Transcript

Welcome and Introductions

Stephanie Paul

[SLIDE 1] Welcome everyone and thank you so much for joining us today. **[SLIDE 2]** My name is Stephanie Paul, and I am the Senior Vice President of Development and Marketing at the American Parkinson Disease Association, or APDA for short. I am pleased to welcome you to this Web/ teleconference education program designed for people with Parkinson's disease (PD), care partners, family members and healthcare providers. I would like to thank Genentech for funding this important program and acknowledge their appreciation for the critical need to provide educational programs like this one to people impacted by Parkinson's disease.

APDA is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than one million Americans with Parkinson's disease live the best life possible in the face of this chronic neurological disorder. Founded in 1961, APDA has raised and invested more than $185 million to provide outstanding patient services and education programs, elevate public awareness about the disease, and support research designed to unlock the mysteries of Parkinson's that will ultimately put an end to this disease. APDA distinguishes itself as the national organization working one-on-one with the Parkinson's community to make each day better.

And now to our program. **[SLIDE 3]** We welcome our distinguished presenter today, Dr. David G. Standaert, John N. Whitaker Professor and Chair of Neurology at the University of Alabama Birmingham School of Medicine in Birmingham, Alabama. Dr. Standaert is also the Chair of APDA's Scientific Advisory Board.

Today we are delighted to have Dr. Standaert share with us the latest information about clinical trials for Parkinson's disease. After the presentation, we will open the program for questions from both telephone and Web participants. We encourage everyone on the line to complete the evaluation after the program because your feedback is instrumental in helping us plan for the future educational offerings, including teleconferences like this and other programs. You may view the materials for this program and today's slides by clicking on the Files button in the lower left-hand corner of your screen.

It is now my pleasure to introduce Dr. Standaert.

Presentation

David G. Standaert, MD, PhD

thank you, Stephanie, and I'm really pleased to have the chance to talk with everyone today about a really important topic in Parkinson's disease, which is clinical trials, the role that clinical trials play in developing new therapies and new treatments, and in our search for the cure for Parkinson's disease. This is, I think, what drives all of us at APDA and other investigators around the world. We're all searching to make things better and to move the field forward and, ultimately, to cure this disease.

clinical trials are an integral part of this. I'm sure we probably have some people out there on the line who've participated in a trial. We probably have others who've thought about participating and haven't made the decision yet. And others that are still interested or maybe want to learn a little bit more about what a trial is, what's involved in a trial, what kind of trial might I participate in? And these are some of the topics I hope to touch on today.

We'll also talk about some specific trials that are in progress. I always get a lot of these in my clinic when patients come to see me and other settings, and we'll touch on a few, although there's far too much going on out there to be comprehensive. So, really, just some highlights of what's happening.

To give you a flavor for the excitement in the field and what is going on today, **[SLIDE 4]** I do have a few disclosures here you should be aware of. I do serve as a consultant to a number of companies that are developing different therapies in Parkinson's. We're actually not going to talk about any of their trials today, but I wanted you to be aware that I do work as a consultant in a part-time role with some of these companies. I don't own any equity in any of these companies, and I don't participate in paid speaking of any kind.

[SLIDE 5] So what is a clinical trial? This is a topic that I think is something that many of my patients ask me about. They've heard this phrase clinical trial. What does this mean to be in a clinical trial? And I think one thing to remember about this is that there are different kinds of trials, and these have different purposes in our efforts to understand Parkinson's and to find new treatments.

The first group of trials and one kind of trial is what we would call an observational study. It's called observational because these are studies that don't involve a treatment. We're really just observing what is happening to people with Parkinson's disease and sometimes to controls, controls meaning otherwise healthy people who are similar in age and gender to those we're studying. And so, the purposes of an observational study are to learn. One thing an observational study can do is help you determine what the cause of a disease or condition is. For example, if you have questions about whether Parkinson's is found more often in one country than another, you might do an observational study. That kind of study has been done. Parkinson's is a worldwide problem and is found in every country, but that is knowledge that was gained through an observational study.

You might also ask questions about whether it's more common, for example, in men than in women? It actually is more common in men than in women. This has been established through observational studies. And that's also how we've learned a lot about the nature of the disease, the age of onset, how it progresses over time. And these things really fall into this category of the natural history of a

disease. What is the normal average course of Parkinson's? Now, of course, no one is actually average. I do get this question all the time. Patients will ask me, "Have you ever seen anyone exactly like me before?" And I've seen many thousands of patients with Parkinson's disease, but I've never seen two that are exactly the same. Everyone is different and everyone has unique aspects, but there are more general questions about, what's the duration of the disease? How quickly can I expect these symptoms to change? What are the symptoms that might develop over time? And these are really questions about what we call natural history of a disease. And so that's a critical thing to know as well. If you want to change the outcome, you first have to know what the normal course of the condition is.

And then you get the questions about the long-term outcomes of treatments. So, there are many treatments for Parkinson's. We're fortunate that we have so many in the field, but many of the studies that are done in clinical trials are short term. If you really want to know what happens in five years or 10 years, for example, after deep brain stimulation (DBS) or some other treatment of this kind. These are also observational studies. So the key to an observational study is we're not imposing a treatment. These are patients who are experiencing their condition, they're being treated by their physicians, and we are collecting information about them to find out these features of what is the cause, what is the natural history, and what is the long-term outcome. So that's one kind of clinical trial.

