TRANSCRIPT
Module 9: New ways forward in MS clinical trials

- [Therese] Hello again and welcome to Module 9, which will be our final module in this series. Today we're going to be looking at new ways forward in MS clinical trials. So taking a look at the outline for today, we're going to look at the unmet needs in MS. Then I'm going to introduce you to adaptive clinical trials, which are a new way of doing clinical trials. We're going to talk about what they are, which components can be adaptive, and what the benefits of adaptive clinical trials might be. We have four videos in this big module today. Two of them will be from the Adaptive Health Intelligence group who are a health and medical research team based in Perth in Australia, and they've very kindly shared two videos with us to talk about adaptive clinical trials and the benefits of adaptive clinical trials. Then we're going to have a discussion with Jacqui Hanley from the MS Society in the United Kingdom, and she's going to talk to us about the OCTOPUS trial, which is currently underway in the UK. And finally, we're going to turn the tables a little bit today, and Dr. Julia Morahan, our Head of Research at MS Australia is going to interview me about a very exciting new adaptive clinical trial for Australia called PLATYPUS. So first up, let's take a look at what is an unmet need. So an unmet need is something that we still haven't found the answer to. And in the health and MS arena, this is usually something that is needed in medical care. It can be very highly individual. We all know that everyone with MS has a different pathway, there's different issues and there's different symptoms. And if they can't be managed or solved, that's an unmet need to that person, and this could be managing a symptom such as ongoing fatigue, it could be looking at managing spasticity or managing depression. It is a potentially long and very personal list. In MS, if we're generalising a bit more broadly, we still don't have a cure. So at its most basic, that's an unmet need. We also don't have effective and accessible treatments for everybody with progressive MS. It seems that we have so many for relapsing remitting MS and so few for progressive MS, but there's some exciting new trials underway, which are looking to change that. Also looking at remyelination and neuroprotection, we currently can't undo the damage that's been done and the loss of brain and spinal cord tissue, which later leads to disability and progression. But what if we could remyelinate? That's an unmet need. We are also looking at ways of monitoring disease progression in MS. We don't have any simple tests that tell us if a relapse is coming, if MS activity is changing, or if disease modifying treatments are working in the way we need them to be working. The list is potentially endless. But internationally at the moment, we are managing progressive MS and finding ways to be more effective with our treatments to both remyelinate and neuro protect, and this is a global goal of MS research. So let's take a look at what are adaptive clinical trials. So adaptive clinical trials are new ways of running a clinical trial which are more efficient, more timely, and more flexible in approach to traditional clinical trials. They can be adaptive in many different ways, which we'll talk about in more detail in the coming slides. Essentially, they allow an interim review of the data whilst the clinical trial is still in progress, rather than waiting until the end of a trial to look at the data to see if an intervention or a drug has been effective. The adaptive clinical trial design allows for modifications to key components along the way once we have these new learnings, which is incredibly useful for making a trial more flexible and more patient focused. There has been a surge of interest in adaptive clinical trials in recent years. This is following learnings from the field of oncology and cancer care where time is always of the essence. But we have a similar theme in MS, where brain health reminds us that preserving brain and

spinal cord tissue is critical. Some of the new studies we will discuss today target progressive MS in particular with the new adaptive clinical trial design. So which components of an adaptive clinical trial can be adaptive? There are many different ways, but I'm just going to give you some examples, one of those is adding different doses of the same medication in a study in different arms, or we could be looking at different drugs or different interventions as part of the trial. We could stop treatment arms which look like they're being ineffective, and this is fabulous because it results in less exposure to inferior treatments for patients. We can identify participants that are more likely to benefit as the trial goes on. An example of this is if we look at the results in certain groups in the same study, it might be that people respond better to a new drug if they've had certain other drugs before this one, or they might do better in the trial if they're treatment naive or they've had no MS treatments in the past. We can look at changing the number of people required, and that's called the sample size. And so that may lessen as a trial goes on, if things become more obvious. We can also bring forward study end dates if the research question is already adequately answered instead of traditionally where we have to wait for the passage of time, and this might be for whether a drug or an intervention is effective or ineffective. And for some adaptive clinical trials we will have the capability to transition more seamlessly from one phase of the study to another rather than finishing that phase up, waiting a period of time, and then starting again, it will be more seamless transition. I should also mention here that adaptive clinical trials are still relatively new and they require very intense statistical knowledge, which is still accumulating. Statisticians involved in adaptive clinical trials often have additional specialised training, and that's a crucial component of the successful adaptive clinical trial. Now we're going to have a look at a video from Adaptive Health Intelligence, which is going to more generally talk about adaptive clinical trials and how they work.

