

## A Conversation About Clinical Trials

### An Interview with Dr. Mark Stacy and Dr. Peter Schmidt

Davis Phinney Foundation

*Note: This is not a flawless, word-for-word transcript, but it's close.*

Chris Krueger (Manager of Content, Davis Phinney Foundation):

Hello, everybody. Welcome. I'm Chris Krueger, and I'm the program manager for education and content with the Davis Phinney Foundation. And I'm here with Dr. Peter Schmidt and Dr. Mark Stacy to talk about clinical trials for people with Parkinson's. As a person with Parkinson's, I've been interested in many trials. I've chosen to participate in some of them and not to participate in others for just personal reasons, and I'm really excited for our conversation today.

So, to start off, maybe each of you can just introduce yourselves.

Mark Stacy, MD (**Associate Professor of Neurology**, Medical University of South Carolina):

I'm glad to be here, and it's good to be able to have these conversations, particularly when everybody's scattered across the country. My career is kind of scattered across the country. I started at the University of Missouri in 91, then went to Phoenix and started the Muhammad Ali Parkinson Research Center. In 2003, I went to Duke University and was there till 2017. Pete and I worked together to run the medical school at East Carolina University from 2017 to 2021. And now, I'm at the Medical University of South Carolina, where I'm seeing Parkinson's disease patients again.

Chris Krueger:

Very good, thank you, Mark. And Pete, can you tell us a little bit about your background? We just heard a little bit that there's a partnership at work here, but give us a little more background about you, please.

Peter Schmidt (Senior Vice President, Government Partnerships of Rho's Federal Systems Division):

So, I'm Pete Schmidt. I have a PhD in applied math, and I have done a ton of different things. I started out working primarily in the simulation of clinical trials. Then, I wound up getting engaged in actual clinical work. I went to the National Parkinson Foundation back when that was a separate entity in 2009 and led the programs there until 2017 when I joined Mark at the Brody School of Medicine. After leaving there, I joined AACRO, a contract research organization that does the operations of clinical trials for pharma and for NIH. And my main focus is NIH trials. I'm the PI on AU, one running clinical trials in immunology. And we'll get to immunology, which is part of an interesting new way we're thinking about the brain. There's a lot of immunology now in the brain, and I also go back and do clinical trials. I'm a neuroscience

advisor on clinical trials that we're doing in the commercial space. My title here is chief Scientific Officer. I'm also a board member of the Davis Phinney Foundation. I think the work you guys do is amazing, and I am fully committed to supporting the Foundation and your mission.

Chris Krueger:

Well, thanks so much for your time today and your time throughout the previous work we've done together, both of you. So maybe to start off our conversation about clinical trials today, it'd be great if we could just kind of get an overview.

Mark Stacy:

Our clinical trials have been focused on kind of three major areas. One would be to try to slow the progression of Parkinson's disease. The other would be to try to treat the symptoms of Parkinson's disease. The third one would be more neurosurgical to try to look at better surgical interventions and more effective ways to treat Parkinson's when medications are not enough. And so, if you look at the pipeline at any time, you will see trials that are looking at those three different areas as well as increasing areas interested in genetics as we become closer to defining more homogeneous Parkinson's disease populations rather than the heterogeneous Parkinson's patients that we enroll in typical trials. Pete, it's your turn.

Peter Schmidt:

So, I think that this is a really exciting time in trials for a long time. For a long time, we were very limited in our vision. If you look at how people thought about the brain just a decade ago, we really thought about the brain as being neurons that form a network and the way they communicate through, across synapses, the sort of standard brain functioning. We thought that the pathways to the pathways to addressing Parkinson's disease would be about supplementing neurotransmitters, putting more of the stuff into the brain that sends a signal from one neuron to another, surgically rewiring the brain, taking out sections of the brain, or modulating sections of the brain that were, that we felt were malfunctioning or sticking more neurons into the brain, the cell-based therapies.

And none of those seemed [...]. There was a breakthrough, an absolute breakthrough—the kind of thing that you don't see anywhere in medicine—in 1975 when they approved Sinemet, absolutely tremendous. I had a friend who was a pharmacist, and he was telling me that they would talk about it. He was active in pharmacy at the time, in 1975, and he would talk about how it was amazing to people how much of a difference the introduction of Sinemet made when there was no effective treatment. But since then, things have been, we've kind of pursued those same avenues and have had gradual progress. There have been some incremental benefits today. We've kind of gone back, and we have the advances in neuroscience have introduced all sorts of new ways that we can, ways that we can try to address Parkinson's disease, all sorts of things that seem to work on the lab bench or in the, in an animal model.

