Zac Getty:

Good afternoon or good morning, everyone. Thank you for joining us today for our Clinical Trials: How do I get involved? webinar. My name is Zac Getty and I am the Disease Awareness Program Manager here at Fight CRC. Fight Colorectal Cancer is the leading patient empowerment and advocacy organization in the United States, providing balanced and objective information on colon and rectal cancer research, treatment, and policy. We are relentless champions of hope focused on funding promising high impact research endeavors while equipping advocates to influence legislation and policy for the collective good.

Before we get started today, let me go through a few housekeeping items. We will have some time at the end of the webinar for general questions, but please, please feel free to use the Q&A panel on the right side of your screen to ask any questions that come up along the way. We will do our best to address them at the end. This webinar is meant to serve as an overview of what clinical trials are and things to consider when looking for a trial to participate in, but also to serve as an opportunity for you to ask your questions. So please don't be shy. We will do our best to answer every question that we can.

We will have a recording of this webinar available on our site within the next few days. If you registered for this webinar, you will receive a direct link to that recording via email as soon as it's available. We will also provide a transcript of the webinar on our website for those of you that would prefer to read the information that's being discussed today.

Also, feel free to Tweet along with us. Is it still called Tweeting since it's turned to X? I'm not sure, but you can use the hashtag #CRCWebinar.

Please remember to stop by our website at fightcrc.org to check out all of our patient and caregiver resources. This includes your guide in the fight meetups, which are in online space to meet with other patient and caregivers, which are held three times per month. They touch on a variety of topics but are also just a great place to find a sense of community. We also offer our free Community of Champions app where you can connect with other people in the colorectal cancer space, and keep in touch with Fight CRC and know what we're up to. And we also offer an assortment of print and digital educational resources that are free to request and download that are all medically reviewed by our medical advisory board.

We are also now hosting monthly mega meetups, which are similar to our regular meetups in format, except they address a specific and unique topic each month. You can RSVP for mega meetups and regular meetups in the community of Champions app that I mentioned earlier. Links to that can be found on our website or in the App Store or Google Play Store. On your iPhone or Android phone.

I do have a quick disclaimer. The information and services provided by Fight Colorectal cancer are for general informational purposes only. The information and services are not intended to be substitutes for professional medical advice, diagnoses or treatment. If you are ill or suspect that you're ill please see a doctor immediately. In an emergency, call 911 or go to the nearest emergency room. Fight Colorectal Cancer never recommends or endorses any specific physicians, products or treatments for any condition.

Okay. Now, with all of that out of the way, I would like to briefly introduce our participant today. Joining us is Dr. Smitha Krishnamurthi. She's medical Oncologist and Associate Professor of Medicine in the Department of Hematology and Oncology at the Cleveland Clinic.

Dr. Krishnamurthi, thank you so much for taking the time out of your busy schedule to join us today. I'm going to give Smitha a chance to provide a bit of her background before we begin going over some questions that we have prepared and have also received from our Community of Champions members. I

want to stress again that this webinar serves as an opportunity to ask questions. So please don't be shy. Use the Q&A box and I'll hand it over to you, Smitha, to introduce yourself a little bit more thoroughly.

Smitha Krishnamurthi, MD:

Well, thank you so much, Zac. I'm so honored to be here. I've always enjoyed partnering with Fight CRC, admire all the work that Fight CRC is doing. I'm a GI medical oncologist, as you mentioned. I've been doing this for 24 years. That time really flies, and right now I'm the lead physician for our GI clinical trials at Cleveland Clinic, and I just welcome the opportunity to raise awareness about trials and demystify them. So really thrilled to answer any questions that come up today.

Zac Getty:

Thank you. Yeah, you mentioned demystifying, which I think is a big problem when it comes to clinical trials, and so that's a good way to kick us off today with just a pretty straightforward basic question. Can you provide just a general quick overview of what a clinical trial in the medical setting is?

Smitha Krishnamurthi, MD:

Sure, yeah. Clinical trials are research studies in people, so they could be a treatment trial, so which treatment A versus treatment B is better for this cancer or could be supportive care studies like treatment of a nausea medicine to see if it's better than what we currently have. There could be studies looking at how to prevent cancer or how to diagnose cancer. So they come in different flavors, but they're all studies in people where we're trying to systematically collect the data. So there's high-quality information that can change practice.

Zac Getty:

So they aren't necessarily only about testing medications or surgical techniques, there's other types of trials besides those?

Smitha Krishnamurthi, MD:

Yes. I could go into more detail, sorry. Treatment trials could be surgical trials, so more or less surgery. There could be trials of radiation. There could be trials of chemotherapy, immunotherapy, but goal is to treat cancer. But then there are other trials that might be looking at trying to make the treatment easier. Those are the supportive care trials or studies of tests like a blood test to diagnose colon cancer, looking at ways of early detection and then also studies of prevention.

And I should clarify, not all studies are meant to be practice changing because those are those large studies, usually randomized control trials, but many studies start smaller where it's a newer drug and we're looking for a signal of activity and what are the side effects. And then, if it's looking promising, moves on to larger and larger studies.

Zac Getty:

Interesting. So is it safe to assume that any treatments that are being recommended by a physician have at least been studied somewhat in the clinical trials process?

Smitha Krishnamurthi, MD:

Yeah. Very important to keep in mind, the drugs that we use now that have been proven to work. We know that they worked through clinical trials. So all the information about treatments now are because

people went on clinical trials, they took that leap of faith and went on the study so that we could learn if something worked or didn't work, and it all advances medical knowledge.