- Regular clinical trials run a bit like trains on train tracks, everything is pretty much fixed from the beginning to the end. The design, the treatments you offer and how many people you will enrol are all locked in before the first person is enrolled. You do the trial and then you look at the data at the end to see if you've answered your question. Sometimes the trial fails to reach an answer because we have had to make assumptions or guesses about the patients and their responses to treatment, and those guesses have turned out to be wrong. Adaptive trials are different, instead of being like a train on tracks, an adaptive trial is more like setting out on a hike with a map and a compass, you know where you want to end up, but the exact path that you will take depends on the conditions that you encounter on the way. You can adapt the design, how many people you will enrol, and how many people receive each of the treatments being evaluated while the trial is running. The adaptations are made according to rules based on the data or the information that we collect from patients already in the study by observing how well they have responded to the various treatments. There are more possibilities with adaptive designs, over time, we can assign more participants to whichever treatments appear to be performing best, and fewer participants to those treatments which are not performing as well. We can also eliminate any treatments as soon as it's clear that they're not best or it's clear that they are less safe than other alternatives. Eliminating inferior treatments means that we might be able to introduce new treatments that become available. While regular fixed trials assess the average effect of treatments for an average patient across the whole trial group, adaptive processes can be used to learn which treatments are best for different types of patients. We think that because of their flexibility, the adaptive approach is a better way of doing trials

and that they will become the future of clinical research. We think that they're fairer for participants and can greatly improve the efficiency of research, allowing clinicians and researchers to answer increasingly complex questions faster.

- [Therese] Now we're going to have a look at a second video from the Adaptive Health Intelligence where we're going to specifically look at what the benefits of adaptive clinical trials might be.

- Clinical trials are important from two perspectives, new therapies emerge, and there's an absolute importance to evaluate a new therapy against nothing if that's what's available currently, or against the best available alternative. A second situation in which clinical trials are important are when doctors have many treatment options, they're all regarded as a legitimate treatment option within the spectrum of standard care, but it's just not known which is the best option. And it's often not well understood how frequently doctors face this dilemma of having multiple treatment options, but not knowing what the best option is. Traditional trials are a very sort of static approach. First of all, a trial needs to be conceived, it then needs to be planned. So if at the beginning of the process there's an awareness of the importance and relevance of the question, there's already a substantial delay even before you start recruiting into the trial. Additionally, trials that use traditional frequenter statistics will then have a fixed sample size that has to be reached before the trial can be analysed. And so the length of time that it takes for the trial to recruit is often very difficult to predict in advance, but nothing can happen until the sample size is achieved, and then you finally get the opportunity to analyse the results. And even at that point, there'll be a result known to the investigators, but there's then frequently several more months at least before presentation and publication can occur. And that's the process of dissemination of the results. And yet even at that point, we are reliant on clinicians being aware of the results, maintaining constant vigilance with the literature to be able to translate those results into practise.

- Adaptive designs aim to be more efficient and aim to reach a clear answer faster, which is really important for diseases with significant health consequences. Faster and more efficient learning should mean that new treatments that work can be introduced into routine care faster, while treatments that don't work as well can make way for better ones. The efficiency of adaptive designs means not only can we ask whether a treatment works overall, we can start to ask which treatments work best for which types of patients. This will allow us to better personalise treatment according to patient factors like age, gender, the severity of symptoms, perhaps even genetic and other factors. Whereas regular fixed trials focus on answering a single question, adaptive designs on the other hand can help us to answer multiple questions at the same time. For example, whether a range of different treatments are effective and whether they work best when given either alone or in combination. Because adaptive trials are designed to stop as soon as the research questions are answered, they can help to avoid wastage in research. When adaptive designs are embedded into the routine care of patients, they can also be much cheaper to implement than a regular trial. This also reduces the burden of participating in research and allows us to focus our research effort where it's most needed and most likely to result in a positive outcome. Regular fixed designs are finite once the trial is complete, whether it's been successful or not, all of the infrastructure created to design and run the trial is dismantled,

even when there are many unanswered questions still remaining. For complex diseases with a number of research questions is very large, adaptive trials can be designed to be perpetual, that is designed to keep going until all research questions about managing patients with that condition have been answered. We think adaptive trials are fairer than regular fixed trials because they can be stopped sooner as soon as one treatment is clearly best or as soon as it's clear that the trial is futile. If adaptive randomisation is used, we can ensure that new participants are increasingly likely to receive whichever treatment eventually proves to be the best.