The other is an interventional study. So, in an interventional study, this is a study where we actually impose a new treatment or something to change the course of the disease. Might be a new drug, might be an exercise regimen. It might be something else, a device, a surgery, something like this, some kind of new therapy or treatment. And we give this to people and ask the question of, how does this affect the outcome? It's usually done sequentially, and we'll talk about the sequences and steps in a minute of the different aspects of a trial. But you may be interested early on in safety. Obviously, that's very important. We want our treatments to be safe. And once you know it's safe, then is it effective, and can you say anything about the efficacy of this intervention for the symptoms that you're after?

These interventional studies, unlike the observational ones, often involve a placebo control, meaning a treatment that is inactive. This is really the gold standard for establishing effectiveness. And I get the question a lot of, "Why do we need a placebo? Can't we just try this treatment and see if it works?" The truth in Parkinson's is that the mind is a very powerful treatment in itself as well, and if you do these treatments without a control, you can often be misled. We will find people that participate in a trial, often being in a trial is a very positive experience. You get a lot of time and attention from the clinicians and many people will report, at least for a little while, that their symptoms get better simply from participating in the trial. It's actually a good reason to get involved. Actually, people feel this is a positive experience. But that may cloud the question of whether the treatment is actually working. And to be really sure, you need the placebo control so that neither the patient nor the doctor really knows whether they're getting the active treatment or the placebo. And this is the only way you can be absolutely certain that a new treatment is effective. And it is usually required by most regulatory agencies before a new trial or a new treatment is approved.

[SLIDE 6] So, what about these phases of interventional trials? You always hear about different phases of trial. What are the phases of a clinical trial? The earliest phase is actually the preclinical phase. So, this is when new treatments are tested not in humans but usually in some kind of model system. Usually an animal model. Sometimes a cell model, something like this. This is where we get the basic information about, well, does this new treatment have any possibility of working? Does it affect the symptom we're after? In Parkinson's one symptom we're often after is replacing the dopamine. Like missing dopamine is one of the major features of Parkinson's, so does this drug do that? And we can test that in animal models.

There's also a very critical aspect of safety testing that goes on before a drug is ever given to a human to ask, is this drug toxic? We hope not, but we certainly like to find that out before it gets to treatment in humans. So, there's a safety and efficacy component that comes before any person is actually treated with a new drug, and this is an important aspect of it.

Once you've crossed that line, you get to this question of, all right, so this drug appears in these model systems to be safe and effective; how do we go about testing this in humans? And so phase I is the earliest stage of testing in a human patient. Often this is the first time a human has ever received this particular treatment. This may be a chemical that the scientists had discovered in the laboratory. Looks like it works, but at some point, we have to bring this and be the first human to be exposed to this chemical. Obviously, we want to do this very carefully. Usually, it's done for short term. Sometimes there's only just one dose. We use a very small amount. Small numbers of people are involved. These are usually all volunteers. And oftentimes they are normal volunteers. They're just healthy people who've agreed to be the first person to try this drug. And a lot of information is collected about them. There's a very careful search for any evidence of toxicity or side effects, and this is a critical step.

If that drug passes that, it often moves on to phase II. And phase II I think of as first in patient, so if we're talking about Parkinson's disease, which we are today, this would be the first phase where a new treatment was given to a patient with Parkinson's. And the questions we would ask in phase II are, "Well, what is the right dose? How do you know that? Well, you start very low typically and work your way up gradually till you've reached a point where you have some evidence that the drug is doing what you want it to do. You're also very interested in safety. Does this appear to be safe? Does it cause any problems in people with Parkinson's that maybe you didn't see in normal volunteers in phase I? So phase II, again, these are typically small studies. It's a few dozen people, maybe 100. Small numbers of people involved in these, but it's a very critical phase.

And if it's successful at that level, you move on to a phase III study. A phase III is the definitive test of whether something works. And in phase III, you're often talking about a lot of patients. In Parkinson's disease, it's not unusual to see a study that might involve 1,000 Parkinson's patients in a phase III study. Almost always these are blinded, meaning there is a placebo and neither the patient nor the investigator will know which patients are getting the active therapy and which are getting the placebo. And this is the way that we can be sure that any effects we see really are related to the active drug and not the placebo.

And these take a while. A phase III study can take a year or two or maybe three from beginning to end. So when you think about 1,000 people being involved for two or three years, there's a lot of work and time that comes both from the investigators and from the patients who've agreed to participate. So this is a critical phase.

And then, if you're lucky and it's surpassed all of these phases, this is the phase where you'll actually get approval in the U.S. from the FDA (Food and Drug Administration) and other countries from their regulatory agencies to actually bring this to market and make it available in the drugstore to patients who have Parkinson's.

Beyond this, there is a so-called phase IV. This is often a phase where the drug is approved. It's available through pharmacies, other places, but we have additional questions. "Well, what happens if we take this for a really long time? What happens if we take this for years?" Or, "What if we use it in a new situation that wasn't really thought about early on?" And so these are the major phases.

The other thing you'll notice is I've drawn this as an upside down pyramid over here on the right. And the reason for that is that not every drug makes it through every phase. Many drugs are considered in the preclinical phase, a smaller number make it to phase I and of the ones in Phase I, even smaller numbers make it to phase II. And then the numbers that make it out of phase III and to approval is even smaller. Many times, the estimate is for every 1,000 treatments that are considered in preclinical, maybe one will actually make it to approval because they fall out or don't succeed in these pathways along the way. So, it is like a funnel in a sense that we're taking a lot of ideas and, ultimately, hoping that a few of these are both safe and effective, which is what we're searching for. So these are the phases of clinical trials.

