Episode 251: Migraine Clinical Trials

Lindsay Weitzel, PhD:
Hello, everyone, and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel. I have a history of chronic and daily migraine that began at the age of four. We have a special episode today, and I have the honor of speaking to two guests.

Our topic today is migraine clinical trials. Why are they important, what are the benefits, what are the risks. We're going to address all the myths and all the facts about migraine clinical trials today. We are here with Dr. Tim Smith, who is a regular on head bias due to his extensive experience in migraine clinical trials as the CEO of StudyMetrix Research in Missouri. Dr. Smith is also a board member of the National Headache Foundation. Hi, Dr. Smith, thank you for being here.

Tim Smith, MD:
Thanks for having me again, Lindsay. Good to see you.

Lindsay Weitzel, PhD:
We also have Tierra Lillard. Tierra is here to give us the patient perspective of being involved in migraine clinical trials as she has been in more than one clinical trial. So, thank you for being here Tierra. Hi, how are you?

Tierra Lillard:
Thank you. I'm excited. I'm super excited to tell my side of the story.

Lindsay Weitzel, PhD:
Well, thank you for being here. We are excited to have you. Let's go ahead and start with Dr. Smith. Dr. Smith, can you tell us some background on why migraine clinical trials are so important? Can you just speak to that for a second?

Tim Smith, MD:
Sure. Well, in a nutshell, if we didn't have migraine clinical trials, we wouldn't have any migraine medications. And I've been doing this long enough to be able to say that when I started doing migraine treatment and migraine care, there weren't any good, approved medications for migraine management. We had opioids and ergots and that was about it. And if they made you sick or they didn't work or caused side effects, it was just part of the landscape and that's what we had. I got

started doing clinical trials in the 90s when the triptans were being developed. And so, we've gone triptans, lots of preventive care, CGRP blockers. And so, we have an array of treatments now, and it's all because we have had these high-quality clinical trials that have shown results. And we've had good people like Tierra and others that have volunteered their time and helped us gather data about the effectiveness to help the FDA get these drugs approved. And it's all about the clinical trial process. It has to be done right, and it has to be very stringently conducted, and all the documentation has to be perfect. And the FDA scrutinizes these data books very carefully. And I think when we have an approved medication, we can rest assured that these trials have demonstrated what they intended to demonstrate and that we can be confident in the effects that the drugs have and the safety that we have in using them.

Lindsay Weitzel, PhD:
I can speak to that a little bit, because I was 17 years old when the first triptan was released. And I remember that because I had had migraine constantly since the age of four, and they kept telling me I had sinus headaches until they gave me my first triptan and said, oh, maybe it's migraine. So, this is all thanks to clinical trials. Let's move on with how important this is and learn about it. So, Tierra, what has been your motivation for getting involved in migraine clinical trials?

Tierra Lillard:
My biggest motivation is really spreading the word and getting it out there to the community, out there to my family members, because they to suffer from migraines. And I also have been suffering from migraine since I was four years old. And they said it was sinus issues, and I didn't believe them because I still suffer from migraines and they can be very debilitating. They can take me out days at a time and then disrupt my normal like day-to-day things that I want to do. So, my biggest like motivation is really just spreading the word and getting people involved. And they're kind of nervous when it comes to trials. They're like, I don't want to be a guinea pig. I don't want anybody like sticking me with anything. And I'm like, you guys, it's not that. It's not that. It's actually really amazing. So that's my biggest motivation is really just spreading the word and trying to help as many people as I can, because nobody likes migraines. Nobody. And I'm really just, like I said, trying to spread that word around.

Lindsay Weitzel, PhD:
Dr. Smith, there are technically four phases of clinical trials. Can you please summarize for us which phases are most important to someone who might want to participate in a clinical trial?

Tim Smith, MD:
Sure thing. The four phases are the human studies. And obviously there's a lot of work that goes on even before that, computer modeling and test tube studies and animal studies and eventually get to human studies. And the first ones are the phase 1s are the first in human studies, and they usually will involve a small number of people. And they are usually done in a phase 1 center where the patients will actually spend the night, or may spend several nights, and have drug administered. And they do a lot of testing, draw their blood every hour or 2 or 3, something like that, all night long, doing the characterization of how the drug is handled in the body.