And we really need to understand those things that are going to change the experience for people. So why do we need patients to participate in clinical trials when there are so many things that, on the whiteboard or in a cell, in a Petri dish, look amazing, but you can't approve a drug on that basis? We need to know if it improves a patient's life when it comes down to it; for all that, we can say that we can modify how aspects of a cell in a dish work or even aspects of how the brain works. If it doesn't give you a better life, it's not worth putting into the healthcare system. It's not worth people paying exorbitant amounts to get access to something that changes chemistry but not experience. And so, that's why we desperately need people to get involved, especially in some of these novel approaches, these things where we're looking at how neurons how they're the metabolic cycle of neurons work, or how the helper cells in the brain, they're cells called glia and astrocytes. People are thinking about how those can affect Parkinson's disease.

We can show that we can make a difference in a cell, in a dish, or sometimes we make little things called organoids, which are clumps of human neurons and cells that float in a solution of sugar or water. And we can show that though we can modify how those things behave, but it doesn't mean it changes somebody's life. So that's what we, that's what the sequence of clinical trials is about. Can we show that it's safe to give somebody something? Can we show that it's actually doing something? And then can we show that we can reliably give somebody relief from symptoms, hopefully, something permanent, slowing the progression of a disease so that that can then become part of clinical practice?

Chris Krueger:

And I'm interested in looking a little bit at people are living with Parkinson's. What should we be thinking about as we look at clinical trials? What do we need to know? Things like, "What are the safety protocols that are put in place before a trial is approved to start? And what risks are there? What are the stages of the trial?" There are early stages: phase one, phase two, and phase three. So, can you just give a detailed sort of overview of what things we might need to know as we think about participating in a clinical trial, just so we can lay the land for everyone?

Mark Stacy:

Pete, why don't you take the phasing? Then, I'll talk about what I think a patient should think about on that scaffold.

Peter Schmidt:

So, it's very hard to guess what is going to work and what's not going to work. I've heard people come in with ideas that I thought were crazy, and I and they've run a trial, and they've gotten something really positive out of it. So, there are very strong regulations that I spend a lot of my time thinking about for protecting the safety of people who participate in trials, and the staging of trials. The first thing we do is phase one. And phase one is really where we're, where we take as small a group as we can reasonably use and say, is this drug safe to run trials in humans with? So, we're really not looking for you. In the first part of it, I'm working on a phase one trial

now where the first part, we just get people who are healthy, and they will try a drug, and we'll see how it affects them.

We'll try it at different doses to see how different doses affect them. Then you get to what's called a phase one B, where you get people who have the condition you're hoping to treat. And again, what you're really looking at is a safety-focused trial. We have a strong safety team. For a trial like that, what I look for is a physician who has an understanding, who's worked a lot in diverse clinical trials, who can see who will recognize side effects, and who will recognize a pattern of side effects. So, we're super careful in phase one phase one and phase one B trials. When you get to phase two, that's where we say, okay, Dr. Stacy, you come up with this idea. Can you show us how it works when you do it? So, phase twos are usually fairly small studies run by centers that will put in some time to understand what they're supposed to be doing.

And we say, does this thing show a sign that it really works? Can we really understand that it works? And can we get out this a signal showing us that this is giving patients a benefit? And what dose should we be using? So, these days, clinical trials are really expensive. So, if when you get to phase three, phase three is technically where you prove it works, but you really want to know that the drug works before you get to phase three, or else, you're going to spend a lot of money and not get anything from it. So, when we get to phase three, what we're really testing is this works in Dr. Stacy's clinic. Does it work when everybody does it according to a set of instructions that we give them about how to use it?

