Announcer: [00:00:03] Welcome to the Science is the Best Medicine podcast with your host Dr. Abhinav Sharma. Exploring the pressing scientific and healthcare issues of our time.

Dr. Abhinav Sharma: [00:00:16] Hello everyone. Thank you for joining us today on the Science is the Best Medicine podcast. I'm your host Dr. Abhinav Sharma. Clinical trials - what are they? Who should be in it? Should you be in it? Today we're going to be talking with Dr. Eugene Braunwald, a professor from Harvard University, and arguably, if I may say so, one of the most distinguished cardiologists alive today. Dr. Braunwald will be taking us through the turns and tribulations of a clinical trial. What does it mean to be in a clinical trial? And, why these are so important for our society. Let's dive right into it.

Dr. Abhinav Sharma: [00:00:54] Dr. Braunwald, thank you very much for joining us on the podcast today. Just a little bit about yourself with regards to the audience. What exactly do you do at this point in time?

Dr. Eugene Braunwald: [00:01:04] Well, I'm a cardiologist, I'm a professor of medicine at Harvard Medical School, and I have been in cardiology for about 60 years. And, at the present time I spend most of my time in cardiovascular research and particularly in clinical trials.

Dr. Abhinav Sharma: [00:01:24] So Dr. Braunwald, you spend a lot of your time in the clinical trial world. Taking a bit of a step back, what exactly is a clinical trial?

Dr. Eugene Braunwald: [00:01:32] Well a clinical trial, it's really a scientific experiment in medicine which new treatments, or new diagnostics are studied in a very rigorous scientific way. I think that if we go back to the 1960s, medicines could get on the market with relatively little information about them. And then the Food and Drug Administration in the 1970s came up with what seems like a very simple idea: in order for a drug to be approved, it had to show both efficacy, it had to be efficacious, and you had to define what the efficaciousness was for.

Dr. Eugene Braunwald: [00:02:24] Let's say for the treatment of high blood pressure, doesn't mean that you could use that for treatment of urinary tract infection, or vice versa. In other words, there had to be a specific application and you were obliged to show that the drug was efficacious and relatively safe. Now that was required by regulation. So in clinical trials, much of what we do, not everything, but much of what we do, is to study new treatments. But they involve not only drugs, but they involve devices as well. For example, in cardiology, which is my field, we study pacemakers, and we study artificial hearts before they can be placed on the market. There are some very rigorous studies that have to be carried out. Now I think that before you can do a clinical trial it has to be approved. First of all, if it's a trial to get a therapy marketed the FDA has to approve the trial and say yes, 'if you do this and if it shows that', and 'the safety is there, then we will grant approval.'

Dr. Eugene Braunwald: [00:03:44] So they raise the bar, and the institution out of which you work has what's called an institutional review board, and their job is to see that the trial is done safely, and there is a third party involved, it's called a data safety monitoring committee, and they are a group of scientists, usually physicians, and their job is to protect the patient, and their job is to look at the trial, and to look at the trial as it is proceeding, and to give you a green light or a red light. So there are three places where these trials are under review simultaneously.

Dr. Abhinav Sharma: [00:04:34] And so one of the big challenges with regards to conducting clinical trials, especially in a way that's cost effective and pragmatic, is the difficulty in enrolling patients. What are some of the challenges in enrolling patients in these clinical trials and what are

some ways that we could potentially overcome that?

Dr. Eugene Braunwald: [00:04:54] Well I think that some of the clinical trials are very demanding of patients, they are demanding of patients time, they are not dangerous, otherwise it couldn't be done, but they may be uncomfortable, and there may be side effects of drugs. And that's what you have to learn. Not going to learn about it if you don't test it. And so sometimes people get discouraged. But there are two areas in which the clinical trials have really done very well, in two areas of medicine: one is cancer, patients come to a hospital or a cancer center and they get desperate, they say put me into a trial. So that's one community where there has been very little problem. The second is the community of HIV AIDS, and they actually push for clinical trials.

Dr. Eugene Braunwald: [00:05:53] And I think that in other areas, for example, in the study of antibiotics. And the study of drugs that affect the central nervous system, in cardiovascular, it's been somewhat more difficult.