[SLIDE 7] Now, how many clinical trials are there in Parkinson's disease? There are a lot of clinical trials in Parkinson's disease. I'll show you this map. This comes from a website called clinicaltrials.gov. It's run by the U.S. government, which is an excellent source. And we'll talk more about clinicaltrials.gov. But they provide this map which shows the number of clinical trials in Parkinson's worldwide today. And as you can see, there are over 1,000 in the United States, 160 in Canada, another 776 in Europe, and almost every country in the world has a fair number of trials in Parkinson's disease going on. So there's a lot of activity in this space. A lot of different strategies and approaches are being tested, which really reflects the worldwide prevalence of Parkinson's. This is a global, worldwide problem that we're all trying to tackle here.

So this is the world view of clinical trials in Parkinson's. How can you learn more about this? And we'll give you some resources at the end. **[SLIDE 8]** But much of the definitive information comes from this website called clinicaltrials.gov. And this is available to anyone; you can go on this and take a look at this and search for trials. Now it's a little bit complicated sometimes. Sometimes the language is complex, and I'll show you some other resources at the end that may be a little simpler to use. But in terms of a definitive, comprehensive source for clinical trials, I would say this website is really it. As you may be able to read there, it says that they're currently listing 320,474 research studies in 50 states and 209 countries. And this is for every condition that they consider here.

What about trials in the U.S. for Parkinson's disease? Well, if you go to this website, you'll find that they have 307 currently active clinical trials in Parkinson's disease. There are 214 of those which are

interventional. And of those 214, 141 are open to recruitment. They're looking for new patients. So quite a lot going on there. And about 70 are observational and are open to recruitment. So there are at least 210 trials out there today that are looking for patients with Parkinson's to be part of them. And I hope that some people on the call will think about these opportunities, and I'll tell you how to find one that may be close to your home, which, of course, would be important. But there's a great need and it is important that people with Parkinson's participate in this. We can't solve this problem alone. We really need people to step up and be part of this process if we want to find a cure.

[SLIDE 9] All right, so let me talk a little bit about some current clinical trials in Parkinson's. What's out there? What's exciting? What do I think may change the field here? And I'm going to just hit a few highlights. I'm sure that I will leave out one that you may be interested in. Hopefully, we'll have some time for questions, and I'm happy to try and answer any questions about any trial I know about. There are quite a few, but I'm going to try and hit some of the highlights here.

So, on the interventional side, some current interventional trials that I think are interesting or important. I get a lot of questions about a trial called NILO-PD (nilotinib in Parkinson's disease). This is a trial run by the Parkinson's Study Group, which was looking at nilotinib, and we'll look at some of the details of that.

Synuclein antibodies, this is a very hot topic. There are several big trials of this going on, and I'll talk to you a little bit about the status of those and where those are going.

What about new technologies? Deep brain stimulation, or DBS, has been around for quite a long time, but there's some new technologies, there's new devices, there's new electrodes, there's new ways of doing that. There's also a technique called focused ultrasound, which is getting very interesting. Another way of really performing surgery on the brain to treat Parkinson's. And we'll talk about exercise. Exercise, I think most experts in Parkinson's recommend exercise for Parkinson's disease, but we have a lot of questions about, well, what kind of exercise? How much exercise? What's the best exercise for Parkinson's? And we don't actually know all those answers, and that's why we have trials which are trying to figure that out.

On the observational side, there are also some important trials going on. One big area is inflammation. What's the role of inflammation in the immune system in Parkinson's, and I'll talk a little bit about some work we're doing here funded by NIH (National Institutes of Health) on this topic.

Another big area is biomarkers. What are the markers of Parkinson's? Can we measure something in the blood or somewhere else that tells us about the state of Parkinson's and how it's responding to treatment?

And, lastly, what about the outcomes? What are the long-term results of Parkinson's? What are the things that change over time and the treatments that we really should be thinking about in the long run? So, we'll hit on all of these different topics as we talk today about some clinical trials.

[SLIDE 10] Now one thing I wanted to say about trials before we start to dig into the details of this is that it is true that trials are generally posted on clinicaltrials.gov when they begin. The reason for that is that most of the agencies that fund trials require this, and also, the journals that are going to publish

the results require that the trials go up on clinicaltrials.gov. And I think it's an important step for all of us. This was to shine a light for the public on what's being done in clinical trials. Trials are possible only because people like you out there on the phone agree to be part of them or participate. And I think it's important that we all understand what trials are being done, who's doing them, and ultimately, what are the outcomes of these trials. And so this mechanism is a very valuable one which lets us see what trials are going on, what's happening and, ultimately, what the outcome of these are because they do post results on this as well.

But one thing to know about is that when trials are going on, it's usually really hard to find out what the results are so far. I get this question all the time. "Well, this trial is already started. Do you know anything yet? What's happened to the first people who were in this? Can you tell me what's going on here so I can decide whether I want to get involved or not?" And it's really hard to find that out. And that's on purpose. There's two reasons for that. One is that if we started releasing results of a trial halfway through, that's obviously going to change the way it goes. It's going to change whether people get involved, it's going to change who gets involved, and it may even change our impression of the results. So, generally, these interventional trials don't release their results until they're done. So, when they're running and people are participating, and data is being collected, generally speaking, you're not going to find out what the result is until it's done, everyone's finished, and it closes out.