Mark Stacy:

The way I look at patients for clinical trials is every patient has a level of interest in clinical trials. And that interest changes, I think, with an early disease. And then with disease progression. Phase two is a trial that I'm more cautious about because, as Pete said, we don't really know the full safety profile in that area. Phase three is one that I'm always going to be much more encouraging for patients because we really kind of think the drug works then. But the population that I'm really trying to talk to about entering medical clinical trials is in very early Parkinson's disease. We have a neuroprotective agent and then in patients for symptomatic therapy when we run out of really good options. But I don't think in patients with symptoms of Parkinson's disease, you should skip the proven drugs that work to go look at drugs that aren't proven. And it's just my philosophy that physicians' jobs are to keep people with Parkinson's disease as mobile as possible for as long as possible. And if you skip the medicines, we know they're going to make them mobile to test something. That's just something I don't think is the right thing to do.

Chris Krueger:

So, just to zero in on that for a second, I think what you're talking about is a trial that might preclude a participant because they're taking levodopa or a dopamine agonist, right? And if, and I think what I'm hearing you say, one thing to think about is if you are limited in your physical ability or your movement abilities. If you're to participate in a trial, you would have to

withhold that medication or not take a medication that can help. That's something to think very seriously about, and maybe it's not advisable.

Mark Stacy:

Agreed. and if I had anything that I would do to change neuroprotective trials, I would try to figure out where you could have an independent monitoring to say, okay, you have participated in this trial as long as possible, but your mobility is really impaired. And it may be your doctor has not noticed your mobility is really impaired because it's so gradual. Or maybe you have not noticed your mobility is so impaired because it's so gradual. But when I look at your numbers here and your numbers here, you've had a marked change, and you need to go on therapy, so your life is better.

Peter Schmidt:

And I'll say I'm working on a trial now where we're recruiting participants who have not yet started medication. We've been very careful to write the protocol so that you are allowed to start medication without withdrawing. It makes the study harder to execute, and the numbers are harder to analyze, but we don't want to have patients not take medication when it will benefit them. And just to give you an idea, there's another study I'm working on that is about measuring Parkinson's disease. It's an observational study, a new approach to measuring Parkinson's disease. And I was on a call with them. I said the, right now, the holy grail of measurement is something that can, that you can read through the initiation of medication that if somebody, if you're recording something before the patient's on medication, and then when they start medication, you can still track their progression through that. We really don't have good ways to do that in a clinical trial. And so, that makes the trialist job harder. But what it illustrates is what an amazing benefit the be the medications are providing, right? It's so much that we can't, that we, that every measure we have says you've restarted and gone back to baseline.

Chris Krueger:

That's really interesting. I want to just draw attention to the specifics of what you just said, which I think is really important that you just gave an anecdote about the efforts to which people designing trials are going to make these things accessible to people who are going to participate in the trials. And I think that's a core message that I think is important and that I experienced in my participation in clinical trials: Not only did I get an increased exposure to and time with specialist care providers, but I also felt that they were really out for my best interest. And that's not necessarily going to be everybody's experience. I don't want to make it seem like that's true. But it's certainly possible that one thing that people get out of these clinical trials when they're participating is more time and more attention from specialists.

And I wonder if you both might say a little more about what you think that a participant might get from a clinical trial. What benefits might they receive? Obviously, people thought, well, oh, I can get early access to the disease-modifying treatment, and that's a motivation, but there's a

risk there. So, what can we get, and what should we be aware we might not get from a clinical trial? Is there any sort of guidance you can provide about that?

Mark Stacy:

Well, participation in a clinical program will involve more members of the clinical program. And so, as you all know, access to a physician is sometimes difficult, but if you've participated in a clinical research trial and the coordinators in that clinical research trial and other personnel, you know that we want you to do well. You also know we believe we owe you something. And while that's a very quid pro quo, it is what happens when we get to know you better. When you can't reach a physician, you can call that coordinator, and that coordinator will get that physician in a hurry. And so, you'll have access to more urgent responses. I think you will also gain a lot of access to information and the ability to think about it, okay? What about me?

And just hanging out matters. And you get to see some other people with similar interests and similar motivations to get better. And so, I think the overall benefit is beneficial to your mood. And to your overall sense of, I have some, a little, I'm a little more empowered because I participated in this clinical trial because I understand my disease better, I understand the medications better, and I understand how I can reach out to this study team for urgent matters. And so, you feel a little bit more in control.