And then once the phase 1s are done, then you go into phase 2s. They are a little bigger, usually about somewhere 100 to 200 patients in those studies, and they're usually done just on an ambulatory basis. So, people come into a clinic like you're going to your doctor's office. This is what we do here, phase 2s and 3s. And that's what Tierra has participated in here with us. And the phase 2s are more for dose ranging, finding what the best dose to be given, and what were the best patients to treat and how often should the drug be given. All those kinds of basic questions get answered in the in the phase 2. And they look for the trend of the improvement and safety.

And then when that's done and they've got enough to go on to feel very confident about moving forward, then they do the phase 3 studies which are large studies and acute migraine studies. For example, there might be 2000, 3000 patients in those studies and they're gathering really large amounts of data. And these are the ones that are used to submit to the FDA for registration for getting it approved. And then phase 4 is our post-market studies, so after the drug is on the market. They can do additional studies to answer additional questions about the medication, about taking additional doses, or using it in different situations and to gather more information to help patients learn how to use the products better.

But that whole process of starting from patent and computer studies all the way through the animal studies, all the way through the human studies, that process takes about ten years. And the last date I saw suggested it takes it's over one billion dollars, billion and a half maybe to get a drug from its inception to the pharmacy shelves, so it's quite a process. It's very extensive and expensive to do. And it's why medicines are more expensive, especially when they first come out on the market, because that process takes so long and is so involved.

Lindsay Weitzel, PhD:
Let's go ahead and let's get another perspective, patient perspective on this. So, Tierra, what reservations did you have about joining a migraine clinical trial?

Tierra Lillard:
I think the same ones that everyone else has like am I a guinea pig, are you going to stick me with 50 million needles. I was terrified. When I knew someone years ago that would do like migraine studies and she was like, Tierra, you should try it, and I was like, no, this is too risky. And I was like, I'm not a guinea pig, nobody's going to stick me with a needle. And it was nothing like that. It was just me being terrified of needles and just scared of the kind of medicine I could get. I was like, what if I get medicine and then, I don't know, I start acting nuts or something like that.

And I just thought of every worst thing, like combination that could happen to me. And when I actually went and I met Dr. Smith and I was like, oh, this is good. He's really nice. He's not mean and he's not scary. He doesn't walk around with like on the movies, like with the gas mask. And I was just thinking about all the craziest things that could happen, but it was nothing like that. So, I think everybody else is just really nervous when it comes to studies because they are like, oh, what kind of medicine could I get? What if something happens? I'm like terrified of needles. And I thought about all of those things and it's nothing like that.

Lindsay Weitzel, PhD:
Why don't we speak to that right now then. Dr Smith, are clinical trials usually safe? I feel that one of the concerns, as Tierra said, is that people might feel they could be dangerous.

Tim Smith, MD:
Well, and they are considered experimental or investigational until they get on the market. But especially for ambulatory trials, phase 2 and phase 3 studies, by the time they get to a clinic like mine, we already have the medications pretty well characterized. And we know a lot about the safety profile and the way the drugs work and what to expect. So usually, serious adverse events are quite rare with especially in the last 10, 15 years. And I think the other thing I'll say about that is that the way companies discover and develop medicines is much more refined now. They can do computerized modeling and test tube studies and animal studies, and with a high degree of predictability know a lot about these medicines and what to expect when the patients take them. And it's exceedingly rare for us to have a medication that causes enough problems that people have to stop, or that we have to stop the clinical trial. It can happen, but we monitor the patients very carefully, and we follow things like their liver tests and the kidney tests. And we do lots of questionnaires and examinations and try to ensure a high degree of safety for the patients that are participating because they're our priority.

I always tell patients and anybody that cares to listen, we have a lot of responsibilities as researchers. We have to be very exact with our data gathering. We have to be impeccable with our documentation. And we have lots of responsibilities to the FDA, to the sponsor companies, to the ethics review committees that we report to. Which they're in place by the way, to assure that no clinical protocol is asking someone to do something unethically or dangerous or that we're not informing patients of everything they need to know about that. So, there's lots of safeguards in that. But I always tell our people that participate is our number one priority as the patient. We have a lot of responsibilities to the grant makers or to the sponsors and to the FDA. And we try to do a solid job on that, but our number one priority is the patient. We have to make sure we're providing the best supervision and care that we can, and we take that seriously. I mean, very, very seriously. Patients are giving us their time and effort, and they're doing a great service for a lot of people, as it turns out. And we want to honor and respect that and make sure they know they're appreciated.