Zac Getty:

Interesting, thank you. So this topic unfortunately does not lend itself well to graphics charts, that kind of thing, but I do have a quick graphic that describes the process that treatments, medications, that sort of thing go through when going through a clinical trial. Are you able to speak a little bit about the different stages involved in this process?

Smitha Krishnamurthi, MD:

Yeah, sure. I love these graphics. I noticed Fight CRC has wonderful information about clinical trials on your website.

Zac Getty:

Thank you.

Smitha Krishnamurthi, MD:

So yeah, this lays it out nicely for, say a treatment trial, a drug therapy. First it's going to be studied in the laboratory setting to see, how does this work? We are interested in shutting down this pathway that drives colon cancer and there are some target drugs. Well, are they really hitting the target in a cancer cell? So that could be done in cancer cells growing in a dish, in the lab, and then could then move on to studying it in an animal model, so an animal model with cancer to see if it's working and what are the toxicities resulting. And then, if it's looking promising, it would move on to first in human study phase one trial where they typically will start with a much lower dose than what was considered safe in the lab setting. And that would be the entry level dose and just a few patients would be treated.

Typically, it might be one to three patients at the initial dose because you want to see is it safe. And then, these studies are built so that, depending on if they see any side effects or are they just mild or moderate, move up a dose level and trying to find out what is the maximum tolerated dose. But along the way, also typically collecting information about how much of the drug is getting into the body. If it's a pill, what are the blood levels? So there'll be some extra blood draws to determine that. Pill or IV treatment, they still want to know what time does it reach its peak level, could there be any interaction with eating a meal or not? All of this is figured out through these phase one studies because people who went on the studies had their blood drawn at various time points after the dose. We call that pharmacokinetics where you're trying to see what's the metabolism of the drug and what levels are we achieving in the body.

These patients are monitored very closely for side effects because these are very new. So we don't know entirely what the side effects will be. We have an idea from the lab, but we have to really listen to what our patients are telling us and then go through the process of trying to determine is this related, this symptom, is it related to the cancer? Is it related to the drug or is it something else? It's some other medication the person's taking or some other underlying condition?

And so it really takes a village to do these studies. And I worked for phase one, in phase one group for many years when I was at university hospitals. And it's a big meeting, typically a weekly meeting running through every person who's on each trial and getting a group opinion to weigh in on, do we think this was treatment related or not, if it's not obvious? Because that's very important in determining the safety.

And so then, once a drug has gone through phase one, we usually have an idea of what's a good dose, what's a safe dose, what side effects to expect, and they're also collecting information on does it work. So there are scans built in before treatment. And then, typically, anywhere every six to nine weeks, there'll be a scan to see is this drug working, is there any tumor shrinkage? That's always very exciting when you see that in a phase one study because typically the patients going on have had all the standard treatments, so the cancer's gotten harder to treat. So we're looking for that as well.

But then, once we have that information, then you want to really give this drug a shot to see how well does it work. So we're not going to enroll patients who have had a lot of previous treatment. You want to see how does it work in somebody who maybe had no previous treatment or one previous treatment or maybe two previous treatments. They'll try to get a uniform population, like one cancer type, a similar number of previous treatments. And it's a smaller study as it says here, maybe 30 to 120 participants.

And then, if it looks like it's active there and you're, of course, collecting the safety information, then that's when you'd want to take it into the definitive trial, the phase three where we may be comparing it to a standard treatment or standard treatment plus this drug versus standard treatment without the drug. And that's a much larger study that typically would be a practice changing study if it has positive results. That would lead to typically to a drug being like FDA approved for use in that setting.

And then, after drug approval, we get a lot of data that companies collect. It's more what we call real world data because the clinical trials, unfortunately, they aren't reflective of our general population because for safety reasons, they have restrictive enrollment criteria. They typically want people who are fitter, maybe doing all their activities except hard manual labor or exercise because in case there is a side effect, want to make sure the patient has some buffer and can withstand it.

But most of our patients are older than the population that goes on trials. We also unfortunately don't have a... Many studies will not be very diverse in terms of who's going on the trials. So we need to collect this real world data to see in the real world setting patients who weren't that fit or maybe their kidney function wasn't that good or they were in a rural setting, how is this drug working? And this is where you really can uncover some rare side effects because even if the phase three trial had a thousand participants, there could be a rare side effect that occurs in one in 2,000 and we wouldn't catch it. So that phase four is also important.

Zac Getty:

Wow. So it's a little more complicated than company X develops drug, tries it, sees if it works and then sells it. There's a lot that goes into getting something to market it sounds like.

Smitha Krishnamurthi, MD:

So much effort and it's so many patients donating their time and so many years to get to that approval.

Zac Getty:

Sure, thank you. Something that we hear commonly from the people in our communities that state or clinical trials are viewed as a last resort, should patients consider participating in a clinical trial regardless of their stage of disease?

Smitha Krishnamurthi, MD:

Yeah, great question. Absolutely. I think that typically whenever there's a situation where standard of care is not curing close to everybody, there's room for improvement. We just had a national trial for

patients with stage two colon that was NRG-GI005 study where it's a bit of a controversy. Chemotherapy is never proven to be helpful for most patients, but we do know that patients have a risk of recurrence. So that was a study for patients with stage two disease looking at determining treatment with circulating tumor DNA. So for somebody with stage two, we definitely wanted to offer that study.

