Understanding the Nuances of Clinical Research

Clinical trials play a major role in the advancement of scientific research. However, people have several misconceptions and are unclear about where to start when it comes to participating in a clinical trial. We are talking to Dr. Emma A. Meagher, Professor, Medicine and Pharmacology, Vice Dean, Perelman School of Medicine, University of Pennsylvania and VP of University of Pennsylvania Health System, about the basics of clinical research, its importance for medicine and public health thereby clarifying related misapprehensions. The discussion will also touch upon the effect of the pandemic and how the clinical research field continues to evolve.

Full Transcript:

Priya Menon: Hello, and welcome to CureTalks. This is Priya Menon your host. Today on CureTalks we are discussing the nuances of clinical research to help participants understand them better. And we have with us Dr. Emma A. Meagher is Professor of Medicine and Pharmacology at the Perelman school of Medicine at the University of Pennsylvania. She's also Vice Dean and Chief Clinical Research Officer and oversees the institutions clinical research infrastructure and its portfolio and sets the strategy for Penn Medicine's clinical research enterprise. Welcome to CureTalks Dr. Meagher, it's our pleasure to have you.

Dr. Emma A. Meagher: Thank you so much for having me.

Priya Menon: Dr. Meagher it's been a very different and difficult last two years with the pandemic and clinical research has been evolving. I would like us to take a step back and go back to the basics to understand clinical research and clinical trials. And so, my first question for today is what is the significance of clinical research to medicine and public health?

Dr. Emma A. Meagher: Yeah, so great question, and I'm probably to give it full justice will take an hour to answer. So, let me give you the cliff notes. Yes, so nearly every way in which we diagnose, treat, cure and prevent disease, came to clinical practice from research. And so, everything starts out with a question, we need to evaluate whether what we think to be true is actually true. And we need to evaluate that in the people in whom we would want to provide that treatment, that diagnostic, that prevention or that cure. So, clinical research is absolutely fundamental to how we advance our approach to the care of patients today.

Priya Menon: So that's a very simple way to explain it and I'm sure like many of us many people who are watching us would feel that wow, clinical research is great. But I guess just they would say it's just not for me. And Dr. Meagher this is a sentiment I'm sure you also heard a lot and ____ quite a bit of it. So, it'll be great if you can talk a little bit about how trials are conducted and why people should consider participating in them?

Dr. Emma A. Meagher: Yeah, so I'm happy to answer that question and you're 100% correct that there is often a disconnect between people's level of interest or people's recognition that clinical research is important and their own individual interests in participating. I think a lot of them is born out of fear that there are concerns that if they enter into any type of clinical research project, not just clinical trial that they are in some way going to be experimented upon and so let me try and dispel some of the concerns. I recognized that I won't be successful in dispelling all of them. But the first thing is and here I will keep my comments focused on clinical trials. Before clinical trial is conducted a lot of research has taken place beforehand and usually in animals to test how do the drug work, where the drug goes in the body, what the effect of the drug is on the body, both good effects, as well as bad effects to try and understand the safe doses in animals. And then before it goes into humans, it undergoes extensive review by regulatory bodies, in the US. that's called the FDA. Every country has its own similar version of the FDA that reviews the safety and the efficacy

profile of the drug that is going to be testing. And the dose that is the dose of the drug that is used in humans when the first clinical trial is done, is the lowest of lowest possible doses. So, low that you may not see any efficacy signal at all. So, we are very, very much on the side of caution and the purpose of that first trial and the second trial in humans is to very, very, very slowly increase the dose of the drug and to measure the safety. And so, when a person let's say I come along, and I'm interested in possibly participating in a trial. One of the things that I want to do is to read the informed consent document to truly understand what I'm signing for and there's a key part of the informed consent document that is consistent across all trials, no matter what country that they are conducted in and that is, I always have the freedom to exit. If at any point after I say, yes, I want to change my mind and say, no, I absolutely can do that in a way that does not jeopardize my care whatsoever. So, there's sort of some fundamental principles by clinical trials. The next thing is to realize that the level of observation and oversight of patients who are in clinical trials is far far higher than the level of oversight if you're receiving care, so imagine you've got a diagnosis of high blood pressure and you go to your doctor and that doctor prescribes you a blood pressure pill. The likelihood is that you won't see that doctor for like two months afterwards. If you are in a clinical trial, you would likely be seen by the doctor a week later, two weeks later, four weeks later, eight weeks later, ten Weeks Later, twelve weeks later. So that level of frequency of observations all with the intention to ensure that the research participant is safe. So, that level of care that we are obligated to provide to our research participants is next level in comparison to what routine care would look like. And it is appropriate because the purpose of the trial is to try and understand the drug and in doing so make sure that we keep participants safe. The last point I would make is that for many of the trials that are being done today, patients have exhausted all of the available approved therapies. So, there are no other options and particularly in the cancer world where the family and the patient are at their wit's end. They want to find something that is potentially new and cutting edge. And in that case, we very much think of clinical trials, as being an extension of clinical care because the options there are either saying there's nothing else available, I'm really really, sorry or whether there's actually a possibility of an experimental drug it does come with some risk, but it could also provide you with additional efficacy or benefit for the treatment of your condition.

