

## **Carlecast #1 – Clinical Trials**

Hello, and welcome to the inaugural Carlecast. This is a podcast dedicated to various medical issues. We will be putting these out on somewhat of a regular fashion. It is hard to say given the beginning how often we will be to do this, but we will get them out there just as often as we can.

We are going to talk about a lot of different topics in the programs to come. My hope is that we will be taking really the breadth of medicine. Everything from cancer to pediatrics, to sports medicine to just general health issues altogether. Everything we talk about is going to be with a specialist in the field so that you can be sure that the information you are getting is accurate and up to date.

We consider that there are lots of different uses for something like this. Imagine talking to your doctor about an issue and being told you know, if you forget what we have been talking about today, you can always go to this website, download a show that in ten or fifteen minutes is going to have a lot of the same information you and I just spent talking about. Also, we hope to make this a little less than totally dry so that it's a least enjoyable to listen to as time goes on.

One unique thing about this podcast as it stands today is that there are very few if any original podcasts involving the field of actual medicine. Sure, there are some repackaged radio shows, but this is the first one I have been able to find that is truly original podcast content. I kind of take pride in that.

I am Dr. David Graham. I am a medical oncologist at the Carle Clinic in Champaign-Urbana, Illinois. We are a large multi-specialty group. We look to use that multi-specialty aspect to great benefit in the weeks to come as we present more and more of these programs. I get the pleasure of serving as your host, at least here in the beginning until someone gets sick and tired of me and tells me to go take a hike. Let us get down into the topic of the day.

Control of LDL cholesterol can reduce your risk of recurrence of heart attack or stroke. Using monoclonal antibody treatment in certain women with breast cancer can cut their risk of recurrence in half or more. These are two recent examples, as of the time of this recording, of great medical advances. They are also great examples of clinical trials, and that is our topic of the day.

These are two clinical trials that have made a huge difference in the practice of medical care. They really show what a difference clinical trials or clinical experiments can bring.

What are clinical trials? Basically, it is just another way to say that these are studies to look at treatment or approaches of care. They look at real people as opposed to lab dishes, cell lines or rats. Another way to think about it is that clinical trials are how we prove something works or that one treatment is actually better than another.

When we look at clinical trials, there are basically three types, or what we call phases of clinical trials. Phase one trials are really not common. You are not going to see them in most clinics, hospitals or institutions across the country unless you happen to live very near to a large university or large medical center such as the Mayo Clinic, MD Anderson or one of those types of institutions. These trials are really looking at the newest of the new. Generally they are done in very limited situations under very specific contracts. Basically, a phase one trial most often serves to figure out just how much of a particular treatment we can give safely. The important word in this whole trial is safely.

Only a few people enter a specific phase one trial at any time. Those few people are then given a treatment and are monitored for which side effects or toxicities may have occurred. Oftentimes these people have to undergo frequent testing to really help figure out just how a drug is eliminated from the body. This can mean lots of blood tests, lots of urine tests, or something not quite as nice to think about as that. The goal of a phase one trial is to make a recommendation of a dose or particular schedule of treatment that gives you the safest outcome with the maximum amount of treatment being given.

The next most common type of clinical trial is called a phase two trial. These are the most common types of clinical trials available. A phase two trial is a way to figure out just how effective a particular drug or treatment is. In the phase one trial, we figured out how much to give. In the phase two trial, we figure out how well it works.

These are usually done at more widespread institutions. At Carle Clinic we are involved in a great number of these phase two Clinical trials in oncology, cardiology and many more areas in the times to come. Generally, the way these trials work is that 30 to 60 people enter a trial. A lot of times, because of the small number of people entered into the trial, it can be done simply at one site. Many times, if a disease is not as common, or larger

numbers are wanted to be tested, the trial can be done at many different institutions at the same time.

In these trials, everyone gets the same treatment. There is no placebo; no random assignment to which treatment you are given. Most times, these trials are looking at new drugs or a new combination of drugs and so we want the best people possible entering the trial. As a result, many times the entrance criteria for getting on one of these studies can be a little bit strict. Your kidneys have to work well; your liver has to work good. Sometimes people joke that you almost have to be able to run a four minute mile to get on one of these trials. That is because many of these types of trials are used to get drugs or treatments approved for general administration across the country. Companies or institutions want to have the best chance of that drug having a good effect.

What we look for as a result of these studies is an endpoint that is really appropriate for the disease being studied. Maybe we are looking for a drop in blood pressure. Maybe we are looking for better sugar control in diabetics. In my field, a lot of time these studies are looking for a very specific reduction in the size of a tumor; something that we can hold a ruler to and actually measure if it has gotten bigger or smaller.