There's a currently open trial, NRG-GI008, or it's called Circulate US, which is for patients with stage three disease or T-four tumors that are stage two. So another important study for our patients with early stage cancer. And then of course there are trials for patient's metastatic disease, whether it's your first treatment, we call that first line, or when the cancer's progressed on first line or first line is intolerable. Then the second treatment, which is called second line. And then there will be trials for people who've gone through first and second line or maybe even all standard options. Those are typically the phase one studies.

Zac Getty:

Wow. So there's options out there available regardless of where you are with your disease?

Smitha Krishnamurthi, MD:

Yes.

Zac Getty:

Good to know. So a follow-up to that, or at least gently related, should you consider a trial that the treatment that you're currently receiving seems to be working well?

Smitha Krishnamurthi, MD:

Yeah, good point. If you're on treatment and it's working, say it's for metastatic disease and maybe you just started it, so you don't know if it's working or you got a scan and it is working, you would generally stay on that treatment. We don't want to burn our bridges. If the treatment's working, let's ride it out. If it's working intolerable, let's continue with it. Because on clinical trials, they typically, once you've started a first line therapy, you can't enroll on a first line trial because they're looking for people who haven't had any previous treatment. So then you're looking at second line trials. So stay on the first line as long as it's working.

Zac Getty:

Okay, that's interesting. That's very helpful, thank you.

Smitha Krishnamurthi, MD:

Sure.

Zac Getty:

So how is eligibility for a particular trial determined? And I assume this depends quite a bit on what that trial is trying to study, I would imagine.

Smitha Krishnamurthi, MD:

Yes, absolutely. And it really should be tailored to the trial and the trial population. So this is for patient safety reasons and also for what makes sense for what sort of cancer is this drug expected to be effective in. So there may be a drug that targets HER2. That study is going to require that this cancer

overexpresses the HER2 protein because this drug is not expected to work unless you have that. So there may be that sort of factor.

But generally, for safety reasons, they will look at the performance status, like how active is a person. If somebody is mostly resting, unfortunately that predicts for more side effects with chemo. And while they need treatment, a clinical trial may not be the best option because if there are risks, this would be considered unsafe for somebody who's that fatigued. Likewise, the trials will be looking at having adequate liver function or kidney function because these drugs are cleared through liver or kidney, or if it's phase one and we don't really know how it's cleared, they'll have very strict criteria.

But having said all this, I do feel like some of our clinical trials, there may be a little bit of cut and paste involved with the eligibility criteria. There's a big movement trying to get investigators and sponsors of trials to think about each criterion, do you really need this? Does it need to be this narrow? If your drug doesn't harm the kidneys and it's not cleared by the kidneys, why do you need such good kidney function? Maybe you could safely enroll somebody who doesn't have such good kidney function. And by doing that, we think that would diversify the enrollment so that we get more of a real world population going on studies, which would then make the results more generalizable.

Zac Getty:

Absolutely. So it's trying to balance patient safety and the integrity of the study and making sure that you get real world results that would actually apply to the general population then?

Smitha Krishnamurthi, MD:

Yes, exactly.

Zac Getty:

Fascinating. A big question we often get is, is this dangerous? So I figured I would ask, can you go over some of the risks that might be involved with participating in a trial and maybe also some of the benefits that participants might see if they participate in a trial?

Smitha Krishnamurthi, MD:

Sure. Sorry, my screen just went blank for a sec.

Zac Getty:

No, you're fine.

Smitha Krishnamurthi, MD:

Yeah, it's like a big step going on a clinical trial, a treatment trial. I'll talk about treatment trials because those are the highest risk trials because in oncology, our drugs do have unfortunately some pretty serious side effects which are tolerated because we're fighting a deadly disease. But the drug treatment trials tend to have higher risk than a supportive care trial or a cancer screening trial, of course. So with a treatment trial, there are risks of the unknown. So it's a study. We're trying to figure out if this drug works or not. So there is some risk of, well, what if this drug doesn't work?

So in a situation where there is a good standard of care, we're typically not giving an experimental drug without any track record versus the standard of care or instead of standard of care. So we typically start off with these brand new drugs where we don't know how well it's going to work in patients who have already had all the standard treatments. So there are patients who are well enough for more treatment,

but we have sadly run out of drugs that work against the colorectal cancer. And unfortunately, this does happen because we don't have all that many drugs that work for colorectal cancer. And so those patients are interested in new trials, something that looks promising in the lab. They're willing to consider it because otherwise we don't have a good option.

So for them, they are looking at something that's rather somewhat unknown, let me say. And then they are monitored though very closely on a phase one trial because of that increased risk. So we have frequent visits. Usually we're often seeing the patients weekly. With clinical trials, participants get a clinical trial nurse that's following them in addition to the usual treatment team. So the nurse is calling, patients are asked to report side effects early or any concerns so that we can try to figure out is this related to the treatment and what should we do? So it is higher risk in a phase one setting, but then there is increased monitoring. There'll be frequent blood work to look for any signs of blood counts going low or any effects on kidney and liver. So all this done to try to make it safer. So there's that risk in phase one.