Dr. Abhinav Sharma: [00:06:09] And so Dr. Braunwald, you mentioned some of the difficulties for patients to be enrolled in the study, but from what literature tells us just being enrolled in a clinical trial regardless of which arm you get randomized to, or whether you're receiving the active drug or placebo, you do better then if you're not in a clinical trial, is this correct?

Dr. Eugene Braunwald: [00:06:27] Absolutely. I've joked a lot and said to my own doctor, I said, when I get sick I want you to enroll me into a clinical trial and give me placebo. Now why is that? It's almost sounds like a ridiculous statement. Because patients in clinical trials are watched, and taken care of much more carefully than patients going through the system. Now I actually don't mean that I want to be treated with placebo. I said that if I were treated by a placebo, as long as I was in the trial, that's what counts. Of course the doctor would not know that I was in a placebo. There's a double blinding, the patient is blinded to whether they get an active drug or placebo. And the doctor is blinded as well. It's only after the trial is completed that people know who they are.

Dr. Abhinav Sharma: [00:07:24] And with regards to patients who are in a trial, or who are going to be in a trial, whenever I've approached them, they often get the feeling that they're guinea pigs or that they're being experimented on, is this true in that sense? Or do patients get a lot of benefit, and does society get a lot of benefit out of these trials?

Dr. Eugene Braunwald: [00:07:42] Well first of all I think society gets a lot of benefits out of experiments on guinea pigs, otherwise we wouldn't do them. But I think the idea that the term guinea pigs has a bad connotation which has a connotation of their being killed, or they are being hurt. And I think that the three rules that I've said, the three observations of the clinical trials at the present time I think should really diminish fears.

Dr. Eugene Braunwald: [00:08:11] Remember the FDA has to review the trial, whether it's ethical. Remember the institutional review board, remember the data safety monitoring committee. All three committees have to approve that this trial will provide useful information, and is safe, or as safe as can be for the patients. Now of course why do patients with cancer? Why do patients with HIV AIDS argue for clinical trials? Because these are very serious illnesses and they are desperate. And I think in my field, in the cardiovascular field, in heart failure, what a lot of people don't realize is that diagnosis of heart failure has serious implications for length of life. And I think that progress can only be made by testing new therapies, and that doesn't mean that all of them work, but I think trials are watched very carefully. And if it looks as if there are some ill effects they are stopped, or the doses changed.

Dr. Abhinav Sharma: [00:09:25] And so with regards to the results of the trial, do patients often

have access to the final result? Can they see what's going on? One thing that I've often noticed is patients are hesitant of the secrecy between what happens. Is there a big push nowadays for these results to be available to the communities that are enrolling in the trial?

Dr. Eugene Braunwald: [00:09:45] Well I think first of all you have to wait until the results of the entire trial are available, and then they're published. Once the overall trial has been published, and the doctors who actually administer the trial to the patient become unblinded, and they can and should be asked by the patient, by the subject which treatment received. So those are the steps.

Dr. Abhinav Sharma: [00:10:15] So a hypothetical scenario: if I'm enrolled in a trial, and I want to find out what arm I'm randomizing, will that really change a whole lot? Even if I did know what arm I was in?

Dr. Eugene Braunwald: [00:10:26] Well first of all you won't know until the trial is over, and you won't be taking the drug anymore by the time you know. But people do want to know, also what people want to know is was this trial or did this move the field forward? Were all these visits that are made, driving in the winter, were they worthwhile? Were they necessary? And what was the impact? So that's why people should certainly see what the overall results of the trial are. I think that by the time the results are available, I think it's useful for the patient to know what they were on. I think that we shouldn't hold back on that information. If people pursue it they'll get an answer.

Dr. Abhinav Sharma: [00:11:12] So as we wrap up this podcast here, one question that I've always wanted to ask is where do you see the future of trials going? Do you see trials being applied to a broad population of individuals, and trying to make them as easy and as simplistic, and as pragmatic as possible? Or do you see trials moving in a direction where they're very personalized, and tailored to each individual person which would be very complex potentially, and have a great degree of difficulty in executing the trial. Or is there some middle ground potentially?