The other reason is a very practical one, is that these are all being done by companies. And if partial results of their trials are released, this could obviously affect people's decisions to invest or not, invest in these companies, and actually has resulted in violation of insider trading laws, which certainly none of us want to get involved with. So, it's another reason that the information regarding these trials is usually kept confidential until the trial is finished, and then it's released to the public through clinicaltrials.gov and other forums. But this really explains why it's hard to answer that question of, "Well, the trial's going on. Can't you tell me what the early outcome is?" Generally speaking, you can't, really. You can't find that out. And I know that's a frustration to a number of people, but it's really necessary to protect the integrity of the result that we get.

And I did want to say today that everything we're going to talk about today is public information and mostly comes from clinicaltrials.gov. And I've tried to put at the bottom of the screen here on the right, as you'll see, a number which actually links back to the clinicaltrials.gov website. So, you can download these slides at the end and go pull up the exact Web pages I pulled these comments from, if you'd like more information.

[SLIDE 11] All right, so let's talk about NILO-PD. So this is nilotinib. And nilotinib is a drug that is approved to treat leukemia, so this is a cancer chemotherapy drug that has been on the market for a number of years and is successfully used to treat leukemia. What's interesting about it in terms of Parkinson's is that studies in animal models suggested that nilotinib could actually slow degeneration of dopamine neurons. And there's quite a lot known about the pathway through which this works. There is a particular enzyme which seems to be overactive in Parkinson's, and this drug targets that enzyme. It shuts it down. And so there was a lot of good science that went into the idea that this might be useful in preventing Parkinson's. Turned out it looked like it was in animal models in these preclinical studies.

There was an early study that suggested, in fact, efficacy. Now this was really an open-label study that was done early on. And so NILO-PD is now a phase II study. So, phase II, it's one of the first studies to really do placebo-controlled study in Parkinson's disease. Its main goals are to look at safety and tolerability of nilotinib in PD. The sponsors of this NILO-PD study are Northwestern, Rochester, Iowa Universities, as well as the Michael J. Fox Foundation. And this is being done in two cohorts. So there's a cohort one. These are people who've had Parkinson's disease more than five years, and they're getting either nilotinib or placebo for about eight-and-a-half months. And they will then ask whether this has changed the features of the disease. It is placebo-controlled and its double blind, so neither the patients nor the investigator knows who's on placebo or nilotinib. And then what's planned is this second cohort. So, if the first one is successful, meaning it's safe and there's some suggestion of efficacy, there'll be a second cohort where they'll go after early Parkinson's and do a longer study of 14-and-a-half months.

So where is this at right now? The cohort one is all enrolled. All of those patients are on treatment or have finished treatment. And essentially the study is waiting on the results, the analysis of cohort one. Of course, you can't analyze it till the last patient takes the last dose. Then all the data can be brought together, and they will look at the result of that before beginning cohort two. So, you haven't heard about this in a little while and that's because it's in a bit of a pause as this cohort one finishes. But I think we'll learn more soon about what happened with cohort one and where they're going with cohort two. So that's the status of NILO-PD.

[SLIDE 12] What about synuclein antibodies? This is a very hot area. It has recently gathered some additional interest from work in Alzheimer's disease, which is pursuing a similar strategy. So this really comes from preclinical studies which shows that alpha-synuclein, which is a protein, builds up in Parkinson's brain. I think this is a very common feature found in almost every case of Parkinson's disease. There's too much alpha-synuclein. It's built up, it's clumped up, it's misfolded and it's abnormal. And it seems to be one of the key drivers of Parkinson's disease.

So the obvious question is, "Well, if this protein is a problem, let's take it out of there and see what happens." So these synuclein antibodies are strategies to do just that. These are antibodies which have been produced which can be given by vein, so they're given as an infusion typically once a month. And what they do is they pull the abnormal synuclein out of the brain and clear it. That might sound a little bit science fictionish, but it does work in animal models. So in rodents with excess synuclein in the brain, you can remove it with this kind of strategy.

As I mentioned, this is also being done in Alzheimer's disease. So in Alzheimer's a different protein builds up, a protein called amyloid, and antibodies have been developed to pull amyloid out of the brain. And you may have noticed recently in the news there's been talk about a particular Alzheimer's antibody called aducanumab which may have a signal of a positive effect. And the company is interested in trying to bring that to market. So there's progress being made in the Alzheimer's front, the same strategy being used in Parkinson's.

What's happening with these studies? Really, there are two large ones. One is this top one from Biogen. Has the kind of unpoetic name of BIIBO54 is the name of the drug. I'm sure they'll give it a better name if it's successful. The study is called SPARK, and this is an infusion study of a particular

antibody in Parkinson's disease. And then there's another one. This study is called PASADENA, sponsored by Roche. Different antibody, but very similar concept. Can we use these antibodies to remove the abnormal protein from the brain? So, both of these are going on. They're both phase II, and the main outcome of these is safety. So these studies are really intended to look at the safety. They're not really large enough to prove definitively that these are effective, but, hopefully, we'll see some evidence of that. Both are fully enrolled, so all the patients are already in both of these studies and they're both expected to provide some results in early 2021. They're both over a year along each, so it takes a while to get everyone in, treat them for a year; get everyone out, gather all the data. But early 2021, we should get information on these. And I think that's going to be very pivotal to the field.