Lindsay Weitzel, PhD:
Something came up when you were talking there that occurred to me that I should ask. Do subjects, once they've enrolled, do they have the choice to leave a clinical trial?

Tim Smith, MD:
Yes. The patient, the ultimate decision making is theirs. They can. We can't ask them to do something, even if they sign a consent form, that doesn't obligate them to do anything. They don't relinquish any of their rights that they're entitled to. And if they decide they don't want to do the study anymore for any reason, it doesn't have to be side effects or whatever. For any reason, if they just change their mind, they can withdraw consent and leave a study. Obviously, we get the best data from patients who complete the study and we don't want to lose them, but ultimately, it's their choice. And my only goal is I want to make sure that they are making an informed choice on that, that they understand what all the possibilities are.

Lindsay Weitzel, PhD:
There is another fear I wanted to ask Tierra about. This one. Tierra, you were in sounds like multiple clinical trials, but did you have to stop your medications or drastically alter your treatment plan in order to take part in these clinical trials?

Tierra Lillard:
Did I have to stop my medication. I think for a few of them, I don't know. I have to think back because I know Tylenol was just my backup medication, right? I don't have any medications that I take on a daily basis, no allergy meds, birth control or anything like that. So mainly it was just Tylenol that I would have as a backup. And I think the majority of the studies said that I could keep the Tylenol as a backup. But the study drug was like first and foremost, that's in the front. But my Tylenol is like a backup drug, just in case.

Lindsay Weitzel, PhD:
I will reword it. Dr. Smith, let me reword it so that they have the whole question. Dr. Smith, do patients often have to stop taking their medications or alter their treatment plans in order to take part in a clinical trial?

Tim Smith, MD:
Well, sometimes we do ask patients to change therapies. For example, if someone takes sumatriptan regularly for their migraine attacks, in some trials, we may ask them to forego using that, use the prescribed study drug. And then what we usually do on acute trials is we ask them not to take any additional doses of anything else for at least two hours. Now, if a patient is just suffering and has to break that protocol there, obviously they need to take care of themselves. But the two-hour time frame is the most important for acute studies. And we ask the patient to take a dose of medication and not take anything else for those two hours.

So sometimes we do ask them to refrain from their usual approaches so we can, and it's obviously that we just have to make sure we remove other variables. If patients take other medicines while they're taking the study drug, and it works, we don't know if it's because the other drug worked or the combination worked, or if the study medicine worked the best. And in preventive studies, we usually will ask patients not to start anything new for prevention. And prevention studies go on sometimes 3 or 6 months or sometimes even a year. And we have patients collect diary data from their daily headache patterns and look for changes on that. And we don't want them starting some other new medication along. We just want to see what the effects of just the investigational drug.

Lindsay Weitzel, PhD:
When you say no new medication, if they were previously taking a preventive, do they usually have to stop or do you usually only enroll people that weren't taking one?

Tim Smith, MD:
It depends on the protocol. Some protocols will allow you to have one stable medicine that you're on. If you still have, say if someone's taking Topamax maybe for migraine prevention, and they've been stable on it for 2 or 3 years, they still have 5,6,7,8 migraine attacks per month, most protocols will allow that patient to stay on that drug and then add a new medicine to that. But some, especially earlier phase studies, they want to see just the effect of just the medication itself. And so, we find people who are not on preventives to start those trials. Or if they are on preventives, we really don't ask people to go off of a prevention drug to participate in the study. We could, but they would have to go off before they came in and screened for the study. And we really don't do that.

Lindsay Weitzel, PhD:
The next question that I have that I think is sort of a fear some people might have is, do all clinical trials have a placebo group? Can you talk about the placebo group and maybe address some fears that some people have coming in about the placebo group?

Tim Smith, MD:
And yes, we do have placebo in many studies. Not all studies have placebo, and it's usually assigned randomly and in a blinded fashion. So, when Tierra participated in a study, we did all the qualifying testing to make sure she was healthy, and we had good baseline data about her migraine attacks. And then the computer flipped a coin basically and assigned some study drug to her. And it's assigned in a number. We have the study medicine we keep in a drug locker. It's locked and temperature controlled and everything. And so, the medication gets assigned randomly and then is dispensed. And usually, it's, for an acute study, if someone takes a placebo and then we ask them to wait two hours before they can take a real medicine, depending on the severity of the migraine that could be asking people to make some sacrifices.

