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If you're new to NETWise, we strongly recommend you go back and listen to the series from the beginning, starting with episode 1. It will give you a solid grounding in the basics of neuroendocrine tumors and how they're treated. You can find the whole series at NETRF.org/podcast and wherever you get your podcasts.

Welcome to NET Wise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. My name is Laran Hyder, from the Neuroendocrine Tumor Research Foundation.

In today's episode, we're going to talk about a subject that many patients have important questions about - clinical trials. What are they? Could they be an effective part of my treatment? And how do I find them and apply?

To put it simply, clinical trials are a crucial part of cancer research. They are the way that scientists determine if a new idea for treatment is actually safe to give to patients and effective at fighting their disease.

Here are doctors Mark Lewis of Intermountain Health Care in Salt Lake City and Satya Das of Vanderbilt University Medical Center,

followed by Josh Mailman, a NET patient and Patient Advocate who serves on the NETRF Board of Directors:

> ***Lewis:*** *"So, literally the only way we get better in oncology, other than by sheer blind luck, is by doing purposeful research."*
>
> ***Das:*** *"So, clinical trials are critical because they're the way we move the needle forward in the field. You know, when we have something promising, a therapy that appears to be showing a signal, a clinical trial and ultimately a randomized clinical trial, is truly the only way to know whether a therapy stacks up against a prior treatment standard and if it really is an improvement."*
>
> ***Mailman:*** *"The whole reason to have clinical trials is to really answer an important question of- 'Do these work in the real world? Is this something that is going to be beneficial to the patient community?' Before that, we're just guessing. And even if you think it works for some people, you're not really controlling for all the variables that are there. And that's why we really need clinical trials and why it's important for patients."*

And so, we hope that more NET patients will at least be open to the idea of joining a clinical trial, and work with their doctors to look for trials that might be a valuable part of their treatment.

Here's Dr. Pam Kunz, head of the program for gastrointestinal tumors at Smilow Cancer Hospital and Yale Cancer Center, followed by Dr. Nitya Raj of Memorial Sloane Kettering Cancer Center in New York City:

> ***Kunz:*** *"Clinical trials are not just for patients without other options. There might be trials that are actually appropriate for patients who've had resected disease or for patients earlier in the disease course."*
>
> ***Raj:*** *"I would argue that clinical trials should be considered throughout an individual's treatment course. A new treatment could be more effective than available, standard options for the cancer, and a clinical trial can offer the opportunity to help others and advance knowledge and the future of cancer care. It should be an ongoing discussion with your oncologist, and I think in particular it's very valuable to discuss clinical trials with your treatment team when you're at a decision point. So, when there's a plan to either initiate therapy or when you're going to have a switch in your cancer treatment, this is a great time to sit down with your team and say, 'Hey, are there any clinical trials that you think makes sense for me? Or what's happening? Can we talk about them?'"*

But before you have that conversation, it's a really good idea to have a basic understanding of what clinical trials are and how they work. To begin with, clinical trials are just one step

in a long process of research and development that culminates in a new treatment being made widely available. These happen in three general steps - basic research, translational or pre-clinical research, and finally clinical research such as clinical trials. The first of these three, basic research, takes a long time to understand how a chemical compound might interact with cancer cells in the laboratory. Here's Dr. John Kanki, the Director of Research here at NETRF:

> ***Kanki:*** *"In a neuroendocrine cell there's hundreds of cellular processes that take place. And an important part of basic research studies is to contribute to our understanding of what these cellular processes are. And in doing so we may be able to identify specific processes - they're also called pathways in a cell - that are abnormal, or sometimes turned off in neuroendocrine cells that leads to them becoming a neuroendocrine tumor cell. Then we have a handle. We have a potential target. So what scientists are always looking for is better targets, better molecules to try and find treatments for, and they do this through increasing their understanding of the basic biology of tumors."*

Once a potential new treatment is identified through this basic research, the next step is to test that treatment in biological models that simulate human disease. This is called "translational research", and it's basically done in two ways- *in vitro* and *in vivo*, Latin terms that mean "in glass" and "in living". In *in vitro* experiments, new drugs are tested against tissue samples called "cell lines".

