where we start having a placebo arm so that we have that control group that we can compare to, so that we can say, half of these people got treated with the study drug and their seizures did much better than the people who were in the control group who had no change on their seizures. Because epilepsy in particular fluctuates over time, and so particularly if you're looking at a short period of time, perhaps

over a 12 week period, 12 to 20 weeks is pretty standard for most of our clinical trials for epilepsy drugs. And even in somebody who hasn't made a medication change, they may just happen to hit on a good time period where their seizures got better for 12 weeks. And so that's our way of trying to control for that.

Kelly Cervantes: 15:52 Okay. So I also know there's all of these acronyms that are thrown into this mix. NDA and also a PDUFA. What do these mean?

Dr. Kelly Knupp: 16:05 Yeah. So an NDA is a New Drug Application. So once you've gone through the phase zero to phase three trials, then you can submit an NDA, a New Drug Application, to the FDA to seek approval. And so that is the goal that everybody's been working towards, and the companies going through this whole process are usually infrequent discussion with the FDA to make sure that they have everything in that package that they want. That package, it's a pretty large amount of data. And with our vaccine trials right now, this is what the FDA is going through. So basically the company will put together all of the data that they've collected, both before humans and after human use. What did those safety trials look like? What do those efficacy trials look like? They actually will submit all of that efficacy trial data to the FDA so that the FDA can go through and review it and make sure that it makes sense, that somebody hasn't fudged the numbers somewhere, are they getting the same numbers that the company said that they had?

Dr. Kelly Knupp: 17:10 And so that is basically handing them a package of all of the information of what's known about that drug so the FDA can make a good choice about whether to approve it or not. So the PDUFA. PDUFA stands for the Prescription Drug User Fee Act. And one of the main components of that is it gives a timeline to the FDA to review the package that's been submitted. So prior to that time, the FDA could take as much time as it wanted, and so it could be a lengthy time from the time that the NDA was submitted until they actually had a response back. So this sets a timeline for the FDA, that in most cases they have to respond within 10 months. So there's a very clear timeline based on that submission date of when a response has to happen from the FDA.

Kelly Cervantes: 17:59 So if the drug is approved, how long does it take from, okay, we have FDA approval and now the drug is on the shelves at the pharmacy?

Dr. Kelly Knupp:	18:11	Yeah. So for most often it only takes a couple of months, if even that. So the company knows that when they're PDUFA date is going to happen, so they know when they expect to have approval. They've often heard from the FDA intermittently throughout that process, whether the FDA has needed new information. But there's been some conversation there. And so they often are poised to get the drug out pretty quickly. But the gap that really happens for patients is for those patients who participated in the study, and then the studies have to be complete, the data analyzed, everything prepared for the FDA, submitted to the FDA, then reviewed by the FDA over a 6 to 10 month period. So that's a pretty long gap from study participation until the medication is approved and available on the shelf. And so most companies have either what they call an open label extension or an expanded access protocol that allows patients to continue to receive the study drug during that time.
Dr. Kelly Knupp:	19:15	So usually the first thing that is done is called the open label extension, which is just the extension of the trial, but it's open label so everybody knows they're getting study drug. And then the company can use that time period to continue to look at dose-finding, what was the dose that works best for the patients? Safety during that time period. And then when the trials are completed and they're working on all of this data that they need to put together for the FDA, particularly if the drug has looked very promising, they will get permission from the FDA to do an expanded access protocol. And so basically this is kind of what most people would consider a compassionate use. This is basically saying, we've recognized that this drug seems to have benefit. It's not yet FDA approved, but we want to make sure people have access in the interim.
Kelly Cervantes:	20:02	Now, you mentioned phase four earlier on. Is that what phase four is, or is phase four something entirely different?
Dr. Kelly Knupp:	20:09	Yeah. Phase four is different, and particularly in the pediatric populations, we don't necessarily see phase four a lot. But in the general population, phase four is once a drug is on the market, you want to continue to study it to look for long-term side effects. So we talked about phase three trials may last 12 to 20 weeks, but what happens if you've been on the drug for four years? And so that's the purpose of the phase four trials is to look at large populations and to look more at long-term safety and efficacy of the drug.
Kelly Cervantes:	20:45	And then, for rare diseases, where do they fall in?

Dr. Kelly Knupp: 20:49 As we look at the numbers from the vaccines that have been studied, it has been literally thousands and thousands of people, tens of thousands of people that have been studied. But if you have a rare disease where there are only 500 people in the country who have that disease, you're never going to be able to reach those numbers. And so having orphan drug status means that fewer people need to be studied, so it identifies that your target disease population is so small that you can't study thousands and thousands of people because that patient population just doesn't exist.

Kelly Cervantes: 21:20 What if there is a drug that is out there that it does work, but only for 10 or 20% of the people who are studied? In a disease population like epilepsy, I can certainly guarantee you that there are 10 to 20% of those people who would desperately want to try and get their hands on that drug. Is there a risk that even if it works for some that it could still get pushed through, or how does the FDA make those decisions?