Peter Schmidt:

And we just did. I was just reviewing a new training yesterday. We're putting a new version of our training on good clinical practice—the standard for how you conduct a trial. The message that is very clear in all of these documents is that the benefit, that the goal is to benefit the participant, and harm to the participant will not justify the benefit to society. We have to be focused on trial participants first. And if we can help, we cannot do a; if we identify that there is a risk that's manifesting from participating in a trial, we have to address that risk as soon as we see it and not continue and not risk exacerbating. So, if you have a mild side effect or a serious reaction to a drug, we can't just keep giving you that drug because we think that more data will provide more benefit to society. We need to focus on the participants first. It's not a sacrifice; it's participation.

Chris Krueger:

So, this points me in the direction of looking backward a little bit at something you had just talked about a couple of minutes ago, Pete, which is the implementation of a way to allow people to transition onto medication if they're initially not on medication at the start of a trial. Right? And that seems like a useful addition to AAAA, the structure of a clinical trial. I'm wondering if you have any other pieces of advice if either of you had any, pieces of advice for someone who is thinking about clinical trial participation. They want to be able to evaluate whether this trial is designed well or if there's anything that is particularly relevant that somebody might want to think about in that regard. How can they know if someone in a trial is well-conceived?

Peter Schmidt:

So, at one point, I had lunch with the chief scientist for Pore: the Patient-Centered Outcomes Research Institute. And he was saying that if he had, if he got sick, his ideal treatment path would be to be randomized to the placebo arm of a clinical trial. Because if you're in the placebo arm, you're going to have a leading expert give you the best care they possibly can, plus a sugar pill. And so, you don't have the risks of the drug, and you get the benefit of the best care you possibly can.

Chris Krueger:

That's really a spin on the way people often think about this, right? I can speak from my own experience. I was thinking, oh boy, I don't know that I want to get the placebo. But on the other hand, if you don't, if you can contribute, you can get attention from people, and you don't have the risk. So, there's an interesting spin. I like that.

Peter Schmidt:

So, if you go to see Mark and Mark doesn't know what you're getting, say, so there's a, I'm a mathematician. So, when we look across a whole bunch of people participating in trials, they'll all differ a little bit, and that creates noise in the data. And we average across people to determine which is better: the active intervention or the placebo. And our hope is that active intervention is better. But if you want to have the least noise in a study, you have to give everyone the absolute best treatment because all well-treated people are similar, and every poorly treated patient is different. To paraphrase, toss the story. So, you wind up with a, with your data, it is terrible if people are not getting great treatment. And so, you can, you can, so they have an in, so everybody involved in a trial has an interest in making sure that every participant gets the best possible management.

Mark Stacy:

And so, a good clinical trial has several components. One is actually an informational informed consent process in which you can understand what's going to happen, and you are able to talk with people freely and openly about that consent process. If somebody sits down and says, sign this, and you can participate, that's not informed consent. And I would not advise signing that. The next thing to think about is how you are randomized to a treatment or placebo arm. How is that done, and how does that, and how do they maintain a blind? And so, if you have a team that talks about whether you're on study drugs or not a lot, that does not maintain a blind very well. Even though you may not know that information. The next is independent assessment. And is it the neurologist or the coordinator that's going to do the assessments, or is it going to be another person doing independent assessment? And if you have good, informed consent, you have randomization that you can believe, and you have independent assessment. I think you have a clinical trial that will stand the test of review for publication of results. But without those as a reviewer for a movement disorders journal, those are the pieces I really pick apart when I'm considering whether a manuscript should be published in the journal.



Peter Schmidt:

So, a couple of red flags. What are the red flags to look for in a trial? A trial should be listed on [clinicaltrials.gov](http://clinicaltrials.gov). If somebody talks to you about participating in research and that research is not listed in the [clinicaltrials.gov](http://clinicaltrials.gov) runaway, they should, the team should engage you in the informed consent. They should take you, talk to you, and give you an opportunity to ask questions. You should, you should understand it. You should have a family member with you. If you're worried at all about understanding, about your ability to understand it and have somebody go through it with you and say, what are the risks and what are the potential benefits? If your neurologist invented something, there need to be independent people involved in the trial. You need to make sure that it's not; I invented this, I'm having a trial of it, and I'll determine whether it was successful or if it failed.

That's a red flag. Clinical trials should not have any additional cost to you. You shouldn't have to pay to participate in a clinical trial. Sometimes, some of the care that's involved in the trial will be billed to your insurer. And you may have a copay for that aspect of the care. That's something that is, 20 or some years ago, they didn't do that, but now they do it more than they used to. So it won't be, it won't necessarily be absolutely free because they may bill some of your, some of the ordinary things they would do for you, to your insurance company.