Kanki: *"These are cells that are taken from NET patients and then grown in a dish, a plastic dish. A certain solution of nutrients is provided to them and the cells under the right conditions will propagate and grow just like they do in the tumor itself. So, you want to be able to use these lines to quickly screen whether or not a drug has efficacy and whether or not it can be safe to use."*

Asking about whether the tissues from their own biopsy or surgery can be donated to create these cell lines for basic research is an easy way that NET patients can contribute to the cause of finding new treatments.

Kanki: *"The ability to find NET cell lines has been a challenge for decades, and it's been really one of the major obstacles to moving therapeutic development forward. And so really, the NETRF has tried to offer prizes, prizes and funding, and most recently just is supporting a program at the Broad Institute to generate these cell lines. Of course, I think you have to acknowledge and thank all those NET patient listeners that have contributed to these tumor tissues, to these causes of trying to develop these cell lines, and you want to urge others to continue to talk to their doctors about doing the same.*

And in fact, if they end up making a line, they might be using your cells to specifically find a cure specifically for you."

A next step is often *in vivo* experiments, which means testing the treatment on laboratory animals.

> ***Kanki:*** *"These are typically mice, but it doesn't have to be mice. It could be rats. A new model that's being used is zebra fish. And it depends on the specific type of experiment you want to run. But the bottom line is that you want to either genetically modify that animal or line of animals so that they generate their own neuroendocrine tumors, or you can use an animal model where you can modify it so that it can accept a transplanted human NET tumor. And in that way, you can look at the human cells actually proliferating and growing within the context of a living animal."*

It's important to note that a lot of care is taken at institutions that do these kinds of experiments to make sure the animals are treated as humanely as possible.

> ***Kanki:*** *"At every institution where animal research is allowed, there's a committee called the IACUC, which is based on evaluating the animal care and use at their institutions and those IACUC groups have to review every single grant that involves the use of animals. And there's veterinarians on those, there's actually people that have worked in the research fields for long periods of times, there's people with their expertise in ethics, and having served on one of these committees, it's a very rigorous procedure that animal research is attended to by most respected institutions."*

This pre-clinical process takes a long time, and it does a good job of weeding out ideas that aren't going to work-and identifying the very small number that show promise. Here's Dr. Renuka Iyer of the Roswell Park Comprehensive Cancer Center in Buffalo, New York:

> ***Iyer:*** *"Between 10,000 and 15,000 different compounds are screened and studied and only around 200, 250 of them look like candidates like they're actually working. And after that five lead compounds that are safe in animal models are finally chosen to develop and go further into patients."*

And that's important to remember when we're all reading articles about promising new developments in the lab- very, very few of the treatments that show promise in a test tube or a cell line or zebra fish actually end up being effective at fighting cancer in humans. Here's Dr. Diane Reidy-Lagunes, also from Memorial Sloane Kettering:

> ***Reidy:*** *"My patients come in and say, 'they cured cancer in this cancer line!' And I'm like, 'yeah, we did that a lot of times, over and over… but we're not cell lines and we're not mice and, God willing, one day we will cure these cancers, but right now those preclinical models help us then go on to develop clinical studies. But these are just preclinical.' So, when you're reading about preclinical studies, you say, 'that's interesting. That's something*

that maybe they could do in the, in the clinic, but we're not there yet."

Once a promising idea makes it through all of these pre-clinical studies, it has to make its way to a different team of scientists who would design a clinical trial to test it in actual patients. This can happen in several ways.