Once we figure out how well something works, then we try to figure out if it is a good thing to do. Is it better than what have already? That is where we get into the option of phase three trials. Phase three trials are generally the big trials. Phase three trials are the trials that make the news as time goes on. These are the trials that have really the greatest chance to impact daily care. There are many times that doctors will look at these trials and decide that this is really going to change how I treat these groups of people.

Phase three trials are truly comparative studies. That is to say, the whole goal of a phase three trial is to decide whether this is a better way to go, or is that a better way to go. There can be different things that are looked at in a phase three trial. There can be outcomes such as survival. There can be outcomes such as control of certain side effects or diseases better than another. Many times, even if we get the same control or outcome between two different treatments, is the quality of life in one treatment better than the quality of life in another.

Usually, and many times, these are comparisons between two different treatments. There are times, there are diseases and there are situations when we honestly don't know that any treatment is worthwhile. Those are the situations where a phase three trial may actually compare doing

something, to doing nothing. That something may be undergoing a procedure. That something may be taking a medicine. Oftentimes when a phase three trial is comparing using a medicine to not using a medicine, they will make it difficult to know whether or not a patient is taking a medicine and give them something called a placebo.

In years past we used to call placebos sugar pills. That is not the best description in the world, we do not make them out of sugar any more, but we do make them in such a way that the pill looks exactly the same. You are taking pretty much exactly the same number of pills no matter if you are getting the active treatment or you are getting the placebo treatment.

In a phase three trial, it is really important that patients are randomly assigned which treatment they get. What we want to do is take doctor bias out of the whole picture so we can get a true result of what is going on. If I as a doctor, want to put a patient on a trial, and I think this treatment may be a little rough on a person; I have someone that is kind of sick sitting in my office and I say to myself, "Well, you know, they are not doing so well. I want to take the arm of the treatment that is easier for them." I would mess up the results of that study. It is going to be difficult for us to know just how effective that treatment is. We really have to make it what I call the computer equivalent of a flip of a coin as to which treatment a patient gets in a phase three trial.

To really prove that one treatment is better than another is where the statisticians get to come in to play and have a little bit of fun. You really need statistics to prove that the result you get is better than what could happen by chance alone. A standard that we use is something called a P-value of less than 0.5. All that is a statistical way of saying that the chance that this could happen simply by pure random luck is less than five times out of 100. The feeling is that if that is the case, if no more than five times out of 100 could you get that result by sheer chance, then it must mean that the result you see is real.

Now the statisticians really get to work. They have to figure out how many events, as they call them, do you look to occur on either arm of the study. How many events do you want to see not happen on one side as opposed to another? How many people are you going to have to treat on each arm to see that kind of difference in results? When the statisticians get done, usually what they tell us is that we need hundreds of people on each arm of the study. Needless to say, this becomes very difficult to get done at one institution. Most of the large phase three studies require national effort and are usually funded by such organizations as the National Institutes of

Health, the National Cancer Institute, various cardiology associations and those sorts of things.

Now wait a minute. We have done these phase two trials. We can see how effective one treatment is. We can see how effective the other treatment is on a phase two trial. Why don't we just compare the numbers between the different phase two trials? Let that tell us which is the best way to go? Unfortunately, we have fallen into that trap a few times in the past. There have been instances; particularly my favorite one to think of is Non-Hodgkin's Lymphoma.

We used to have a treatment that was standard called CHOP. It was a combination of four drugs. What we started figuring was that if four drugs were better, how about five, six, seven or eight different drugs? We came up with this whole alphabet soup of combinations of drugs. They had such great names such as m-BACOD, and ProMACE/cytaBOM which sounded just really nasty and we looked at the phase two studies on those and they looked better than CHOP and there were a number of people that were convinced that they had to better than CHOP because just look at those phase two studies.

We did a big national study. We compared CHOP to three of the best looking other regimens. Lo and behold, they all worked just as well as each other. The interesting thing was CHOP had fewer side effects than any of the rest. After all of that, CHOP was still the winner. The take home message is you really just cannot compare phase two studies and decide that one is better than the other. You need to get the phase three trial done.

So, how do these trials work? Basically, before a trial ever gets to be available through your doctor's office, before it ever gets down to an individual physician, it has to be looked at and approved by a group called the Institutional Review Board, or IRB. An IRB is an interesting thing. It has not only medical people; it has non-medical people as well. It often has attorneys. It often has religious members of the community such as priests, pastors, and just basic, average everyday walking around people.

The most important thing that the IRB does is review each study at an institution for patient safety issues. The IRB serves its biggest purpose in making sure that a study is not going to be hurting patients and that patients are fully informed as to what is going with a patient. One of the closest considerations that an IRB will give is towards a document called an Informed Consent.