[SLIDE 13] All right, what about new technologies? Are there some new technologies for treating Parkinson's that we should be thinking about? Well, one of them is new ways to deliver deep brain stimulation. Deep brain stimulation is a surgical technique where we put a wire in the brain and a battery in the chest, a pacemaker-like device. And this is an FDA-approved treatment to treat Parkinson's disease. But the device we've been using is really a very simple one. It's actually adapted from pacemaker technology, and there is a whole new generation of smarter and more sophisticated deep brain stimulator technologies. A lot of these are being supported by the NIH BRAIN (Brain Research through Advancing Innovative Neurotechnologies®) Initiative. This is a program from the NIH which is investing in new technologies and new ways of understanding the brain.

So there are a couple of big projects funded in this. One is actually here at UAB, Dr. Harrison Walker has an NIH BRAIN grant to look at directional DBS. So this uses a fancy lead. The regular DBS lead has only four contacts. These directional leads can have up to 64 different contacts on them and you can steer the current, the electricity in the brain, much more accurately than you can with the regular four contact electrodes. Of course, because you can steer it, it's now more complicated. And trying to understand how to use that, how to program it, how is it most effective, is really the goal of Dr. Walker's study.

And then a related one funded also by the NIH BRAIN Initiative is being done by Dr. Starr at the University of California, San Francisco, and this is closed-loop DBS. So, he's using a special DBS device where we can actually listen to the activity of the brain, signals that are sent from the DBS device. Some people call it the brain radio, so the wires in the brain. It's being used to treat Parkinson's, but it's also sending out a signal that lets us see what the brain is doing. And so, we can do things like look at the pattern of brain activity and change the stimulation in response to the brain activity, or in response to the movement. For example, if you're treating tremor with DBS, you might be able to have a sensor that measures the tremor, talks to the device, and adjusts the stimulation to reduce the tremor as much as possible. So, this is really sort of automating DBS. That's why it's called closed loop. You have the stimulator which is acting on the brain, and then you have something which is measuring the tremor or the movement of the patient enclosing the loop in a way that you could have automated DBS that would tune against particular symptoms. This is really sort of really exciting technology, and I hope we'll see this come to more wider use fairly soon.

What about focused ultrasound? I get a lot of questions about focused ultrasound. So this is a technique for making a lesion in the brain. So you're using an ultrasound device, focusing its energy and essentially burning a small hole in the brain. And this is an approved technique for treating

essential tremor and is now being studied for treating other symptoms of Parkinson's disease, so dyskinesia or motor fluctuations. The place they would go after would be the pallidotomy, with the pallidum, globus pallidus. And we know that making a surgical lesion in the pallidum can reduce dyskinesia and motor fluctuations. It's been done surgically before, but here you're doing it with ultrasound. It doesn't require opening the skull at all. Now the question is, is that going to be safe? Is it going to be effective? And that's what this trial is asking. So, it's an interesting new technology for surgical treatment of Parkinson's disease.

[SLIDE 14] All right, what about exercise? Let's talk a little bit about exercise trials in Parkinson's. As I said, I think most people in this field agree that exercise is important in Parkinson's and is valuable in Parkinson's patients. So there's not really a question in my mind about whether exercise is good, but there are a lot of details about this that are very important about how much exercise, how do you measure the outcome, how do you know when you've done enough exercise, who should be exercising, that we really don't have a handle on. These are the questions that these studies are going after.

So, one in particular that recently completed is something called SPARX, a study in Parkinson's disease of exercise. This is a phase II trial, and it's been completed so we can talk about the results; they were recently published. Sponsored by the University of Colorado, this used high-intensity treadmill exercise four days a week at 80 to 85% maximum heart rate for six months. That's a lot of treadmill exercise. If you're used to exercising at 80 or 85% of your maximum, it's pretty vigorous. You'll be fit and you'll be in shape after this experience, and I think that's what the participants found. They showed that it was safe for Parkinson's patients to do this, at least in a supervised environment where they had help to learn how to do this and to do this safely. It was well tolerated. And, actually, the exercise group showed less change in their Parkinson's symptoms over six months. So, the group that was not exercising over six months, there was some worsening of their condition, and the group that was exercising showed much less change.

So that's exciting. That's promising. It wasn't a big study, but they are now in the planning stages of coming back with a much bigger trial of this. And I think that'll be an important milestone because it will tell us whether this particular prescription for exercise, high-intensity treadmill, is a good one for Parkinson's patients or not. So that's the kind of question we're seeking to answer.

A few others just to mention. There's a similar exercise-dosing trial for individuals with Parkinson's disease called PDEX going on at the University of Virginia. This is a trial, again, it's asking about what's the right dose? How much exercise is good? Is one day a week enough? Probably not. Is four days a week at 85% necessary? Maybe, but we'd like to know those answers, and those are the questions these studies are after.

Another one just to mention briefly to illustrate a completely different approach is a motor training study which is using adaptive tango dancing. This is being done through the Atlanta VA, and there are several other similar ones around the country. But this is not such a vigorous exercise as treadmill, but it is trying to focus on balance and posture. And there is other evidence this is helpful, and I think this is an important step to try and define how to do this, who is it effective in, what can we expect from this kind of treatment.

[SLIDE 15] All right, what about some observational studies in Parkinson's disease? Are there some observational studies that you should be interested in or know about? And I'll cover a bit of a range here. One of them it's a local study that we're doing here. So I direct the Alabama Udall Center. This is a large Parkinson's research center that's funded by the National Institutes of Health. And we're very interested in the immune system in Parkinson's disease. This is a new hot topic, asking the question, "What does the immune system have to do with Parkinson's?" And if you went back about seven or eight years ago, most experts would say, "It has nothing to do with Parkinson's." It turns out we've learned that isn't true, that there is activation of the immune system. There is inflammation in the brain in Parkinson's. There are immune cells that are involved. And this has really raised the question of whether immune treatments, treatments that changed immune response, would be useful in Parkinson's.