But we just tell people, you got to do what you got to do, but if you can get us those two hours, that'll help us get the primary endpoint. And if we don't get the primary endpoint, then that that may not be as successful treatment as per the trial is concerned. But we don't want to put patients in harm's way in that way. So yeah, there's placebo. I wish I never had to give a placebo to anybody, but it's necessary for the science, and the FDA can't make any conclusions about a medicine if they don't have that placebo comparison arm in the trials. So, it's regrettable when people have to do it maybe, but it's important to the science.

Lindsay Weitzel, PhD:
Tierra, can you tell us what the best and most difficult parts of being in a clinical trial were for you?

Tierra Lillard:
So the best part, I'm not going to sugarcoat it at all. I did like being paid. I think everybody thinks about that, like thinks about the money part. I did like being paid. And then the best part as well, another good thing, was just like the staff and Dr. Smith. Everyone was so warm and welcoming, and I was just like so nervous, each and every time. It didn't matter how many times I've done a study, I was still nervous. And they were always kind each and every time. And then the worst part really is just if they have to do like a blood draw or anything like that. I don't like needles and I'm such a big baby. And

that's really the only thing I can think about that's rough as far, or there's another one. If I have to fast and then I'm coming in later on in the day and I haven't eaten anything, and I'm just like sitting there just thinking about everything I could eat. It's usually just like the needles and fasting. That's it. And then the best parts are just the money and then the staff that I'm working with. Because everybody was, like I said, they were just so warm and welcoming. And then I'm going to add a bonus one in there, another one. I really did like helping. I really did like helping with the studies and just having all of that data and things like that. And I think that's another plus, is just helping.

Lindsay Weitzel, PhD:
Well, I'm glad to hear that it was rewarding. I don't think you're supposed to like needles and fasting. I think it would be weird if you did. Dr. Smith, I feel also that there is a myth out there that only the sickest or most severe patients are supposed to volunteer for clinical trials. Is that true?

Tim Smith, MD:
No. It's not true, just people with what we sometimes call garden variety migraine. They don't necessarily have to have an unmet need. But if they have the disorder we're looking to study, that's the important piece. So, somebody can have 3 or 4 migraine attacks per month. And if they've got a good dose of medicine that takes care of them and they're functioning within an hour, they don't really have a huge unmet need. But they can still participate in the study. They don't have to be disabled by the disorder.

And I was pleased when Tierra was talking about helping and trying to do something good, that's the other really great thing that a lot of patients really just, and I can't emphasize it enough, studies show that something like 3 to 5% of Americans indicate a willingness to participate in a trial, and that is not very much. And we need people to volunteer, participate in studies. If we didn't have people doing study treatments, we wouldn't have any medications at all. So, for everybody out there that's listening, if you're taking a medicine for anything, somebody, somewhere had to do what Tierra has done several times with us and be willing to come in and try these test medicines out and help us get data so that thousands of people can benefit from it.

So, it's very necessary. And I hope people can, if they're afraid or have some fears about it, they can follow Tierra's advice and understand that we're not going to strap you to a machine and come in in hazmat uniforms and torture you for hours on end. It's nothing like that. So, people do well with this and sometimes they get really good care. They learn something about how the drugs work and how migraine works. We try to provide a lot of education around that too. So, I hope there's other upside benefit that patients can get from things like that.

Lindsay Weitzel, PhD:
This is so true. We do need people and it can be rewarding as Tierra said. Do we need people without migraine to volunteer for these studies too, such as a control group or anything like that?

Tim Smith, MD:
Sometimes. Yeah, we do have some studies that may have like a non-migraine control group. The phase 1 studies especially will sometimes recruit patients who do not have migraine because they're not

really trying to treat a disorder or treat an attack or anything in those phases. They're just trying to, in fact, what they need is healthy humans, so healthy kidneys, healthy liver. It's usually younger, healthier people that do those studies. And they sometimes do need healthy, we call them healthy humans, but migraine people can be healthy too. They just don't have migraine attacks, but they can sometimes participate.

Lindsay Weitzel, PhD:
Tierra, would you recommend people become a subject in a migraine clinical trial? Is this an experience you would do again?

Tierra Lillard:
Yes actually. Like I said before, everyone was just so nice and warm and welcoming. And that's why I come back. At this point, it's not even me coming back for the money or anything like that. The first time, I think when I first did the trials, I might have been in school, still in school and things like that, and I had a friend tell me about it. And I was like, well, I guess I could. And now I feel like I've evolved. I'm not younger anymore and I'm not even looking for the money aspect of it. I just, like I said before, I really want to help, and I want to get that data to help as much as I can. So, it's super rewarding and it's different now.