Kunz: *"So clinical trials could be sponsored by three different organizations-so a sponsor really is someone who funds the trial. So, it could be investigator-initiated, that is a physician like myself might think of an idea for a clinical trial, but then I have to go pitch it to get funding. So, I might get some funding from a pharmaceutical company, I might get some philanthropic funding, I might get funding from a grant, but it is the idea of that investigator."*

Das: *"They publish results in many of our larger meetings. And so once we sort of see a signal and see activity from a compound, we can actually directly reach out to the company in what we call an investigator-initiated study to actually propose a trial to the company, to get ahold of a compound that already is available for testing."*

Kunz: *"Industry-initiated, are trials that are thought of by a specific company. And then they go look for sites at hospitals or academic institutions."*

> ***Das:*** *"Another major mechanism that we employ quite a bit is through the National Cancer Institute. They actually form collaborations with pharma partners, and they actually identify early drugs that are active and actually form contracts with pharma companies. And that allows us to collaborate with more than one pharma company through a neutral party."*

Some studies are also funded directly by large academic institutions like universities and teaching hospitals, others are funded by the federal government, and some studies are funded by nonprofit foundations like the NET Research Foundation.

But- however they're put together, any drug that is going to make it to final approval by the FDA has to go through several phases of clinical trials, each of which examines the new treatment in a slightly different way. The first of these is called a Phase One trial, which are usually smaller studies, maybe 15-25 patients, and may not be disease specific, meaning patients with several different kinds of cancer might all be in the same trial together.

Phase One trials are really all about safety-what's the right dose of this medication to give to a patient so you're having an effect on the cancer cells without doing too much harm to the healthy cells that surround them.

Kanki: *"There's many different cellular pathways and processes that may be inhibited by drugs or treatments, that may stop proliferation from taking place. But you also know that many non-cancer cells in the body need to proliferate, so you need to find therapeutics that can block cancerous proliferation but will spare normal proliferation."*

Reidy: *"I have a drug and so we want to test it, but we have no idea in the human, what the safe dose is to give.*

So, we generally put three patients on, we give them, we'll say five milligrams, and we watch them very carefully. And then if they do well, the next three go on at 10 milligrams and then they do well, and then the next three you go on at 15 milligrams.

And, so what happens is, say you get to 15 milligrams and then you say, oops, somebody got a little sick. So, we stopped the trial and then we add on a couple more patients and then we end up sometimes lowering it. So, the Phase One is really, is the drug safe and if so, what is the dose required that won't be too toxic or too unsafe for the patient?"

Iyer: *"And for some of these studies, we also want to know what schedule to give. Should we give it two weeks on, one week off? Should we give it continuously? And we do those*

kinds of things and draw blood to understand how much the drug was in your system. And sometimes a Phase One study is called Phase One, even though the two drugs that are being tested are already approved or we already know how to give them, because we're trying to combine them, and now we're trying to see do we need to decrease the dose of any one of them because the two together might be more toxic? And that's also called a Phase One study."

Reidy: *"And obviously, we're always hoping that in that study the doses that we're providing is also helping the patient in terms of being efficacious, meaning that it's going to shrink the disease, but the purpose of the Phase One trial is really to help us better define the safety of that drug."*

Phase Two clinical trials go a step further, and ask questions about effectiveness- "now that we've determined that the drug is safe, does it actually do what we intended it to do?"

Raj: *"If we're able to establish a safe dose and we think there's a role to study the drug further, then it'll move into the Phase Two setting, and that is... the goal of a phase two study is really to look at efficacy. So, is the drug effective? Do we see some sort of activity in whatever disease we're studying?*

These studies are usually a little bit larger. There's about 25-50 patients in these sorts of studies."

Iyer: *" Phase Two studies are more disease specific. So, now you already know the dose and in that Phase One, maybe you had some neuroendocrine patients, some were lung cancers, but a lot of the neuroendocrine patients did really well, or you think this is the disease where there are more of those mutations that you're targeting, so it's a more disease specific trial.*

Now you're looking for efficacy. Efficacy means, did it benefit you? Did it improve the time 'til the disease grew or progressed? Sometimes these phase two studies have biomarkers where they're drawing blood or they're taking tissue samples or, sequential biopsies to try and understand who responded, who didn't respond."