Priya Menon: Yes, thank you. Dr. Meagher. Actually, that was going to be my second question. The next one where I wanted to explore the many misconceptions about trial participation like you just mentioned now and we have seen that status actually say that 80% of medical research is delayed or canceled due to difficulty in enrolling participants. And I'm sure others all these misconceptions about trial participation play a big role in people not enrolling up for the trials. And you did mention the consent, the informed consent process, which is one of the most significant for any participant to actually understand everything that's going to happen in the trial. There were also some concerns, in fact, there was quite a few articles I was reading which said that many people were worried if they get a placebo Dr. Meagher and then what happens? So, what do we tell those people?

Dr. Emma A. Meagher: Yeah, Priya it's a legitimate worry here, even though when we think as scientists, when we think about research, what's central to us is we want to advance care. We want to come up with new therapies, and we also know from our experience that there's the right way to do clinical trials and the less right way to do clinical trials or less optimal way to do clinical trials. And the optimal way to do clinical trials is to have a placebo comparison group. So that either 30%, 50% will receive an inactive medication and the remainder would receive the active medication. The flipside is that the patients who sign the informed consent documents often do. So, through the lens of what I'm going to get the experimental medication and it's really important that the research team explained that that may not happen. It's also equally important to explain that unless we have a comparison group. We are unable to determine accurately that that drug has the effect that we think it has and I'm going to you use covid as an example. When the pandemic began and anybody who will be listening to this will remember the sense of fear that we had around being infected, because there were no therapies. And in fact, our ability even to diagnose the disease was very limited. So, diagnostics, lab tests to diagnose covid were very limited and so we rushed towards trying to find if there were any existing medication, so we're used to treat other disorders. Convalescent plasma was one, steroid therapy was another, immune Inhibitors were others. We did these very, very quick studies across the country, pretty uncoordinated unfortunately, and there were no placebo groups because it was such a difficult, emotional time. When a patient was admitted to the hospital with a very high prospect of dying to

offer them Placebo. I mean, it's just such a terrible position to be in. And so, we did on control trials. We didn't have placebo groups. We were unable to show to state that those drugs work because they couldn't compare them to anything. And so, it's I would say an unfortunate reality that in order to get the most robust science, the most robust data we need to have a control group and having frank conversations with research subjects to say this is how it has to be done, we understand it's like flipping a coin that you will get one versus the other. I will tell you that we're not always successful, but in that argument, patients very often come to research with yes, a degree of all truisms that they want to help science, but a bigger part is they're looking for something to help them. And that is totally understandable, and it's also understandable and their family members, who we sometimes see the participants as yes, and the family member says no way Mom, there's a 50% chance you're going to get placebo, don't do that. So, it's a huge ask. We as scientists need to and I think we do really, really respect the contributions that research subjects make to the scientific enterprise. We couldn't do research, clinical research without human subjects, participants. So, it is a fact of experimentation, it contributes to the strength of the argument, and it is not always a fact that research participants want to accept.

Priya Menon: I think I just wanted to add that there is one more misapprehension which people have, which I have read very often is about not being able to exit a trial and Dr. Meagher earlier you just made a point. So, thanks for making that. That anytime you're participating in a trial, you can change your mind. Am I right?

Dr. Emma A. Meagher: Yeah, absolutely thank you for drawing attention to that point a second time. It's really critical that the exit ramp is always there. And also, I would say for your caring physician, if you as a patient are participating in a trial being done by another scientist who is also a physician and your caring physician feels that continued participation in that trial is not in your best interest, that relationship that you have with your caring physician is critically important. It's an independent conversation for you to have with your healthcare provider as to whether staying in the trial, is it a good idea. And again, we as clinical investigators know that we know that you commissioned the beginning, that committal is reversible, a 100% reversible at any point without any adverse consequences, whatsoever. It will never impact the care that you would be provided in the medical sense of the world.