Chris Krueger:

So, I just want to look at one, just give a little bit of context real quick. This is all in the, everything that's been said in the past couple minutes has been in the context of I go into an office to talk about a clinical trial, and I'm being told, given information about what the trial's going to consist of and this sort of information about insurance and payments, and that those elements will probably be brought up in the informed consent potentially. And if and they should certainly be parts of the conversation, even if they're not written down in a formal way. Is that right? Is that where we're at right now?

Peter Schmidt:

So, you should ask, will there be any cost to me? And the answer should be either no, or it will be no more than what you would pay to see me normally. So, those are the big red flags. What else? Mark?

Mark Stacy:

So I was, whenever I went back to see my mom in this little town of Missouri, right at our exit, there was a sign outside this little storefront saying, come in and participate in our, "you name the disease" research. That is not funny to me, but kind of funny. And I think that you have to use common sense about charlatans and their willingness to make a buck off of your desperation. The worst would be the people that advertise stem cells for cash come in, and we'll remove some sort of fluid from your cerebral spinal fluid, and we'll send you away for a



day, and we may do something. We're going to tell you we're going to do something with this fluid, and tomorrow, you can come back in, and we're going to give it back to you.

But you have to pay \$20,000 first. Parkinson's disease is a disease that is associated with hope, and hope brings increased dopamine. And so, if you believe you're going to get better from this stem cell thing that I described, you're going to get better for about four weeks because you're going to secrete more dopamine in your brain because that's the way the brain works. And so, if you decide to tell people you're a whole lot better in four weeks after this intervention, more people will go to get that intervention. So, as a community, you need to make sure everybody is making sound decisions. And I think that's what Davis Phinney and other foundations are really helpful around to vet things and to provide reliable answers to people who have every right to have hope and ask, is this something that is real? Is this going to be good for me? However, seeking qualified, independent answers about some of these things is important.

Peter Schmidt:

And some things that are not red flags are, there are a lot of not, we have gotten a lot of new knowledge about how the brain works. And so, lots of people may not have heard about a mechanism of action or a particular intervention. There are very few people whom I'm aware of who, if they said the pathway to a better life in Parkinson's, is only going to be along this channel, there are very few people I would listen to who said that there are so many new insights coming out. I have been surprised. A trial was run in the UK using a diabetes drug called exenatide. And I don't know if it's going to work, but when I first heard about this trial, I thought, what's going on here? That's not a mechanism I'm familiar with. And when the first results came back from the study of exenatide, it was surprising. It had some promise. It's pointed us in directions that my team is now going through two. They are on their second trial, which is inspired by the insights we've gotten from exenatide research.

Mark Stacy:

So, if you wanted to, just one more thing, sorry. If you want to have one question, you want to ask anybody who's trying to enroll you in a trial. Ask them if this is a phase two or phase three trial. If they don't know the answer to that, I would be hesitant to move forward. But if it's a phase, unless—

Peter Schmidt:

It's an observational trial.

Mark Stacy:

It's a phase two trial; you need to know that that's going to be more safety oriented. In the phase three trial, we kind of know this is a really safe drug, and it's going to be more efficacy oriented. But if your investigator doesn't know if it's a phase two or phase three trial, or if he or she responds that it is neither, this is a, this is an early phase trial, I would be leery of that.

Peter Schmidt:

So, in the phase two trial, another thing you'll find is that in a phase two trial, there may be more tests, there may be more blood tests or testing done, a skin punch. These days we're looking at you may see more of that in phase two, whereas in phase three, the FDA really wants to have patient input; they need to have a response from the patient. This made me feel better about giving approval. And so, there'll be much more focus on your experience.

Chris Krueger:

There are a couple of things that have come up in the past couple of minutes of this conversation that are interesting to me, and they're sort of on different ends of the conversation. But one of the things I wanted to think about was you, Pete. You mentioned the diversity of methods of action and the way that sometimes these things are surprising, but that called to my mind the difficulty in recruiting people to clinical trials and the challenges that result from not having a diversity of patient participation in not only in terms of racial or ethnic or sex and gender but also in terms of location. And so, these are really complicated issues to address. How can we involve more people in clinical trials? But I'm wondering if you have any perspective about that; not only do we need to look at different methods of action, but we also need to include a broader range of people and a broader scope of participants. So, do you have any thoughts about that? Is it right to think that that's necessary?