To learn more about this, we're doing an observational study where we're looking at the very early stages of Parkinson's. So, these are patients who have just been diagnosed, not currently on any treatment, as well as controls. And we're doing very intensive study of the immune system. So, it's observational in the sense that there's no treatment targeted, or no therapy here. But that doesn't mean it's easy because it requires a lot of these patients. They have brain imaging with a PET (positron emission tomography) scan, they have a lumbar puncture, they have genetic studies, and they have long-term follow-up. We're about a third of the way into enrolling in that study. That's a five-year project. And we hope to learn a lot about what the state of immune activation is, and how one might use immune therapies to change the outcome of Parkinson's disease.

So, going to a little bigger study, another observational study that's very important in the field is something called the Parkinson's Progression Marker Initiative, or PPMI. There might even be some PPMI participants out there. This is a global study. It's one of the largest observational studies of early Parkinson's. Has about 1,400 participants. And they have been very involved. The study's been running for about seven or eight years now. They've collected over 25,000 biospecimens. And all of the data from the Parkinson's Progression Marker Initiative is posted on a website for investigators around the world to study. So, it's done, of course, in a way that protects the confidentiality of the patients, so it's anonymized; but you can download the data on these 1,400 participants. And that's been done more than 1.7 million times by people around the world. And so that has really crowdsourced the question of how can we understand Parkinson's disease to a lot of very talented people around the world who are producing interesting results and starting to really teach us about what are the relationships between the different features of early Parkinson's – changes in the blood, changes in behavior, changes in thinking, changes in imaging. And this is really a critically important source of information. And it will grow larger: There are plans to continue to grow this study even further.

For a really large study, I would point to Fox Insight. This is a study funded also by the Michael J. Fox Foundation. This is an online study, so this is something that anyone can do. Anyone out there could be part of this. You could do it online, you can do it from home, and, really, we're asking about the patient's experience. What is the experience of the Parkinson's patient? Today it has more than 40,000 participants who are reporting their experiences and their outcomes, and the link is there. If you'd like to click on that, you can join the study and register either as a Parkinson's patient or a control. This is going to be a really powerful study. No one's ever studied 40,000 Parkinson's patients,

and the goal is to grow this beyond 100,000, so I see this as a really important future source of information.

[SLIDE 16] All right, so how can you get involved? It's critically important that we have people involved. We need people to be part of this, otherwise we can't find the answers. So what are some ways that you can get involved in trials in Parkinson's? So here's some resources for you. The first is the Web page of the APDA, which lists some of this information, and lists links to particular clinical trials, as well as more umbrella organizations for the larger scale listings. So, certainly, that's a good source.

Next is clinicaltrials.gov. As I said, this is very comprehensive, but it is rather a technical source. It takes quite a lot of time to wade through the details of clinicaltrials.gov. So, what I've heard from patients is, while it is very comprehensive, it is also technical and maybe not the easiest source to go to to find a trial that's near you.

Two better ways to find a trial near you, one is Fox Trial Finder, which is a website where you can go on, put in your age, some information about you and your zip code, and they will actually tell you what trials are available near you. You can say, "Well, within 10 miles, or 20 miles, or 50 miles" or however far you're willing to go, they will tell you about all of the Parkinson's trials that are available in your area that meet the criteria that you've entered. So this is a valuable way to find trials. It actually has a way to leave your information there and then have them send you an email when something new opens up that might be of interest to you. So that's a powerful tool.

And then the last is the Parkinson's Study Group, which is a group that's been very involved in Parkinson's clinical trials. [They] really designed the field and they have a number of important trials, including things like NILO-PD that you can find on their website there as well.

I really want to come back to this point that if we want to find a cure, we do need people with Parkinson's who are willing to help us join in the search. There's no way to do this without the help of those of you out there in the community who can be part of this.

And both Parkinson's and healthy controls are needed, so there's a trial for everyone. Whether you either have Parkinson's or perhaps you're concerned about this because someone in your family or someone you know does, there's a trial for you as well. So, we can really use the help of everyone, and we welcome their help in our search for putting an end to Parkinson's disease.

So, I think with that, I will bring this to a close, and I'm happy to take some questions.

Question & Answer

Stephanie Paul

[SLIDE 17] Thank you, Dr. Standaert, for your very detailed and informative presentation today.

It's now time for the question & answer session. Let's get started with the questions. Our first question comes from our Web audience. It comes from Lisa, and she asks, "You spoke a great deal about interventional trials." She wants to know, "if drug therapy would have to stop if you were to participate in an interventional trial."

David G. Standaert, MD, PhD

Not necessarily. So, interventional trials all have their different rules, but many of them allow you to continue your current therapy, and then add the new treatment on top. So, you really have to talk a little bit with the investigator about what the goals are. Obviously, if they don't want to create a situation where, for example, two drugs might interact badly, so if it's known that the drug we're testing doesn't get along well with one that people are taking, they might have to come off of that. Also, we don't want two drugs on board that do the same thing at the same time. That might confuse things. So, there may be times when certain therapies need to be stopped or certain people can't enroll because they're already on a treatment that would conflict.

But, generally, we try to avoid those situations. People try to make trials as inclusive as we can, and in most cases, these things are added onto the existing therapy much more often than replacing something you're already taking.