And only after passing through these two phases might a new treatment move to Phase Three which asks a different question than either of the first two phases-now we know what a safe dose of this drug is, and we know that it actually does affect the biological target, but does it actually help the patients improve in a significant way? Is it worth prescribing? These questions are usually answered by comparing the effects of this new drug to the effects of what is called "standard of care", the treatment that is most often currently used to treat the disease. Because if a new treatment doesn't yield better results than the old one, it's not going to be useful to doctors or patients.

Raj: *"They're very large studies, hundreds of patients, usually multi-center international studies."*

Kunz: *"So, patients are divided by chance into separate groups. So, you can't choose which arm you're on. And that's to compare different treatments or interventions, and using chance means that the groups will be similar and that the effects of the treatments they receive can be compared more fairly. So, for example, if it's a trial of pancreatic neuroendocrine tumors, we want to be sure that the age is balanced on both arms, that the perhaps the KI67, the grade balance, then gender, things like that. So, randomization generally helps ensure that balance."*

Sometimes these large studies are not only randomized, but also double-blinded-meaning that even the doctors don't know which patients are receiving which treatment.

Kunz: *"The physician and the patient are blinded to what arm they're on. So maybe both arms are pills- I don't know and you don't know which one you're on. And so that also helps ensure the integrity of the trial so that I'm not biased."*

Because this is such a careful and detailed process, it takes a long time for a new treatment to go from concept to approval.

Kunz: *"Every drug has to go through all of these phases in order to achieve FDA approval. If a drug succeeds at one phase, it then moves to the next, so it does have to be*

sequential. The entire course takes about 10 years. That is painfully slow, both from our perspective but certainly from where you're sitting."

As slow and tedious as this three phase system might seem, though, it's the most reliable way to determine that a new treatment is safe, effective, and worth using in clinical situations-and while we think of it as being a system for approving new drugs, it's used for all kind of other therapeutic tools, from devices to imaging.

Mailman: *"I'm participating in an imaging trial in about two hours from now, which is a twenty person imaging trial on how to better use a type of machine that is the, that is available in a couple of centers around the country and whether this will be a better way to measure something called SUV or "standard uptake value." This is not a treatment trial, but it will help us better understand imaging characteristics. And this is not the first imaging trial that I have been involved with. I have done several in different peptides to see how they compare to other peptides and I have done, you know, not quite back to back scans, but scans within 4 days of each other to determine how these things look."*

Just about all the tools and treatments that have revolutionized NET care from gallium scanning to somatostatin analogues, to M-TOR inhibitors and beyond, were successfully developed using the slow, careful system.

"My name's Carl Remmel, I go by Lee. And, the part of the country I'm in is Tennessee, about 30 miles Southwest of Knoxville. My diagnosis started out with pancreatic cancer and then luckily it turned into P-NETs, Pancreatic Neuroendocrine Tumors.

We were working back in 2005, so in NET time, I'm kind of believing that's all the way back to the day of the dinosaur. So, my oncologist really didn't know what to do with me. I mean, I was the first NETS or P-NETs that she had seen, and I don't think that's unusual for the time that we're talking about, in 2005. So, she used a referral for herself down to MD Anderson, which got me on the standard chemotherapy. And luckily, now I go direct from chemotherapy into my first clinical trial, at Mayo Clinic in Jacksonville.

And the drug I was on is called Nexavar. It wasn't that bad, but there were some side effects that chased me around that were not comfortable and we don't need to go into the personal stuff, but it was a pill form. Uh, glad to have that. I was going to Mayo, maybe every 30 or 45 days for a CT scan because that's where they were doing the clinical part to measure my current lesions against what had happened or had not happened while I was on the next part…until I busted out of that clinical trial. I just, my

lesions had grown too much over that period of time and I was done.