When we go onto phase two and three, at least the drug has... We know the side effects and there's been some early signs of activity, otherwise we wouldn't be going onto these later stages. But yeah, there's always a risk when one goes on the trial that you would go on the study and you got enrolled to the experimental treatment and it turned out it wasn't better than the standard. I mean, sometimes it could be worse. That's a little unusual because usually we have this smaller studies leading up to the big one.

Zac Getty:

Interesting. So potential benefits, can you speak to any of those?

Smitha Krishnamurthi, MD:

Oh yeah, of course. The benefits of the trial are, well, the trial is being done because the drug looks promising. Otherwise, nobody would be bothering to put in all this time and energy into doing this study. So going onto the treatment could be better than the usual care, or if you don't have any other standard treatments, this drug could work against the cancer. There's also the added support of the clinical trial team. So they're helping out not just with the side effects of the trial, but any needs that the patient has, you do have that added layer of support.

Zac Getty:

Interesting. Thank you so much.

Smitha Krishnamurthi, MD:

Also, I'll add one other thing. When we have clinical trials and we are negotiating a budget with industry sponsor for example, we do like to budget in for expenses for the trial, such as mileage if somebody has to drive from far away to get here, or even a hotel stay if they have to stay and have their blood drawn for those drug levels, they're going to stay for eight hours and it's going to be really late to drive home. So many times those are reimbursed or parking is reimbursed, and so that can be a benefit to going on the trial.

Zac Getty:

That's really helpful information because also we get those questions financially what is expected of me. So it's nice to know that sometimes some of those costs are subsidized through the actual trial. That's

helpful. And the last really of these basic clinical trial questions, is it normal to be apprehensive or scared, worried, anxious when you're participating in a trial or looking for a trial to participate in?

Smitha Krishnamurthi, MD:

Yeah, I think it's a completely normal response, to be scared of a trial or even to be apprehensive about a new cancer treatment because our drugs do have side effects and you never really know until you start what it's going to be like. And so when I'm especially meeting somebody, we're talking about the first treatment they're going to go on, I do tell them, "Once you get through that first two week cycle, say it's FOLFOX, then you and I, your family, we're all going to know how did this go." And if there were any bad side effects, we have to make adjustments. We don't want anybody having severe side effects. And the trials are the same way. So if there are any side effects that the study or the investigator thinks is unacceptable or the patient just said, I can't stand this, we would always make adjustments and a person can always change their mind and come off of a trial at any point in time.

So we try to reassure people about this. The consent form is meant to provide information, but they're very long and they list out every possible side effect. And I think it's terrifying to read them. But I guess if we read the package insert of ibuprofen, that Motrin that I might take, it'll list a lot of side effects too. And so try to use the consent process so that a person could get all their questions answered. That's really important, that when they're enrolling, they don't have any lingering questions that haven't been addressed. And while sharing all this information trying to explain, we don't expect that this is going to happen, all these side effects and you're going to be monitored and should we see anything brewing, we can take a pause, stop the treatment, wait for things to get better, etc.

Zac Getty:

Great, thank you. Okay, so moving in a little bit to actually, how would somebody get involved? So if I've decided that I would like to explore participating in a clinical trial, what would you say my first steps are with that?

Smitha Krishnamurthi, MD:

Yeah, first steps would be asking your doctor about it. I think it's important when going in for consultations and hearing about the recommended treatment to ask is there a clinical trial available that I should consider to make sure the doctor's not forgetting something. So I would start with that, to see where you're getting treatment. Is there a trial for you? It's harder when it's not there at that center. Then we have to look where is a trial that could be appropriate. And I can understand this can be really overwhelming because how is somebody supposed to know? So always start with asking your doctor whom even if he or she doesn't have a study, may be able to refer you to a place where they do have a trial. In my practice when this comes up, I'm often emailing colleagues at different places saying like, "Hey, do you have a study in this situation?"

But we also look at clinicaltrials.gov, which we're probably going to get into later, but this website is where all the studies are registered, so we should be able to find a study there. But the key is to learn how to navigate it. And should I say more now?

Zac Getty:

Yeah, sure. So I was about to say I've looked at clinicaltrials.gov and Fight CRC actually offers a clinical trial finder that we curate from clinicaltrials.gov, but clinical trials.gov is overwhelming. There is so much information on there. And you mentioned that discussing with your physician is probably the first step.

Do I need my physician and their assistance to do this? Or if I'm able to navigate clinicaltrials.gov by myself, is that a reasonable option to just find a trial that I think I apply for?

Smitha Krishnamurthi, MD:

Well, I think it's probably easiest to go with the doctor's guidance, but say sometimes I hear this where the patient's doctor just didn't have the time to help out. So then people are looking on their own and going to different centers looking for studies. I would suggest going to a center nearby where it's feasible to go for treatment to see if they have trials, but keeping the doctor in the loop because typically if you enroll on a study somewhere, they're going to want records from the doctor's office and you have to get treatment at the center where the study is open. And if it's far away, you're going to go home in between the treatments. But then, if you have a side effect, you have to go to the local emergency or get hospitalized, or even just need to be seen by a doctor. The local oncologist is super helpful and it's best if they're on board and then they can communicate well sharing information back and forth.

So while you don't have to go through the doctor, I think it would be good to just keep them in the loop. Yeah, clinicaltrials.gov is so overwhelming and it's great that Fight CRC has this app. And it's really nice because you can curate, you could say it's for MSS, you're interested in immunotherapy, and the locations, and it produces a more manageable list. So you highly recommend that.