Priya Menon: Thank you, Dr. Meagher. The next question I'm just going to move on, you mentioned covid and I think we are still recovering from the after-effects, the psychological effect of having seen something that I don't think any of us would have even predicted. So, the pandemic I believe has forever changed the way the clinical research is conducted. Dr. Meagher, how have you seen it evolving in the last two years? And where is it headed?

Dr. Emma A. Meagher: Yeah, so it's a great question Priya and I'm not sure I have all of the answers the little bit about is like looking into a crystal ball. So, doing clinical trials and I'm going to speak specifically here about trials. Doing clinical trials is difficult. It requires a lot of steps, a lot of pieces. What we learned during covid was that we are adaptable as an organization we are adaptable, as people we are adaptable and most importantly, our regulators showed that they are adaptable too. And so one of the key shifts that I see that will go forward into the future is that the previous requirement that all clinical research visits occurred in person can be relaxed and this is hugely significant back to a point that you made earlier about difficulties, completing trials because of research participation is if we bring research to our patients, as opposed to our patients having to come to us for research participation, the barriers to participate are reduced. So, let's for example, go back to that example that I gave you around the hypertension study that you're seeing two weeks, four weeks. Imagine if those visits were done through Zoom calls like this, that it was remote and that the patient didn't have to find childcare, didn't have to find somebody take care of their elder relatives, didn't have to take public transportation, didn't have to take time off work. Imagine if we bought it to them. And so that's one change that I think is here to stay and I think it's the right thing I think of respects the participant's time. It respects the other aspects of regular daily life that are occurring for them. It makes it more efficient. The second is during the pandemic, not only for trial work, but also for care, we delivered medications to the home. That was a monumental shift like delivering oncology care with nurses where infusions were set up in the home, both for trials, as well as for approved medications had an

enormous impact on patients. And so, for the clinical trials that we do in sicker patient populations I think that this sort of advancement will be really noticeable. So, I think leveraging technology in general, particularly technology that allows us to communicate between one another, all members of the research team, the research participants will stay with us. I think our regulators will find a happy balance where this is permissible. I think that's going to make a huge difference. There were several others that maybe we didn't, we weren't as successful in accomplishing. So, I alluded to the multitude of trials that were done across the country by investigators. And so many of those were not helpful in determining new treatments for covid. I think in part that is because we aren't as good working as a large team. So, we're very silent. We do a research study in one place and there may be a very similar research study being done in another place and we don't compare lots of medications against each other within a particular disease state. Covid showed us that we could do that under extreme conditions of the pandemic. I am not as optimistic that we will carry them through into the future in part because that's not how the pharmaceutical industry is organised, it will be unusual for two pharmaceutical companies to be willing to compare their drugs against each other in a clinical trial where it's organized by a central resource that is not under their control. There still is a very much a profit incentive in most countries for the development of new therapeutics. So, we haven't got that piece solved. I hope that we do at some point in the future. We would have to change the government incentive schemes to be able to actually accomplish that.

Priya Menon: Thank you Dr. Meagher. While doing a little research for this session with you, I came across the concept of decentralized clinical trials. And so, it'd be great if you can give your comments on this.

Dr. Emma A. Meagher: Yeah, absolutely. So, thanks for asking that question, Priya. So, decentralized clinical trials actually was a concept that anteceded covid. And it has excellent intentions. So, and I omitted 1 other failing that we have yet to address, which I'll address here in response to this question. So, when we look at clinical trial populations, they generally exist in urban environments, associated with large academic health care centers, hospitals associated with universities and or very big clinics in urban environments. The reality is however that the patients who are afflicted by diseases exist yes in those environments, but they also exist in rural environments. They receive their care and much different single man practice type of or single person practice types of medical care environments. And so, one of the answers to why does that exists is because of how we allocate resources. So, a pharmaceutical company will come to a place like the University of Pennsylvania, but they're far less likely to go into a more rural environment and try and set up their trials. So, the concept and as a result the patients who participate are not truly reflective of the patient population of the disease and that is particularly true when we think about ethnicity and race. The vast majority of time participants in the US are caucasian. So, the concept of decentralized clinical trials is that you remove the academic medical center or the clinical center, as being the hub and you have aspects of the trial being managed outside of that center and the biggest area around which this is discussed is around the drug itself, the experimental product, or what we call the investigational product is managed. Think of Amazon and Amazon warehouse, the drug is managed in the Amazon warehouse and is shipped to the location of where all the patients are, is similar to my previous answer. Bring the research to the patient and then the trial staff also, they are going out into the community to participate in the research as well. So, it's an extra concept, it'll be interesting to see whether it gets reduced to practice.