Peter Schmidt:

I think diversity is crucial in clinical trials. I think that it's really important that we get the genetic diversity of humanity in our trials so that we can understand what a drug means to a human as opposed to a small family of humans. So, it's really important that we do a lot and put a strong effort into getting people who represent the full spectrum of the human experience. And genes are just part of it. Diet activity levels, all of these things are going to go into understanding the effect of a drug across the spectrum of people who might be asked to, who might be offered it by their clinician once it's approved.

Chris Krueger:

Is there anything else that's coming up that you're excited to learn more about?

Mark Stacy:

So, I'll give a philosophical answer and let Pete give specifics. It works better that way. But I've been in Parkinson's disease clinical trial work since 1990, and we've played around one synapse. It is the [...] dopaminergic synapse. And we have beat that synapse to death, in my opinion. And we've never really found anything that has made a bigger difference than levodopa in 1975. And so, we need to go back and think about the mechanisms of how symptoms develop. And when you treat somebody with Parkinson's disease, when I look at you in my clinic, if you don't have any rigidity or stiffness when I move your arms, that means at that moment you don't

need any more anti-Parkinson's medicine. But if you have more rigidity, then I can increase your medicines. I'd like to find something that would reduce rigidity that is outside of the dopaminergic synapse.

So, if I could give you a drug that reduces the rigidity by directly acting on your muscle, you'll move better. And so, we need to start being more imaginative about clinical targets. Pete mentioned a diabetes drug. Earlier, I was very glad he mentioned that because when I was editing for the *Journal of Clinical Neuroscience*, we got this very strange, odd publication in our submission looking at that drug. And it wasn't because of funding; it wasn't the best-designed trial in the world, but it had some signal. And so, we took a risk on that drug. I actually published an editorial about the paper, and I'm pleased to see that it's continued to grow and given other people more ideas about how we can look at the pathogenesis and the symptoms of Parkinson's differently.

Peter Schmidt:

So, I think that this is a very exciting time in Parkinson's research. When I started working in this field, there were so many trials where I said, they're going to try that again. And now that's very uncommon. Now we see a whole bunch of new ideas coming out, a whole bunch of differences as we've zoomed out as, as Mark says, from that tiny, tiny synapse, the tiny, tiny balls of fat-encased chemicals in that tiny, tiny space and thought, what does the larger environment afford us? But one of the challenges that we're seeing is getting better insight into how it's. There's a difference between how the disease starts and how it progresses. And there are different ways that we target how the disease starts and how the disease progresses. There was a time when I was worried that we would have the polio problem, and then, when we talk about polio, we think about Jonas Salk and the Salk vaccine and how that eliminated polio.

But for everybody who had polio before the Salk vaccine, we stopped researching treatments for them. We stopped really working on them. Once we got the polio vaccine, we left that group behind. And what I'm seeing today and in my portfolio is that I now have a Parkinson's study on measurement and observational study. I have a Parkinson's study on an early intervention to stop how the disease starts. And we have a trial to modify symptoms in people who have the disease. So, we're not going to—I don't see a lot of evidence that we're going to forget the people living with the disease today as we focus on stopping the people who will have it tomorrow. And I think that's a very positive thing. Part of the reason why I enjoy staying connected with the Davis Phinney Foundation is that I care about making sure that we do our best, not just for the people who will have it tomorrow but for the people who have the disease now.

#### WANT MORE PRACTICAL ARTICLES LIKE THIS?

You can learn much more about living well with Parkinson's today through our *Every Victory Counts*® suite of resources. Each manual is packed with up-to-date information about everything Parkinson's. Click the link below to reserve your manual(s).

[Reserve Your Manual\(s\) Now](#)

*Thank you to our 2023 Peak Partners, AbbVie Grants and Amneal, and for their ongoing support of these must-have manuals. Additionally, we'd like to thank Barbara and Dale Ankenman, Abby and Ken Dawkins, Bonnie Gibbons, Gail Gitin in loving memory of Gene Gitin, Irwin Narter, and Lorraine and J Wilson for their generous donations that allow us to make these resources available and free to all.*