Stephanie Paul

Okay, here's a question from Jeffrey, and he asks, "What's the typical overall duration of a drug trial through all phases?"

David G. Standaert, MD, PhD

Oh, well, to go from all phases, from preclinical all the way to approval, is multiple trials. It's not just one trial. Because there'll be preclinical work, there'll be one or more Phase Is, one or more Phase IIs, and then often several Phase IIIs. The overall number of years can be as many as 10 years to go through that entire process.

Now, obviously, that's a really long time. There's a lot of interest in trying to shorten that up and make that more efficient. There are some different ways to do that. One way is some of the biomarker work. Can we get earlier indications as to when drugs are effective, or working at the target that we think they work on? But if you look to the drugs we currently have today, most of them were in the pipeline at least a decade before they reached approval.

Stephanie Paul

Okay, Lisa has another question, and her question is, “Are there any studies that are taking place on tai chi or Rock Steady Boxing that you know of?"

David G. Standaert, MD, PhD

Certainly, there have been studies of tai chi that are published. I don’t know offhand of one that’s currently enrolling. But it certainly would be valuable to do that.

Rock Steady Boxing, many of my patients love Rock Steady Boxing, and they’ve had a very positive experience with it. I’m not aware of an actual trial with that. It would be interesting to see, and be interesting to do, but I’m not aware of one that’s currently running.

Stephanie Paul

Okay, another question related to exercise coming from Kathy. “Does the research find that exercise could prevent the development of Parkinson’s disease?

David G. Standaert, MD, PhD

That’s a really great question. So, does exercise prevent Parkinson’s disease? I don’t think we know the answer to that. We’re very interested in questions about what causes Parkinson’s and what things about lifestyle might prevent it. And there also is a phase of Parkinson’s where we think the disease is developing but the symptoms are not really obvious. During a phase where people have, for example, things like sleep disorders, loss of the sense of smell, early symptoms, is exercise valuable in that phase? Generally, I encourage people who are in that situation to exercise, but the proof that it works and the question of how much, we don’t have an answer to; and it would be a great trial to do.

Stephanie Paul

Okay, here’s a question from Yung, and he’s asking, “What kind of research has been done on Azilect® (Rasagiline).”

David G. Standaert, MD, PhD

On Azilect. So Azilect’s been studied very extensively; so Azilect is an FDA-approved drug, so it’s been through all the phases of clinical trial, beginning with safety studies right through to Phase III efficacy studies. And I’d say that, so Azilect is a monoamine oxidase inhibitor; and the Phase III studies show very clearly that it does reduce the symptoms of Parkinson’s disease, and that’s what it’s approved for by the FDA is to reduce the symptoms of Parkinson’s.

The controversy around Azilect was in the later stages of studies where they tried to ask the question, “Well, does it slow the disease down? Does it have a long-term effect on the course of Parkinson’s disease?” And some very large studies were done. I was part of some of these. I think in the end, we were unable to prove that it has a long-term disease-modifying effect. So, clearly, it has a beneficial

effect, and, clearly, the FDA has approved it for that beneficial effect. But the question of whether it slows long-term progression has never really been resolved completely.

Stephanie Paul

Okay, thank you. Here's a question that comes from Frank, and Frank asks, he says, "I'm 81 years old. Are older patients discriminated against for studies?"

David G. Standaert, MD, PhD

No, I don't think so. Many studies allow patients of any age, or certainly into the 80s. We have a number of studies that allow that. Usually it's more around other medical conditions. So, it is true that studies will exclude people with severe heart conditions, sometimes people with severe memory disorders, other kinds of things. If you have active cancer, obviously, it's problematic to be in a study of an experimental drug. So that's often what excludes older patients, but aside from that, many studies do allow patients certainly into their 80s.

Stephanie Paul

Okay, here's a question from Jeffrey: "What Parkinson's patients are best candidates for DBS?"

David G. Standaert, MD, PhD

Well, that would be, it's an important question for a clinical trial in a way. What's been studied, typically, is patients with more advanced symptoms who have reached the point where they can't control their symptoms with medication any longer. So, patients who've been treated with levodopa or other drugs perhaps develop wearing-off dyskinesia. The trials have shown that these are good candidates for DBS because DBS is quite good at fixing both wearing off and dyskinesia.

A question, of course, is, "Well, what about doing DBS earlier?" And there have been some small studies of this, so-called early stimulation, using DBS as an earlier treatment in Parkinson's. Would that be beneficial in the long run? The studies that have been done have been small scale, but they're suggestive that it may be valuable, and that's an area we need to go. And so, defining the borders of where is DBS effective is an area that there needs to be more clinical trial work.

Stephanie Paul

Okay, thank you. Here's a question from Mary: "How do I proceed if my physician does not think clinical trials are worthwhile, but I want you to explore this option? Do I need to get my doctor's approval to participate?"

David G. Standaert, MD, PhD

No, you don't actually need to get approval from your doctor to participate. That's really your decision. Now, of course, I think it's always best to work in harmony with your physician, that partnership between a patient and the physician who's taking care of them is very important. And I think good

communication between the two of them is very valuable, and I always encourage that whenever possible.

But it's also true that it's your decision as to whether to participate in a clinical trial or not. And one way to approach this is to find out more about the trial. Typically, if you ask the investigator, there's a document called an "informed consent" document. This will explain in a lot of detail what's involved in the trial, what are the risks, is it observational, is it interventional, how much time are we talking about, what's known about the risks and benefits of this? That's something you can look at, and you can share that with your physician, too. And that may be helpful to persuade them.