Dr. Kelly Knupp: 21:47 This is a really good question, and it really comes down to how the study is designed to begin with. In general, what the FDA likes to see is two studies that have met their primary endpoint. And so this really goes back to the very beginning in setting up that study, that it's really important to identify a reasonable study end point that you think the drug can meet. So we wouldn't want to say that the goal of this drug is for seizure freedom in 50% of people. Of course, we would love to see seizure freedom in 50% of people. That's a really high bar to reach. And so, in most of our epilepsy drug studies are set up to demonstrate improvement compared to the control population, and usually it's a percentage of improvement. So with perhaps a 30% reduction in seizures compared to the control population.

Dr. Kelly Knupp: 22:42 And so it's really important as they're initially designing the study to have a study end point that seems reasonable and acceptable to the patient population. The more defined the patient population is, the more you know what to expect as an outcome. But there are a number of children who don't fit into those buckets and boxes, and that is a challenge for pediatric epilepsy. In addition, a number of our studies are studied in adults and not so much in children, although that has been changing recently, which we're very thankful for. So a number of medications come on the market for adults, and it's only after they're on the market that the company goes back and starts doing pediatric studies.

Kelly Cervantes: 23:23 I understand the logic behind that. You want to make sure that it's safe and adults before trying it on children. However, there

		are some epilepsies that are strictly pediatric, infantile spasms among them. So what is being done? Is there anything being done to try and get these drugs to our pediatric epilepsy patients faster or at the same time as the adults are getting them?
Dr. Kelly Knupp:	23:49	Yeah. Well, I think they're kind of two things, and they're probably somewhat related in the grand scheme of things. But there was another regulatory thing that was put in place called PREA, which basically says if a medication is coming on board, that it needs to be studied in the pediatric population. And so as an application is going into the FDA, if the disease exists in children, the FDA and the company need to work together to come up with a plan to study it in pediatrics. Now they can get a waiver, but those waivers are pretty hard to get from the FDA. So that's sort of the stick, is that they're required to do it.
Dr. Kelly Knupp:	24:35	The carrot is that if they're able to generate a study that gives them a pediatric indication, they get an extra six months on that exclusivity, which doesn't sound like much, but the adult population is far larger than the pediatric population, so it really is a financial incentive to that company to even get that extra six months exclusivity on their medication. So I think those two things are very helpful in studying the pediatric population. Parents are also banding together in lobbying for this, and so this really is pushing companies and researchers to find drugs that will help our pediatric populations.
Kelly Cervantes:	25:16	Well, I have to say, I'm very encouraged that there is recognition about these patient populations. And I also appreciate you giving a little bit of credit to the parents, because 500 patients may not be a lot, but when you have 500 patients lobbying and raising money for research, that can actually go a long way. And so I do really believe that the patient populations have so much more power here than I think that they realize.
Dr. Kelly Knupp:	25:46	Absolutely.
Kelly Cervantes:	25:48	It's almost overwhelming to hear about all of the steps. But I do think it contextualizes and helps, I hope helps our patient population understand what it actually takes. I mean, we're just talking 10 or 12 years right now in this clinical phase trial. That doesn't even include the time that was spent on basic and preclinical research that it took to get to the point of now having these phase trials.

Dr. Kelly Knupp:	26:18	Yeah. It's important for people to understand how research works and why it's important. And particularly in our epilepsy community, it's really scary to sign up for a research protocol, because you don't know what you're going to get, and you don't know what to expect and nobody can tell you whether it's going to work. But we can't do it without patients. And I think compared to some other disease populations, we're a little bit behind. Whenever somebody has a diagnosis of cancer, everybody thinks right away of what research is out there and how can I participate in a research protocol? And that's not necessarily the first question that people think about when they get a diagnosis of epilepsy, and we need to be thinking about that. Now I have this diagnosis, what research is out there so that I can have access to the best therapies that are out there, and so that in the future we'll continue to have great therapies to treat this?
Kelly Cervantes:	27:11	That is an excellent, excellent point. We have to be in this together, patient community and our scientist friends. It takes a village. It takes us all. Dr. Knupp, thank you so, so much for chatting with us today, for sharing this incredibly valuable information. I really think it will help so many people understand what this process looks like. So thank you so much and for your dedication to our community.
Dr. Kelly Knupp:	27:40	Oh, you're welcome. Thank you for doing this. I think this is so important for everybody to understand.
Kelly Cervantes:	27:48	Thank you, Dr. Knupp, for helping us to better understand the drug development process and for all you do for the epilepsy community. Despite the emergence of new epilepsy drugs, one third of epilepsy patients do not respond to traditional treatments and therapies. Those patients continue to experience uncontrolled seizures, and they continue to hope for a new drug or therapy that will bring them seizure relief. Cure Epilepsy is committed to supporting research that will lead us to those new drugs and therapies. For more than 20 years, Cure Epilepsy has been dedicated to funding patient-focused research, raising over $70 million to sponsor more than 240 grants in 15 countries. To help us continue this work, please visit cureepilepsy.org/donate. Your support and generosity are greatly appreciated. Thank you.
Brandon:	28:47	The opinions expressed in this podcast do not necessarily reflect the views of Cure. The information contained here is provided for general information only and does not offer medical advice or recommendations. Individuals should not rely on this information as a substitute for consultations with qualified

healthcare professionals who are familiar with individual medical conditions and needs. Cure strongly recommends that care and treatment decisions related to epilepsy and any other medical condition be made in consultation with a patient's physician or other qualified healthcare professionals who are familiar with the individual's specific health situation.