Zac Getty:

Thank you. Yeah, that was the goal with, and I'll talk just a little bit about our clinical trial finder just a little bit later in the webinar, but it's helpful to know that you should probably start with your healthcare team when you're starting this process. So thank you.

So moving on from there, we found a trial that I think I might qualify for. Do I need to interview to be accepted? Do I just apply to the trial? Does my doctor handle that for me? What does that process look like?

Smitha Krishnamurthi, MD:

Yeah, so say you do find a trial through the app or clinicaltrials.gov, there's typically a contact person to call or email, and you can do that yourself. And it may be a research nurse often. Sometimes it's like the investigator actually gets the email, and then they'll advise you. It's nice if they would do a little conversation so that if this is totally not a good study for you, like, oh, they're looking for a completely different type stage of disease or characteristic that they could let you know. Or sometimes clinicaltrials.gov is not up-to-date and then they'll say, "Oh, we're actually not enrolling now." So that can be helpful to get that info. But then, typically, if it looks like a possibility, then the next step is come on in and have an appointment and get to meet somebody on the team, one of the physicians to go over the history and see if you look eligible.

Zac Getty:

Excellent. So you won't just be thrown into a trial blind. You'll have the opportunity to talk to potentially the investigator or at least some staff involved with the actual trial before you get enrolled and you start the process.

Smitha Krishnamurthi, MD:

Absolutely. Typically, if it's a colon cancer trial for somebody looking for a second line treatment, you're going to be seeing a GI oncologist at that study site who would become the treating doctor. So they know all about colorectal cancer, would be looking at your case in terms of is this a good idea for you to go on this study. And then if you hear about it and you decide, yeah, I'm interested, then they call in the research team to come and meet. Typically, we give a person the consent form for the study and ask them to take it home and think about it and go over it with family, friends, mark it up with all your questions, concerns, and then the research team usually follows up with going through it in detail and then sign the consent.

And once that consent is signed, then we do these eligibility tests to see are you eligible for the study? We can't do certain things unless the person is given consent. Some studies will require an EKG. We don't normally get that before treatment standard of care, but for a study, they want it for safety reasons. Well, we're not going to do that unless they've signed the consent and they're giving us permission to do this. And then that extra test, then it gets billed to the study. So it's quite a process. It's not jump right in.

Zac Getty:

And it sounds like they want the participant to be informed to the best of their ability as well.

Smitha Krishnamurthi, MD:

Absolutely.

Zac Getty:

Good to know. So it sounds like they'll need access to all your health records or at least for recent treatment, that kind of stuff?

Smitha Krishnamurthi, MD:

Yes. Yeah, definitely. They need to know prior treatments. They want the whole history, but then many studies will also require that you get all new lab work, and if you're CAT scan for if it's metastatic disease, if it's a little too old, it's more than 30 days old, they get a new one, things like that.

Zac Getty:

Excellent, thank you. This next question is generally broad and I can't expect a broad answer for such a broad question, but once I've been enrolled in a trial, what could I expect my care to look like?

Smitha Krishnamurthi, MD:

Yeah, it is quite variable, depending on what the trial is. Some studies may be minimally involved. If you were going on a trial for screening for colon cancer with a blood test, just a quick consent process and have the blood drawn and then get the results. And if it's positive, get navigated to the right in studies to make a diagnosis. But if it's a treatment trial, it's more involved. Sorry, my screen keeps going blank. [inaudible 00:34:54] clinic, if I don't press a button, it goes...

Zac Getty:

Oh, of course. [inaudible 00:34:57].

Smitha Krishnamurthi, MD:

Okay, so I'll be back. If it's a treatment trial and say it's standard therapy with an investigational drug and it's a phase two study, it may not look too different from your normal care because you're getting the standard treatment, maybe it's every two weeks and on the same day you're also getting an investigational drug. There's usually extra blood tests involved, but when you're getting your labs drawn like you normally would, there might be some extra research labs there. There could be some few extra tests like an EKG or an Echo of the heart before enrolling.

Some studies though will be more involved and have those research blood tests to see drug levels. So there might be a long treatment day where a person's there eight hours or overnight having these blood samples drawn. They don't keep poking. The report would probably use for giving the treatment than an IVs in the arm and drawing blood out of that. So variable. There's the usual team, but the research nurse is probably more involved than the usual clinic nurse because they really need to know about all the side effects that a person's experiencing so that they can record it. And so then that gets recorded into the study database, so that's why you'd be seeing them a lot.

Zac Getty:

Sure. So pretty intense monitoring while you're participating, it sounds like, just to keep track of side effects progress, how your body's clearing the drug, all that sort of stuff. Is that generally-

Smitha Krishnamurthi, MD:

Exactly.

Zac Getty:

Okay.

Smitha Krishnamurthi, MD:

Yeah. And normally, there'll still be the CAT scans, if it's a treatment trial for somebody with metastatic disease, generally every two months. And so getting the results of course in real time. But on the physician side, we're also collecting measurements, which we don't normally do for standard care, but we're trying to see if these measurements are meeting the criteria that the drug has caused a response. And what a response is is it means that when we measure these tumors, like the longest diameter on the CAT scan, and typically two per organ, say there are two nodules in the lungs are following two in the liver and maybe one other lymph node, if the sum of those measurements decreases by 30%, then that's considered a response. It's somewhat arbitrary. And if it's increased by 20%, that's progression. But of course, if it's anywhere in the middle that's stable disease. But these are the sorts of things we have to collect for the study. Sometimes we do that in the room with our patients, so they see us go through the process.