So here we go again, just like getting into the first clinical trial. My daughter again goes into her research mode, and we find an honest to goodness Neuroendocrine Tumor Clinic at the Ochsner Hospital near New Orleans, which completely threw me for a loop. Nobody talked…I didn't know it existed. Uh, but this is how I get into the second trial, the one for Everolimus.

So, I was accepted into it, luckily again. And believe it or not, that was 2009, and I have been on Afinitor ever since that time that I went through the clinic. And then of course you're all familiar with the FDA approving Afinitor, for I believe it was colon cancer. So, as a clinical trial, it goes away, but now I can get a script for Afinitor also.

I'm so happy that NETs and PNETs has made the positive steps that it has through the research community."

Mailman: *"I think, actually, in the NET community, we're really good in clinical trials. We have a patient population that is eager to participate in trials that make sense to them."*

And it's a good thing that so many NET patients are willing to participate in clinical research, because with a rare disease like NETs, it's much more challenging for researchers to find enough patients to fill the studies they want to perform.

> ***Reidy:*** *"You look at breast cancer for example, there's 200,000 patients a year with breast cancer. We have thousands of patients in those trials that allow us to ask questions and provide really good answers. We don't have that in our disease. And in fact, our disease is so complicated because what's in a name, our diseases, many, many different types of diseases, right? And so, because of that, we need these trials to help guide our management, but it can be tricky."*

> ***Mailman:*** *"You know, patients are a resource. We are a scarce resource. There are only so many of us who are undergoing change in therapy in a given year. So especially in a rare disease we are a resource and it is really important that we don't squander the resource".*

Even in a motivated group of patients like the NET community, though, there are challenges to getting patients in to appropriate studies. Let's look at some of these challenges and talk about how we can work to overcome them.

To begin with, it can be a real challenge for patients to find clinical trials that might be a good fit for them. Interestingly

though, this often isn't because there aren't enough trials recruiting new patients at any one time, but rather because there are too many. It can be very confusing and time-consuming to make sense of what your options are. To get a sense of this, Josh Mailman and I took a minute from our conversation for this episode and went to ClinicalTrials.gov, the largest and most comprehensive directory of currently active and recruiting clinical studies, where we did a search for Neuroendocrine Tumors.

> ***Mailman:*** *"In the world, there are…615 active clinical trials in neuroendocrine tumors that are currently recruiting, and 264 studies that are recruiting in the United States alone. Which seems to be…a lot. And so, this becomes a challenge of almost too much information, and a little confusing both for patients, but also for physicians to understand what is a clinical trial that they should be enrolling patients in."*

> ***Das:*** *"Exactly. Even for us. I mean, even for physicians, it's just so overwhelming, because you don't know what population, is this trial for my patient, you know, it's just not well delineated."*

As with so many aspects of NET care, the best course of action is to get to a NET specialist. They follow the newest developments in the field and will work with you to find the best opportunities to participate in new research.

Das: *" Because in general, what I've found from my experience is that whenever I see patients as a referral or as a second opinion, that's when I discuss studies, and that's when I talk about, for example, resources, such as the NET Research Foundation or Carcinoid Cancer Foundation, where there is information about studies. So, I think the big thing is access. And I think by getting access to a NET specialist or a NET provider who conducts studies, I think that's the key step for how to get on a trial.*

Many researchers are finding that a big part of successfully attracting patients to their studies is to involve the patient community in the design of the study from the very beginning. This serves two purposes-to inspire patient advocates and community leaders to promote the trial to their networks, and also to make sure that it is designed in a way that will be attractive to patients to begin with.

Das: *"We have patient advocate liaisons who actually sit on our study boards to give input on, you know, what would make this study exciting or interesting and how to actually promote it to patients in the region and nationally. So increasingly, getting our patient advocates to buy in and also recognize why a particular study may be important is absolutely instrumental to sort of, as the study opens to also disseminate that information so that patients can be aware of what studies are opening."*

A big part of this push to make clinical trials be as attractive as possible to patients has to do with "clinical endpoints". Simply put, these are the things a particular study is actually trying to measure. It's not enough for a researcher to say, "this drug will fight cancer", they have to be very specific about exactly what effect it's supposed to have and exactly how they intend to measure it.