- So to illustrate what an adaptive clinical trial is, an excellent example is the OCTOPUS study, which is currently underway in the UK and funded by the MS Society of the UK. Now we look at OCTOPUS as referring to multiple arms of the study. It's also going to target progressive forms of MS, which we've already identified earlier in this module as being a huge unmet need. The study will be looking at repurposed drugs, that is drugs that have been approved for other conditions and other illnesses that show signs that they might be good for neuroprotection and remyelination. There's going to be three arms to the study, we're going to have two, what we call active arms, which will be two of these repurposed drugs, and the third arm will be a placebo or a dummy drug arm. Now they're going to do an interim analysis at certain points of the study to see how these drugs are progressing and how the patients are doing. And based on that information, they'll make decisions about whether some of the arms need to be stopped and replaced with another repurposed drug or whether they can continue. Now we're going to talk to Jacqui Hanley who's based at the MS Society in the UK, and Jacqui is going to talk to us about the rollout of the OCTOPUS clinical trial and how it was developed. Today in Module 9, I've got a very special guest, so I have Jacqui Hanley from MS United Kingdom, and Jacqui is going to chat to us about OCTOPUS and how this world first clinical trial is progressing. So firstly, Jacqui, welcome to our educational modules, and welcome to Australia even if it's only virtually. First up, can you tell us a little bit about your role both at MS United Kingdom and more specifically in the OCTOPUS trial?

- Sure. So hello everyone, my name is Jacqui. I'm the Head of Research here at the MS Society in the UK. We are the largest charitable funder of MS research here, and we fund projects to help improve diagnosis, treatments and services for everyone with MS because our number one goal is for everyone with MS to have effective treatments to slow, stop and one day reverse disability progression. And although we've all kind of made great progress in finding treatments for relapsing MS, there's still too many people with progressive MS who don't have anything to slow or stop progression, for example, here in the UK we only have two disease modifying therapies or DMTs that some people with progressive MS can take. So not everyone can access those treatments. So we need more options for everyone. And that's why I'm really excited to say that we are the funder of OCTOPUS our new multi-arm multi-stage trial in MS that's being led by Professor Jeremy Chataway and Professor Max Palmer from University College London here in the UK. It's been nearly 10 years, well, over 10 years actually since Professor Chataway first had that idea about speeding up clinical trials in progressive MS. And a lot has happened kind of over those 10 years, we have been able to demonstrate that we can run more efficient trials. So we have our MS SMART trial, that was a multi-arm clinical trial that tested three drugs against a placebo. So kind of now we're excited to combine that with the multi, kind of multi-stage approach. And so this is the

first time it's ever been done for MS, but we have seen this kind of approach revolutionise other conditions. So Professor Max Palmer led a team to pioneer prostate cancer, prostate cancer trials. He had a platform called STAMPEDE that has improved the survival for men with prostate cancer. That was, you know, they found treatments within 15 years, whereas if they'd done things in the traditional way, it would've taken us more than 40 years. So it's really exciting that approach now in OCTOPUS will help really speed up getting treatments available to people.

- Yeah. Gosh, that's fantastic, what a great story. So these educational modules that we are taking part in now, they've been developed to help our MS consumers understand more about what clinical trials are all about. Consumer involvement in OCTOPUS has been a specific goal I know for MS UK and a very important one for you. How have you included people living with MS in this clinical trial process?

- We've had people affected by MS involved throughout the whole process at every stage. We worked with the community at the beginning to develop and test this idea of kind of running a trial like this, you know, thinking about how we might be able to recruit across the UK, people are involved in the treatment advisory committee and various other kind of working groups or governance groups. We also have people kind of involved in helping design like the patient information sheets that participants see as part of the trial to make sure that you know who best to say what people with MS might want and need than people with MS. You know. It seems so obvious to include people, and it's really exciting that we're kind of building that momentum, and now that it's just so exciting, everyone's so excited that the trial is now open. You know, we've got to this point where the trial is open and actively recruiting, but it doesn't mean that involvement has stopped. You know, we've still got, you know, people are helping us to promote the trial, share their experiences, people are working with us to help make the trial as inclusive as possible. And also helping us as the funder to monitor the progress of OCTOPUS and how things are going.