Zac Getty:

And then just a quick question that we've received related to this. If I'm involved in a trial, will my relationship with my current oncologist, my current care team, is that relationship over? Is my progress communicated to them? What does that look like?

Smitha Krishnamurthi, MD:

Yeah, great question. Say you are going to a different center for the clinical trial, so your local oncologist is not there, then the study team really is taking over for your care, but it's always good to have the local

doctor involved. We typically would want to send our notes, copy them to the local oncologist. It's great when we can see each other's notes through the computer because when the person's home, and again, if they get sick and they're getting their care locally, it's great for the oncologist to know that they're on the study and what to expect and to be able to call the study center and have a conversation so the information is shared freely. So I think that's always best when they're involved.

Zac Getty:

That's helpful, thank you. And I know some people develop pretty close relationships with their care team and don't want to lose their physicians, so that's good to know. Excellent, thank you. Will I be kept informed about my disease progress during the trial?

Smitha Krishnamurthi, MD:

Absolutely. Like I was saying, sometimes we do the tumor measurements just right there in the room, in the exam room. So yeah, we want to be completely transparent. We're always going over the lab results and then the scan results. Certain things we don't know, like if blood is being collected for research related tests, it might be banked and the studies might be done way later, even after the trial ends, or the studies are being done, but that isn't being shared in real time. If data is presented, then we are expected to share that with the study participants. We had a study of immunotherapy open and when results were shared at national meeting, I told the patients, "This is what they're seeing so far." Likewise, when a study ends, I don't think this happens enough, but it's really nice to let patients know this is how the study turned out.

Zac Getty:

Interesting. Yeah, it's like you helped, here's the information and what we learned from it.

Smitha Krishnamurthi, MD:

Absolutely.

Zac Getty:

Kind of a follow-up to this, if the treatment, experimental treatment or there's treatment I'm just receiving during the trial isn't working for me, can I quit the trial?

Smitha Krishnamurthi, MD:

Oh, yes, absolutely. That's really important about the scans because if we see that this cancer has grown enough... And on the study, it's like actually progression is that there's 20% increase in those tumor diameters or there's a new lesion, looks a new convincing lesion has grown while on treatment, then this treatment is not controlling the cancer, not in the person's best interest to continue unless there's some situations where we treat beyond progression. And so with immunotherapy, sometimes things will look worse and then they'll get better and the tumors might look bigger because all these white blood cells are moving in to fight the cancer. So things could look worse. But if a person is feeling well, we would discuss, do you want to continue another two months and we'll see? And at that point, if the scan looks worse, okay, let's stop. But sometimes it'll look better and then we know, okay, they actually were not having disease progression.

Zac Getty:

Wow, interesting.

Smitha Krishnamurthi, MD:

And again, a person could change their mind at any time about staying on the trial. There's no requirement to stick it through to the end.

Zac Getty:

So the participant's in control of their care? They can leave if they'd like to or continue if they'd like to?

Smitha Krishnamurthi, MD:

Yes, absolutely.

Zac Getty:

That's good to know. This question was brought up by somebody that I actually work with and they knew somebody who was on an ALS clinical trial, and the trial ended I think before completion, but they were seeing progress from the treatment and the trial ended. So what happens if the trial ends while I'm still receiving treatment? What happens to my care?

Smitha Krishnamurthi, MD:

Yeah, that's such an important question. If the participant is getting benefit from the treatment, we will ask the sponsor if they could continue to receive the treatment.

Zac Getty:

Oh, wow.

Smitha Krishnamurthi, MD:

Sometimes that happens. I remember a patient on a phase one study at my previous job and it involved Lopatinib before it was approved and was clearly benefiting, and the study had come to an end and that person just stayed on it for years. So I think it would be a case by case or trial by trial basis, but we would always advocate for our patients that if they're getting benefits, we don't want them to lose that drug.

Zac Getty:

Interesting. Well, that's good to know. In that specific case, let's say it was a stage one trial, I would assume if the drug is already FDA approved, you would have access to it [inaudible 00:43:08]?

Smitha Krishnamurthi, MD:

Yes.

Zac Getty:

If the drug wasn't FDA approved at that point, you probably would no longer be able to receive it after the ending of the trial. Is that correct?

Smitha Krishnamurthi, MD:

Right, unless the study sponsor will provide it, which I have seen happen, and until the drug is FDA approved that the patient was able to continue to receive it.

Zac Getty:

Interesting. Well, that's a unique-

Smitha Krishnamurthi, MD:

You should always ask for that.

Zac Getty:

Yeah. Interesting. Well, thank you very much. That's very helpful.

This is actually the end of the questions that I have prepared, and I do have some questions coming in through the Q&A and I also have questions that were given to Aspire Community of Champions members. So I am going to move to the questions that have been asked by the audience here. I want to again reiterate, please ask any questions if you have them right now. We've got probably about 10 minutes or so to answer questions, but the first one here is, should patients giving close consideration of academic consortium trials?

Smitha Krishnamurthi, MD:

Oh, that sounds like the NCTN National Clinical Trials Network trials perhaps, or there are other consortiums like Hoosier Oncology Group or ACCRU, which is run out of Mayo Clinic. I think all of those trials are worthy of consideration. All these trials are very thoroughly vetted. A lot of minds were put together to come up with a trial design and the trial's done because it looks promising. So yeah, I would definitely consider those studies.