> ***Reidy***: *"There's something we call an "endpoint", so the investigator that runs the study has to say, 'We're looking at tumor shrinkage. We're looking at if the quality of life is better and their diarrhea has improved. We're looking at did the cancer treatment put the brakes on the disease.' We call that 'progression-free survival'. We're looking at all these objectives when we're running these trials to be very objective on does it work or not."*

As you can see, some of these endpoints are more technical, like "how many millimeters did the tumor shrink", and some of them have more to do with improving the daily lives of patients, like "can we control someone's diarrhea". As researchers work together with patients to construct studies that are more compelling and easier to promote, they often find that patients are much more likely to enroll in a study that clearly shows how to make them feel better and live longer, rather than one that is attempting to show something more esoteric. This has led to an increase of the use of "patient reported outcomes", or PROs, in trial design, where results like "my symptoms were more under control and easier to live with" are as important to the

researchers as a decrease in tumor size or the lessening of a particular chemical signal.

> ***Mailman:*** *"The things that I look for and that I work with are types of trials that will change how we practice medicine. The things we need to do is to take that question out of what's next? What is the right thing to do? Or what is the best decision that can be made? And maybe in this era of using more patient reported outcomes, maybe quality of life and dealing with what are tolerable risks or being able to better identify them, are going to help us in the next set of understanding what makes a drug better than another drug that one is considering for treatment".*

Another challenge to successfully placing patients in clinical trials are some long-standing fears and misconceptions that can drive people away from the whole idea of participating in research. One of the strongest of these has to do with randomization and how it works.

The "standard of care" arm of a Phase Three trial is what's called the "control group", these are the people who are not receiving the new treatment, so the researchers have something to compare against. Sometimes though, a trial needs to be done for a condition that has no current standard of care…and in these cases, sometimes a different kind of control is used-a

placebo group. This means that some of the randomized participants receive the experimental treatment and some receive a dummy medicine- something like a sugar pill or a saline solution that has no medicinal effect.

Many patients are scared of receiving a placebo, sometimes so much so that they'll refuse to participate in clinical trials altogether…but there are a couple of things you should know about placebos that might reduce the concern. First-there is a standard of care for most types of neuroendocrine tumors, so placebos are very rarely used in NET research. Second, no researcher in any clinical trial will ever give you a placebo unless you have been thoroughly informed that it is a possibility and you have agreed to participate anyway.

> ***Kunz:*** *"So some people think that they don't want to go on a clinical trial because they don't want to be, quote "a guinea pig". Well, this is clearly explained for patients who consider clinical trials-some clinical trials do have placebos, but you are informed about that and told about the chances you might get a placebo. And if that's not for you, that's okay. You will not unknowingly get a sugar pill. I should also mention that clinical trials that have placebos are only ethical and allowed to have a placebo, if in that setting it's acceptable to do nothing".*

This explanation of the kind of control being used is an important part of the larger issue of "informed consent", which is the responsibility of researchers to make absolutely certain that patients in a clinical trial understand what is expected of

them and what the risks might be before they agree to participate.

> ***Mailman:*** *"There are, with any therapy and mostly and trial, risks that need to be clearly delineated and clearly understood by the patient entering into them."*

> ***Raj:*** *"So what informed consent is, is let's say we've established, you know, there might be a good study that we think you might be eligible for, well then we really need to sit down and speak with you about the risks and benefits, the rationale behind the study, why we're doing it, why we think it might be good for you, compare it to what's currently available that we could offer you off of a study…and ultimately, if you as a patient think it makes sense, you will actually give your permission to participate".*

> ***Iyer:****"Risk vs. benefit- once you hear about the toxicities, you may say, 'Oh, I don't know if I can do that.' Risk of neuropathy, 'I already have neuropathy. I'm a musician. I can't afford to have more neuropathy.' Some drugs can worsen blood sugar levels. If you're already diabetic and having a hard time controlling your sugars, that might not be the right therapy for you."*

And the challenges of participating in clinical trials can go beyond potential side effects. It's important that patients understand that there will be demands on your time as well.