The Informed Consent basically details how the study works. It details any risks or side effects a patient may go through by being involved in the study. If you are looking to be involved in a trial once it has been through the IRB and your doctor says I may have an interesting study for you to be involved in, you really should have an Informed Consent explained to you very, very carefully. You will need to sign an Informed Consent prior to entering any clinical trial.

Exactly what happens after that point really varies widely depending on the study you are involved with. Certain tests may need to be done before you enter the study. Sometimes you may have had these only a month or so earlier, but the study will require them to have been done within a certain period of time prior to you entering the study.

Now, if you have gone through the Informed Consent, and you still do not know how the study works or what happens next, you need to ask. The most important thing you can do is not hesitate to ask questions. If you go through the Informed Consent and something about the study just does not sound right to you, it does not make you comfortable, just say no. It is ok to say no to being involved in a clinical trial. It really should have no impact on the relationship between you and your physician. A doctor offers you a clinical trial in hopes of giving you interesting options in your treatment or your care, but no physician should say I am never going to see you unless you get on this trial. If that is the case, the physician probably should not see you any more any way.

That is how a person gets on to a clinical trial and how clinical trials in general work. Now, a lot of people may still have a question about how much impact can these clinical trials have in the care of patients. Certainly, we may see new drugs come out, but do a lot of these drugs have a big impact on how people do?

I suppose if I want to take a field of medicine that really shows us just how important clinical trials can be; I really have to use pediatric hematology/oncology as a good example. About 80 percent of kids with cancer get entered on the clinical trials. That is compared to about five percent of adults with cancer. What we have seen over the past 15 to 20 years is that there are now literally thousands and thousands of kids who are alive who would not have been living if we had not had these clinical trials showing us better ways to treat these kids.

There are a lot of diseases that sound really scary to parents, leukemia, sarcomas, that not that long ago were truly a death sentence for a child.

Now a child has a great chance of surviving, living and growing to be a healthy adult. None of these results could have been possible without people being willing to have their children involved in clinical trials. I can think of no more selfless act for a parent to go through.

One thing that I would like to do in a lot of these programs is once we get through the basic topic that we are looking at, is to throw in something a little fun, some sort of medical story that you may not hear through the common news, but I kind of have fun searching out and finding for you. I will be the first one to admit that these stories are not ready for prime time. These are not things that are going to impact your care in the days, weeks, months or years to come. They all tend to fall into the category of "Oh my God, is this cool," or "Do you believe this?"

Today's story was actually reported in the Australian, August 25, 2005. The headline? "Mice Regrow Hearts."

Dr. Ellen Heber-Katz, a professor of Immunology at the Wistar Institute, a U.S. Biomedical Research Center has developed a clone of Miracle Mice that regenerate amputated limbs, or damaged vital organs making them able to recover from injuries that would kill or permanently disable normal animals. They are able to re-grow heart, toes, joints and tails.

What they have done is that they have found about a dozen genes that seem to control these mice's ability to regenerate organs. They have actually amputated several different things like toes and the toes grow back, joints and all. They even took apart and used a freezing technique to freeze part of the animal's heart and the heart grew back.

What is even more interesting is that they took fetal liver cells from these animals, injected them into ordinary mice, and the ordinary mice got the same power. It persisted for six months or more after injection.

Here is where we get to have fun thinking about things. What if we were able to make this type of clone of cells in people? When someone has a heart attack, we are able to inject them with these clones of cells and help them to re-grow the damaged tissue back. Imagine the impact that could have on medical care in years to come.

That is about enough for now. I promise to keep these programs relatively short as we go along. I would not see anything going on longer than 15 or 20 minutes and right now we are at around 11 or 12 minutes here so I am keeping right under that goal.

I want to thank you for checking out this inaugural Carlecast. I promise that in the future it is not going to be just me prattling on. We are going to get some other people to listen to and as I said when we started, my job is to find the experts in the field to give you the best information that is out there.

We have lots of great ideas for future topics, but we would love to hear from you for your ideas for topics. You can email us at [carlecast@carle.com](mailto:carlecast@carle.com). I have to tell you right now, we cannot address specific patient cases, but we would be happy to look at any topics you would be interested in times to come.

Personally, I have to thank Adam Curry. Adam Curry for those who may or may not know is the person who has really spearheaded the whole notion of podcasting. He has really made it easy for me to realize just how doable this can be and really give me an image and a vision of what medical care can use, grow and podcast to in the future.

Until next time, this is Dr. David Graham from the Carle Clinic. Stay healthy!