Zac Getty:

Interesting. Okay, thank you. I've got another, seems like a technical question, so forgive me if I'm not able to explain this correctly. I'm going to read it verbatim. Do we need washout periods for all of these question marks? So chemo, targeted treatment or biologics, and then parenthetical TAS-102 or regorafenib?

Smitha Krishnamurthi, MD:

Yeah. Yeah, great point. Washout periods are required for these treatment trials that are beyond first line because our drugs have toxicities and we want participants to have recovered before they get the experimental treatment. Certain things are not going to recover like neuropathy from Oxaliplatin. So typically, studies will allow that. It bugs me sometimes when they'll say they won't allow grade two neuropathy. And it's like, well, if the investigational drug doesn't cause neuropathy, why are we restricting that? But they'll typically allow some degree of neuropathy or hair loss. But other things they want to have recovered, especially LONSURF TAS-102, it is myelosuppressive. So you take the treatment for two weeks, you have the two weeks off to allow the bone marrow to recover. So that drug does need that washout to make sure that the blood counts have recovered. Regorafenib wouldn't have such an effect on the blood counts, but could have high blood pressure, Hanford syndrome. So there will be a washout period.

Used to be every study said four weeks since your last anti-cancer treatment, but I'm seeing now newer studies that they are... Sometimes they'll even saying two weeks since the last chemo or they'll allow

two weeks since the last biologic treatment. Typically, it's two weeks since radiation, so may not be such a long washout.

Zac Getty:

Thank you. I do have a fairly specific question and I will ask it on this webinar. I do just want to point out to attendees that we can't give medical advice or anything like that. So I do like to practice questions like that with that disclaimer. "My wife has stage four CRC and we have found a trial for one of her cancer mutations, which is KRAS G12D. However, when looking at her garden or foundation results, she has a lot of different mutations. How do I know this specific inhibitor would work as it only blocks one specific mutation and likely not the other ones?"

Smitha Krishnamurthi, MD:

Such a great question and I'm really glad that was asked because we didn't talk about tumor genotyping or next generation sequencing, but especially for our patients metastatic disease, that's very important, to try to select the trials just as the questioner is asking. So how can we be more about finding a study that's more likely to work against this cancer? So while there'll be a list of mutations, it's important to discuss with the treating doctor which mutations are most important. And usually, when there's a KRAS mutation, it's an oncogene, it drives cancer, it's usually driving the cancer, but it would be important to look at the whole report to make sure that's the most important one.

Zac Getty:

Excellent, thank you. And I would like to take this opportunity to just touch briefly on the importance of understanding and knowing your biomarkers when you start looking for trials. I would assume that's probably a pretty integral part of knowing whether or not you're going to be eligible for a particular trial or not. Is that right?

Smitha Krishnamurthi, MD:

Absolutely. Yeah. With many treatments, they're targeted treatments like treatments that target HER2 or BRAF V600E, or now there are studies of KRAS inhibitors. And so it's super important everybody should be having next generation sequencing done, everybody with advanced disease so that we can give them the appropriate treatment because if somebody has a RAS mutation, we don't want to be using EGFR antibodies like cetuximab and panitumumab because they won't work. And also, for clinical trials, very helpful to navigate to the right trial.

Zac Getty:

Sure. All right, thank you. Got a few more questions. I'll just ask it. Finding trials in the UK seems very difficult. Do trials come up often or not so much there?

Smitha Krishnamurthi, MD:

Oh, I am sorry, I'm not so familiar with the number of trials there, but typically trials in the UK would also be on clinicaltrials.gov. Typically, those are worldwide listings. So one could use that to find studies. And I think, like here, it would be a matter of going to the referral center, like a busy university would be most likely to have trials.

Zac Getty:

Okay, thank you. A question about expenses, are trial expenses covered by insurance?

Smitha Krishnamurthi, MD:

This is a little tricky in that if you ask your insurance and say, "I'm going to go on a trial. Will you cover the costs?" many times people will be told no. And I think it's just a routine answer that's just given. Like no, we don't cover clinical trials, but the fact is that there are laws in the US that they have to cover the routine care costs of trials. So typically, when enrolling on a study, the routine aspects of the care, like getting a CAT scan every two months, seeing a doctor maybe every two weeks, having blood work for safety reasons every two weeks would be considered standard of care and would be billed to the insurance. But purely research-related aspects like the investigational drug, research-related blood tests, EKGs, those biopsies would be covered by the study. So there really shouldn't be extra cost to somebody for enrolling on a trial. And of course, like we mentioned, you might have to travel for a trial, and so definitely ask if there could be some reimbursement for the travel costs.

Zac Getty:

Sure. Okay. I got another question here and I think it's a good question, but I'm going to ask a lead-in question just to help set this. Will patients receive a placebo in a treatment trial?

Smitha Krishnamurthi, MD:

A placebo would only be given if there were in a couple situations. So if everybody's getting, say a study where it's a randomization between standard of care treatment versus standard of care plus an investigational drug, they might include a placebo to be given with the standard of care. So it could be standard care plus a placebo versus standard of care plus the investigational drug. Say the standard of care is IV and the investigational drug is a pill, they might give the standard of care arm a placebo pill so that nobody knows whether they're getting the investigational pill or not, but everybody's getting the standard of care treatment. That would be ethical. And the benefit of that kind of a study is that, especially if it's double-blind, the doctor also doesn't know whether the patient's getting the placebo or investigational drug is that it's more objective in terms of ascribing side effects or benefits of the study drug because we might tend to think, oh, it's working better if we know the person's on the study. So this is a more objective way of collecting the data. But again, the placebo would only be given on top of standard of care.