> ***Mailman:*** *"There might be, you know, X multiple times of coming back for blood draws or extra imaging or extra biopsies. Like the one I'm doing today- I'm going to have to take a second imaging exam four days from now that I wouldn't normally need to take, and so it's going to cost me an extra day in time."*

There can also be financial costs to participating in a trial that patients might not be expecting.

> ***Mailman:*** *"And, especially the ones that aren't sponsored by pharma or the National Cancer Institute can actually cost patients money. I don't think patients completely understand that. Some of the challenges of clinical trials is it requires you to do things you might not normally do- like extra imaging, extra biopsies, extra blood work-some of these are going to get covered and some of them aren't."*

All of these are reasons why it's important to be as informed as possible before agreeing to participate in a trial. Read everything carefully, get input from people you trust, and don't be afraid to ask questions.

> ***Raj:*** *"I encourage people to take the informed consent home, read it over the weekend or spend a few days taking a look at it, and then we'll sit down again in a few days. We'll go through all of your questions. We'll again discuss the rationale why we think it might be a good study before we decide, 'Yes, I'm going to sign the informed consent and I'm going to go on the study.' And I think that's very*

important…I think it's very helpful to have someone there with you to help you ask questions and help recall things you might not remember after the visit. Write down all of your questions and just don't hesitate to ask us questions. That is super-duper important, and that's why we're here."

Another source of fear and confusion about clinical trials is the frustration some patients feel when they are unable to join a study for a new treatment that they think might be able to help them.

Kanz: *"So, there are really strict eligibility criteria. Think of it like a checklist that we have to use to also uphold the integrity of the trial. So which NETs, what grade, what primary site is it growing or not?"*

Here's Dr. Daniel Halperin, from the MD Anderson Cancer Center in Houston, Texas:

Halperin: *"Sometimes there are a number of hurdles that people have to clear, things we call the inclusion and exclusion criteria on the trial, which are ways that the investigators and usually the FDA agree that they're going to try and pick a group of patients and work with a group of patients where they think that the potential risks are worth the potential benefits. So, it's a patient population where the need for a new treatment is real and they are*

healthy enough to sustain the risk of new and potentially unknown toxicities."

In some studies, these criteria can also include things like the age of the participants, or their gender, or where they live, or any number of things. Some feel that these criteria needlessly stand in the way of patients receiving medicine. A few people even go so far as to think that the clinical trial system is some kind of conspiracy to deny sick people care. This, of course, just isn't true.

Mailman: *"You know, some of the barriers are preconceived notions of 'I only want this kind of treatment and I don't want to be randomized to that other arm.' But the reason we randomized to that other arm is we don't know whether it will be better than the other arm. If we knew we wouldn't actually go through the clinical trial."*

Halperin: *"And so, those criteria are really there to keep people safe and ensure that we don't essentially take advantage of patients at risk so that we do harm in people where the potential risks and potential benefits don't line up. If this were a treatment that we were certain would work, it would be unethical to be conducting a clinical trial, and by definition, the fact that it's in a clinical trial means we do not know."*

Carefully selecting the people who participate in a study-called the study's "cohort"-is crucial for two reasons. The first is

for safety-to make sure that the participants aren't being subjected to undue risk.