Priya Menon: Thank you, Dr. Meagher for explaining that. We are on the topic of pandemic and the mRNA technology that was instrumental in getting the covid, vaccines ready and we are privileged, we were able to talk to Dr. Drew Weissman here on CureTalks. Dr. Meagher, what other interesting research is PENN OCR looking at currently?

Dr. Emma A. Meagher: Oh, my goodness there are so many.

Priya Menon: Maybe you can pick one or two.

Dr. Emma A. Meagher: Yeah, so let me just clarify OCR supports the faculty, OCR doesn't do the research. So let me describe a few. So, we've got an incredibly exciting clinical trial that involves uterine transplantation. That provides and I think you may have done a CureTalk or plan to do one on this topic,

provides the opportunity for women who have been unable to conceive because they don't have a uterus to participate in a trial in which a uterus is transplanted and a pregnancy is conceived after the fact that as you might imagine is such an emotional topic. And the outcome is one that is, is just so happy, so full of joy. So, that is one that we are particularly proud of our investigator team there that is not involving a pharmaceutical company, that has done, that was designed by a scientist here at Penn who we not only are pride of her accomplishments, but she is actually one of our trainees. So, we're really pleased at her productivity. We have another incredibly exciting program for the management of patients with epilepsy where we place an implantable, electrode to detect early signatures of a seizure developing and it sounds terrible, but it's like minor, minor, minor shock therapies to eradicate the evolution of the seizure and that can just have monumental improvement on the quality of life for patients. We have lots of research on the development of devices. Device to address people with cardiac valve issues, device to deliver drugs internally more slowly, slowly, diffusible drugs. One area which I think will revolutionize our treatment of type 1 Diabetes is islet cell transplantation. Islet cells are really small cells in the pancreas that tat help to regulate glucose levels and type 1 diabetes is an awful disease. And so islet cell transplantation has an extraordinary prospect for future improvement of patients with type 1 diabetes. As you might imagine Priya, I could go on and on it's hard to select just one or two, but let me just say that the University of Pennsylvania is an unbelievable place to work. And I'm going to guess that by your interactions with Maha, Tom and others, you've got that sense of energy. We are very, very fortunate to be in the position where our role is to facilitate excellent science and increase our ability to communicate to clinical research participants or potentially future participants how incredibly important our partnership with them is in order for us to be able to bring new treatments to into the future.

Priya Menon: Great. Yes, I have actually had first-hand experience with all the discussions we've been having over the years. So definitely, I kind of second that Dr. Meagher. One last question, what is your advice to a person who has been given a diagnosis? Where should he start?

Dr. Emma A. Meagher: Yeah, so I think the first thing is pursue medical care. Never jump straight to a trial. Establish a relationship with a physician or a healthcare provider I should say that you trust that you feel is knowledgeable, who understands you as well as your condition. Have a conversation about available therapies, explore those pathways and if in the unfortunate event that those pathways are not sufficient to address the diagnosis that you have, Google Google, or whatever other search engine, you like to use and start to learn about the experimental work that is being done around the country. It is extraordinary the number of contacts we get from people who just Googled whatever the condition was. The other place where patients can go to find out if there are specific trials available is to go to a government-managed website called clinicaltrials.gov. That's the website in the US and there are several websites in other countries that are organized the same way. And the purpose of that website is to try and create transparency for patients, their families, and their health care providers about potential clinical trial opportunities with novel therapies, and it's organized by disease, by disorder. So, that is a very, very useful website. And then the final suggestion I would say is to both healthcare providers as well as patients and their families who may listen to this podcast is identified the closest academic medical center, a University Hospital medical school, that has an associated health system and just in their search engine plug-in clinical trials and is likely going to bring to you to their central chemical research management office that much like OCR has a central way in which you can discover what trials are available within that institution. So, the web is our friend for sure when it comes to trying to get information about what other opportunities may be available to you, and I would say that there's one caveat there, as much as the web is helpful have a degree of circumspection that at least 50% of what you're going to see may not be totally accurate. And so, use it as your initial search and then go to the experts and the expert institutions to get more information.

Priya Menon: Thank you Dr. Meagher with that we wrap today's show. I think it is a very interesting. We talked about many misconceptions surrounding trials and what the future holds for clinical trials. So, thank you very much without volunteers' new medications can't be approved by the FDA and therefore can't reach patients. So, research matters, so start your clinical trial search today. Dr. Meagher thank you once again, we also thank the University of Pennsylvania. This talk will be available on curetalks.com. Thank you, everyone. Have a great day.