And now that I think about it, I'm like, it's different. I don't look at it like that. When they call me and they're like, Tierra, are you interested, and we'll read over everything. And I'm like, you know what? I think this one will be good. I think I'm interested, you know what I mean? So, it's not even about the pay like it was before. Like that was one of like the benefits because, like I said, I was looking at it because I was a student and things like that. But now that I've evolved and progressed, it's more so I do want to help in any way that I can. And especially, Dr. Smith, like when you call and you're like Tierra can you help me? Yes. I'm onboard.

Lindsay Weitzel, PhD:
Well, that's great to hear that it's so rewarding and that you would recommend it. Dr Smith, can you talk to the listeners about where they can learn more about where there might be clinical trials that they can participate in their area?

Tim Smith, MD:
Well, there are probably lots of places you can look at. I think sometimes we have study listings on the National Headache Foundation website. We used to have a link to the big government clearinghouse thing is something called clinicaltrials.gov. And that's the URL, the web address. And you can go on there and type in a few search terms, type in migraine studies and it'll show you, sometimes there might be a hundred different studies. And if you go on each one, it's got the title of the study, and you can look and see. You can open it up and you can peruse and see where the different investigative sites are. We've had people find us that way looking for a trial and found it on clinicaltrials.gov, scrolled down, and look, there's a St. Louis site. And they'll call and set up an appointment. So that's probably the single best place to find that.

But you can also go to different pharma sponsor's websites. They have their pipeline on there and what phase their studies are in. And then just google search in your communities to look for clinical trials. And each clinical trial site has a website of its own. We're required to do that. And it's sort of that grant makers and sponsor companies and patients can have ready access to learn who we are and what we do. And we have descriptors on our website about what it means to be in a study and what the steps are involved, what you can expect when you come in to do a study visit with us. And so, I would just recommend people kind of pay attention to those things. And whatever your community is, there are clinical trial centers. They have them and essentially every, certainly every metropolitan service area, probably several of them actually, where you can go. So clinicaltrials.gov, sponsor's web pages, the various pharmaceutical companies, and then the local clinical trial websites.

Lindsay Weitzel, PhD:
And if you want to go to the National Headache Foundation website to get there, it's headaches.org And you can go to "Navigating Care". And that is another way to get there and to see where some of the trials are. And also, depending on where you live and where you're getting your care, you might be able to ask your doctor because they may be involved, or some of the centers they work at could be involved in some clinical trials. Is there anything else you guys would like to add before we go today?

Tierra Lillard:
I was thinking about something. I know some people what would deter them away from doing the studies as well would be, I know some people feel like they don't qualify, right. I've gotten that from other people before. They would tell me, Tierra, I don't think I would qualify. I feel like I've had X, Y and Z or my weight or something like that. I say, you just don't know until you try. So, you really just have to give them a call and then you'll talk with them over those certain situations. But I really think that keeps them away. They really don't think they would qualify. And I really kind of like pushed that just to call and get the information, see what you need. See if you're having any issues, you can talk to them about that. But I've gotten so many people that would tell me I wouldn't qualify. I don't think I want to waste my time.

Lindsay Weitzel, PhD:
So true. Thank you for that. And anything else from you, Dr. Smith?

Tim Smith, MD:
I guess just reiterate the necessity of good clinical trial data so that we can get more access to better care for many people. I mean, we have so many new developments over the last 30 years, but there's still a pretty significant unmet need, as we all know. And we would love to be able to avail patients of more treatments. And I guess I would just finish by saying our volunteers, I was on a local TV program a couple of years ago and I basically said our volunteers, they are our medical heroes. They give us part of their time, and just the little time they spend with us, the data that we gather is so, so important. And we just have such a debt of gratitude to them and just appreciate people like Tierra so much. And then I guess the last thing is, our logo for StudyMetrix Research where I work, one of our slogans or catch phrases is that we're "improving lives. maybe yours." So, the hope is that people by participating will get improvement. But then also I think the bigger patient population, just to make treatments available, that's the total goal.

Lindsay Weitzel, PhD:
Thank you so much to both of you for being here to record this important episode. And thank you to everyone for listening. Please join us for our next episode of HeadWise. Bye bye.

Resources:

Headache and Migraine Clinical Trials
https://headaches.org/resources/headache-and-migraine-clinical-trials

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