> ***Reidy:*** *"If your liver enzymes are very high and the study is saying you're not eligible, it's probably because there's a potential for that drug to cause really bad liver injury. And so, we don't…we can't put on patients that may be vulnerable and may have risks of potential harm. So, the eligibility is generally, to make sure that the drug itself won't harm the patient that's participating."*

The other reason is that researchers need clear comparisons to see the actual effect of the drug being tested-comparing apples to apples. If a study also includes two pears, a mango, a banana, a can of peaches, and a chicken-fried steak, it can be pretty difficult to understand what is actually happening. Particularly in a complex disease like NETs, different patients with different tumor characteristics might respond to a treatment in very different ways, so it's important to separate out some of those variables in order to make an accurate assessment of what a medication is actually doing or not doing. There are many real-world examples of times when choosing the wrong cohort led to misunderstanding a drug's effectiveness.

> ***Das:*** *"So, for example, you know, looking to the approval of the drug Sunitinib, which is an FDA-approved treatment for pancreas neuroendocrine tumor patients that you know, I think, some of the initial studies that sort of looked at Sunitinib's efficacy included all neuroendocrine tumor patients, and that signal was masked. And it really was*

after the initial studies were done, when patient populations were examined and it showed that in pancreas neuroendocrine tumor patients was this drug effective, that a study was conducted in that specific population.

And honestly, some of the net studies that perhaps have been negative, I think we have to do some further digging to see that maybe if we did or did not include the right population."

However, there is a very valid frustration with the narrowness of clinical trial eligibility requirements that is widespread and growing within the research and patient advocacy communities, and it has to do with health disparities. Because researchers want to make sure they are able to fill their studies with a cohort that is healthy enough to complete the trial and well-resourced enough to be able to travel to the study center and be available for tests when needed, not to mention having the time and resources to research clinical trials in the first place, there is a growing realization that clinical trials have far too often skewed towards cohorts that are disproportionately white, male, well-resourced, fit, and middle aged. This is a problem because people with different profiles can often respond very differently to medication, and if we're not testing drugs in different kinds of people, we won't really know how to treat them.

Mailman: *"And, you know, honestly, one of the trials that I was most proud of was a pancreatic cancer trial to which was really looking to recruit post-70-year-old people, because most of the trials were, you know, the average age was somewhere between 52 and 60.And that really wasn't representative of the sample of the real world data of who was getting it. And so, there was very little known about, you know, even an elder population that would get a disease. And I think that the real interesting thing is trying to understand the natural population of a disease and trying to faithfully represent it in the clinical trials so that you get an idea across the spectrum of those with the disease- how this is going to do, how this is going to do in the real world, as opposed to people who can get to a doctor at the exact moment in time, and really bring it to trials that represent the population to which the trial will ultimately be used for.*

The worst thing that can happen if you deliver a therapy and it has some quirk that you didn't find out because it works differently in different populations that you had no way of looking at, cause you really didn't have a diverse population when you went into it. And certainly, this is a large topic and it's not an easy one to address all the time."

In spite of all of these challenges, though, we hope that all NET patients will actively keep an eye out for clinical trials

that might be a part of their treatment plan and be open to the idea of participating in a trial if your care team suggests one. Make sure your care team also knows that you would be interested in participating in a clinical trial. This is an amazing time for NET research, and there are current and upcoming trials that are pushing the envelope in all kinds of new directions, from improvements to things like PRRT to groundbreaking new avenues like immunotherapies.

> ***Kunz:*** *"This is a very hopeful time to have this disease, because I think that there has just been an explosion of research in the last decade. Many patients that I was taking care of 10 years ago benefited from ongoing research and FDA approvals in the last 7 years, and I would anticipate that we will have more advances in the field."*

> ***Mailman:*** *"Really, clinical trials are paying it forward. If it helps you, that's great, and I hope that it does, but really you're doing it for the betterment of those who come after you."*

Thank you for listening to NET Wise. My name is Laran Hyder. I'm the Director of Education and Outreach for the Neuroendocrine Tumor Research Foundation and the Executive Producer of this series. It was produced by David Hoffman of CitizenRacecar.

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Do you have a story to tell about your own NET journey? If you're a NET patient who would like to participate in a future NETWise episode, please email us and let us know:podcast@netrf.org.

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