But, at the end of the day, it's really your decision as to how you want to proceed. But I think we all want to see good relationships between ourselves and our physicians who help take care of us. So, working on communication is the best approach, but in the end it's really up to you to decide.

Stephanie Paul

Okay, thank you. Here's a question that comes from Nancy, and the question is, "[Are there] Any studies using stem cell therapy that are beyond Phase I?"

David G. Standaert, MD, PhD

So, stem cell therapies are really approaching maybe Phase II at this point, so there's been interest in stem cells and ways of regenerating dopamine neurons in the brain for a long time. And these have finally reached a point where some of them are entering human trials. I'm aware of one group in New York that's doing this at Sloan Kettering. There's a group in Japan that's doing this as well. They're Phase II in the sense that they are actually using these treatments in Parkinson's patients, but it's small numbers, and the focus is on safety, which is what makes it a Phase II trial. So, you're talking about maybe less than a dozen people are going to be treated in these early phases.

But, if that's successful, that is a beginning; and I think this is a new era where we're actually taking stem cells, reprogramming them into dopamine neurons, and putting them in the brain with the hope that they'll grow into dopamine neurons.

Stephanie Paul

Okay, here is a question from Gil, and the question is, "I recently heard about using hyperbaric oxygen treatment for Parkinson's. Is there any information on that?"

David G. Standaert, MD, PhD

It's been done, but there's not a lot of data in terms of convincing clinical trials in my opinion. I think it's an interesting idea, but I wouldn't recommend it outside of a trial. I think if someone wanted to mount a really careful trial of this, I'd be in support of seeing that done. But it's not a treatment I currently recommend.

Stephanie Paul

Okay, thank you. The next question comes from Dan, and he asks, “Can you provide any additional information on a once-a-month infusion therapy similar to one used in other chronic diseases like Crohn’s disease?”

David G. Standaert, MD, PhD

Well, I think what you’re talking about there is probably the synuclein therapies. So synuclein therapies are once-a-month infusion therapies that have been used to try and clear synuclein. So that’s one approach. The other possibility is you may be talking about the therapies that are actually used in Crohn’s. So, in Crohn’s, they use antibodies that reduce tumor necrosis factor or TNF. And one interesting observational study that was published recently looked at people who have Crohn’s disease who are getting those infusions for their gastrointestinal disease and found that those people have a much lower rate of Parkinson’s. So that suggests that those therapies might actually reduce the risk of Parkinson’s.

How would that work? Well, this ties back to the question about the immune system and inflammation in Parkinson’s. So, here’s an observational study in which they’ve gone out and looked at people who are getting treated for a gastrointestinal disease and asked the question of, “Well, does that affect their risk for Parkinson’s?” It seems it does, and that opens the door to saying, “Well, maybe this is actually a treatment for Parkinson’s disease.” And the next step would be some small-scale studies, Phase I and Phase II to think about that, and I’d love to see the field go in that direction. Very new idea. I think people are just catching on to this, but it may be important.

Stephanie Paul

Okay, terrific. I think we have time for one more question, and this comes from Dave. “Is there a stage of the disease that is most desirable for clinical trials?”

David G. Standaert, MD, PhD

There are trials for all stages of disease. I will say that one area where there’s a lot of need is the newly diagnosed patient, because in Parkinson’s, we have a lot of medications, and they’re actually quite effective. Levodopa’s a good drug for many patients. And the problem is once you get on those drugs, it’s hard to know how much of the condition is related to the medicines, and how much is related to the Parkinson’s. In that early stage where people are not on any medication, many of those trials are focused on that. And, again, it’s hard to reach people. People who’ve just been diagnosed, many times they’re not connected to the Parkinson’s community. So that’s an area that we need to reach. That’s an area where we need more people, are the people who’ve just been diagnosed, because that is an area where many of the trials are focused.

Closing Remarks

Stephanie Paul

[SLIDE 18] Well, thank you, Dr. Standaert, and my thanks to everyone for participating in today's telephone and Web education program. I do apologize that we couldn't get to all of the wonderful questions. But if you have a question or would like to speak with someone from our Scientific & Medical Affairs Department, **[SLIDE 19]** I do encourage you to visit our website at apdaparkinson.org or call 1-800-223-2732, and you can ask your questions there.

I want to emphasize to everyone on the phone that we really do appreciate your feedback and comments and want to make sure that you complete the program evaluation form.

APDA has introduced an easier way to track your symptoms and manage your care through the APDA symptom tracker mobile app. Download to your mobile device today to keep track of your symptoms, create your reports, and share them with your care team or your doctor for more personalized care and support. This app is available through the App Store or Google Play.

APDA is proud to support those living with Parkinson's disease by helping them live life to the fullest every day. We do this each year by providing more than 1,700 support groups that serve more than 75,000 people with Parkinson's disease and their family members, and through running 770+ exercise groups attended by more than 21,000 participants. These exercise programs help improve the symptoms of Parkinson's and lessen the impact of the disease.

We also offer educational symposia across the country on living well with the disease. These programs have been attended annually by more than 5,500 people impacted by Parkinson's. But we rely on the support of the entire Parkinson's community to help accomplish all of this.

To join us in the fight against Parkinson's and to learn more about the support APDA provides across the country through our network of chapters and Information & Referral Centers, as well as our national Research Grant Program and Centers for Advanced Research, please visit us at apdaparkinson.org.

We all agree that being informed about your disease and treatment options is the best way to empower yourself and take control of your care. Have a wonderful day, everyone.