Dr. Eugene Braunwald: [00:11:42] Well I think trials are moving in two different directions. One direction falls in the category of making trial more complicated, is to do determine to use trials to answer an important scientific question. For example, what is the mechanism of blood pressure elevation? It's important to know whether that blood pressure elevation, is how important is the kidney to blood pressure elevation? How important is the heart? How important are the blood vessels? And, can you distinguish between different people with high blood pressure? Whether the kidneys are at fault, the heart is at fault, the blood vessels or fault, or some combination of these. So that would be a clinical trial to advance understanding. And that's not pragmatic to make complicated measurements. A pragmatic trial is: you have two medications, and the V.A. now is doing a trial, about a million patients, and they are studying two very commonly used diuretics, Clothaladone and Hydrochlorothiazide which are taken by millions of people, and which is more effective? It's very simple to do, and you basically count bodies at the end of the trial. So you have to be sure that it's safe and it's ethically high because millions of people take both of these drugs. And the question is: if one is better than the other we should certainly know that. So that's a pragmatic trial. So those are two examples. So the trials of the future I think are going to continue to bifurcate.

Dr. Abhinav Sharma: [00:13:43] Well I think that wraps up an answer most of the questions that we've had today, in terms of any final comments that you may have with regards to clinical trials and how the public should engage with clinical trials.

Dr. Eugene Braunwald: [00:13:56] Well, we do hear occasionally of things that have gone wrong. There is no human endeavor that is 100 percent correct 100 percent of the time, but we have to be very careful not to throw the baby out with the bathwater because we are where we are in medicine

compared to a hundred years ago, there's no comparison in the way we can handle conditions such as high blood pressure that I talked about.

Dr. Eugene Braunwald: [00:14:32] Franklin Delano Roosevelt certainly got the best of medical care, but in 1945 died because there was no treatment for hypertension, and it was a whole series of clinical trials that has brought us to the point now where the big issue is let's make sure that patients take the medication, not 'is the medication effective?'. So we have gotten there and have saved gazillions of lives, and have extended life, now has everything been perfect? No, no. You know there is some risk to when we cross the street, and when something happens there, it is called to people's attention and sometimes they have to put in the new red light somewhere, and so forth. So I think that to ask for perfection in clinical trials I think is naive. But if you look at the net benefit to humankind, it's extraordinary. There are very few human activities that have done so much for people as clinical trials.

Dr. Abhinav Sharma: [00:15:40] Today in our discussion with Dr. Eugene Braunwald a couple of things really struck my attention.

Dr. Abhinav Sharma: [00:15:45] The first is that clinical trials are really important to our society. They're one of the only ways that we can tell if a drug, or device, or treatment strategy, actually has meaningful impact on the lives of patients. The second is that regardless of what arm a patient is randomized to in a clinical trial, they will do better than someone who is not in a clinical trial. Now why is that?

Dr. Abhinav Sharma: [00:16:12] Well, its most likely that these people are being seen regularly by doctors, specialists and nurses throughout the course of the trial itself. So they'll probably end up doing much better. And the third thing is that you really can't tell if a therapy is effective unless it's been through a randomized trial. You may hear a lot of things out there in the news that a particular drug or intervention has benefit, but unless it's been tested in a rigorous clinical trial, you really can't say if it's going to have any meaningful impact on your life.

Dr. Abhinav Sharma: [00:16:44] So is the clinical trial process perfect? No. But for now, it's one of the best ways that we have to really understand if drugs, devices and therapies actually have any meaningful impact on our lives. And until something better comes along, we'll have to stick with the randomized clinical trial as one of the best ways of determining what therapies actually work.

Dr. Abhinav Sharma: [00:17:06] I'm Abhinav Sharma, and I want to thank everyone who made today's episode possible. Until next time, I hope you've enjoyed today's dose of the Science is the Best Medicine podcast.

Announcer: [00:17:20] You've been listening to the Science the Best Medicine podcast with your host Dr. Abhinav Sharma. This episode is brought to you by the Duke Clinical Research Institute.