The other situation would be if it's a setting where there is no standard of care option left. So basically, it could be a randomization to getting the investigational drug versus a placebo or no treatment to see if the drug is having any activity at all.

Zac Getty:

Excellent, thank you. And so that kind of ties in a little bit to this question that was asked is, how do you determine or educate the patient if the patient should receive the approved existing treatment or the experimental treatment?

Smitha Krishnamurthi, MD:

Yeah, it's a very important discussion. I think we talk about treatment options. I typically talk about, okay, what's the standard treatment option? Say it's like we're starting off treatment or adjuvant treatment, talk about what's the risk of the cancer coming back, what are the standard treatment options, why should you consider this, what's the benefit, what are the risks because there are different choices. And then, okay, now that we've talked about all that, there's a clinical trial I'd also like you to

consider and then we build upon that information with, well, this is why the trial's being done, because there's still a significant risk of recurrence with standard and this approach may reduce that or this approach may be less toxic. So I think it's important to explain the standard of care first and then discuss the trial.

Zac Getty:

All right, thank you. I do want to be respectful of your time. We've got about five minutes left. I have one more question in the Q&A panel, which thank you, [inaudible 00:54:05], everybody viewing this for asking your questions. This is another fairly specific question. How do you stage your trials to try to have options as long as possible? So as an example, is it better to start with a specific mutation like KRAS G12D or pan mutation, pan KRAS, or maybe immunotherapy and then, I'm unfamiliar with this BOT/BAL, B-O-T, slash, B-A-L? If you don't have access to trial, what is the best way to access a compassionate program?

Smitha Krishnamurthi, MD:

Yeah, that's a complex question, but a good one of course. I guess it's very much dependent on what are the trials that are available that you're considering because it's possible that a person could go on one trial and then burn their bridge for another one. But you can only answer this question if you have some studies in mind and you know what's out there, what's available, and it's like I could go on this one or this one or this one, then you definitely want to look and go through it with the doctor in terms of what's the best approach to get the most treatment options.

In terms of what if you just can't get a drug, like BOT/BAL is given as the example, it's showing some efficacy in the current studies, and so there's a lot of interest in it. And actually, one of my patients told me that they do have a compassionate use program, so I love learning from my patients and I think there's a lot to learn from online forums and people sharing information because that wasn't widely publicized. But then I reached out to the company Medical Science Liaison who told me, "Yeah, we do have a process for that." So I'm going to try it out and see how that goes. We haven't finished it yet. But could inquire is a compassionate use available and then it requires the doctor contacting the company to ask.

Zac Getty:

All right, thank you so much. I appreciate you taking a whack at some of these complex multi-part questions. I appreciate you.

I do want to start wrapping us up just to be respectful of your time. I do have a couple of things that I want to just touch on from Fight CRC's perspective. We do produce a variety of printed and digital resources. Specifically, our clinical trials brochure's available. It covers important information about colorectal clinical trials from what to expect when enrolling in a trial to a list of questions you should be sure to discuss with your provider. A lot of the material we have covered in this webinar today, so thank you, but it's always good to have a little bit of a physical reference in hand. So if you'd like this brochure or any of the other materials that we offer, please feel free to email me directly, zac@fightcrc.org. And that's Z-A-C is how I spell my first name.

We also offer, as mentioned earlier, our clinical trial finder. This is hand curated by trained advocates here at Fight CRC and we use clinicaltrials.gov and curate trials specifically for colorectal cancer. So it's a great tool. It's free to use. You can find trials that are open to recruitment based on phase, based on drugs that have been used, location, countries. It's pretty broad and covers a lot. I do want to note that it is specifically right now for patients with stage four disease that either have the MSI high biomarker or

the microsatellite stable status. So if you're interested in looking for a trial and you fit those criteria, please visit our website.

And then, as of yesterday, I know I mentioned the Community of Champions app, as of yesterday, we launched Clinical Trials School in our app. It is a great interactive tool to test your knowledge about clinical trials and see what you've learned, see what there is left to learn. It's really a broad topic, so it's a great place to start if you're interested in learning more. Like I said, you can access that app through our website or on the iTunes store or the Google Play Android store.

I do want to take a moment to thank Dr. Krishnamurthi For volunteering her time today and doing such a great job answering all of our questions. Thank you so very much. I would also like to thank our sponsors, Agenis, Merck, Maradi and Takeda for supporting this webinar and our general clinical trials educational efforts.

Dr. Krishnamurthi, thank you so very much for taking the time out of your day-to-day to join us. I really appreciate it.

Smitha Krishnamurthi, MD:

Oh, it was my pleasure and honor, and I love the opportunity to talk about clinical trials and we have great questions. I thank everyone for attending.

Zac Getty:

Thank you so much. I do like to end every webinar with just our mission statement. Fight Colorectal Cancer mission is we fight to cure colorectal cancer and serve as relentless champions of hope. We're all affected by this disease through informed patient support, impactful policy change and breakthrough research endeavors. Thank you to everyone who took the time to join us today. I appreciate it. And Smitha, thank you again so much for joining us. Have a great day.