- It must be so reassuring for other people with MS then to know that people from their own community have had such a huge role in developing this to be something for them and for their community. That must just be an incredible feeling. And last one Jacqui, how is MS UK keeping the MS community connected with OCTOPUS? I know the study's started now, so what's in place to let everybody know what's happening?

- We're really conscious that we won't know if the initial drugs that are part of the trial will slow disability progression until likely 2028 at the earliest. So it's really important that we keep people connected to the trial and keep kind of that excitement and that momentum. So as I said, we've got people affected by MS kind of working with us to promote the trial, you know, helping us with our comms, our social media posts and sharing stories about OCTOPUS and the good news that's coming out of it. One thing I particularly like is we have a behind the trials blog, which shares usually kind of three people's experiences of being part of the trial, so that could be a participant, it could be the trial coordinator, it could be a nurse involved, like lots of different stories kind of looking at the one trial. So I'd say kind of keep an eye out on our social media, our website, because we'll be posting updates and sharing stories, as more sites open, as we start to get those results in. And we're also kind of talking to the research community around the world. We'll be sharing updates on OCTOPUS with

our colleagues, for example, as part of the international progressive MS Alliance, which I know MS Australia is part of because this trial won't just help people here in the UK, the results are going to be potentially applicable across the world. And of course that's why we're absolutely delighted that we have PLATYPUS that will be allowing people with MS in Australia to take part too.

- Yeah, we're so excited too, Jacqui. And especially want to say thank you to all of the very brave participants in OCTOPUS. They're sort of paving the way for the rest of us, aren't they, to come afterwards. And it's very brave and courageous, and we'll keep an eye on things. We'll have in our links at the end of the module how you can keep in touch with what's happening with OCTOPUS. Thank you Jacqui. Thank you. Thanks so much.

- [Therese] Now we're going to turn the tables a little bit and Dr. Julia Morahan, our head of research at MS Australia is going to talk to me about a special project that I've been involved in called PLATYPUS, and how it compliments in with the OCTOPUS platform.

- Hi everyone, my name is Dr. Julia Morahan and I'm the Head of Research at MS Australia. We're going to reverse the format today and I'm going to interview Dr. Therese Burke to talk about some of the specific projects that she's working on for MS Australia. So Therese, welcome. We have a couple of interestingly titled projects on the go called OCTOPUS and PLATYPUS. Can you tell us a little bit more about what that entails?

- Yeah. Really cute names by the way, aren't they? But in clinical trials, there's usually a very long technical title which describes the study and the types of interventions that are being used or the types of medications that are being used. So to save the sanity of both the researchers and the participants in the study, we usually give them a shorter snappier title so that we can refer to things more easily. So in the case of OCTOPUS, we take the OCTOPUS acronym from the proper name, which is optimal clinical trials platform for progressive MS. So we take out some of those letters and we make OCTOPUS. It's doubly cool in a clinical trial if you can do that with an acronym, but if you can also come up with a name that somehow describes the study, and in OCTOPUS it does that perfectly because we're going to be looking at having different arms of the study and obviously in OCTOPUS with many arms is hopefully where we'll end up. Now as for PLATYPUS, that's got a slightly different story but based on the same work ethic, and that is that PLATYPUS stands for platform adaptive trial for remyelination and neuroprotection in progressive MS. So we take out those letters like we did with OCTOPUS and we made PLATYPUS. But obviously PLATYPUS for the Australian environment is a really cool way of looking at the similar thing and making it instantly recognisable as being from Australia.

- There is so much excitement around these two trials. Can you tell us a little bit about why that is?

- Yeah, I'd love to because we're all feeling it through every phase of these studies coming to life. So we're tackling progressive MS in a really different way to what we've done before. It's been very frustrating I think for people with progressive MS over the years because it seems like relapsing remitting MS gets all the glory. You know, we've got so many medications today that we can use to treat relapsing remitting MS and I think people with progressive MS have

sometimes felt a bit left behind. So it's really exciting that we've got something that can tackle progressive MS but also in a new way. And we're going to be targeting both secondary progressive MS and primary progressive MS, so that's really a lot of people that could potentially be helped by this study. So I think as well, the adaptiveness of the trial is what really makes it exciting. So rather than just a standard trial where we run along for several years and then look at the results to see if something has worked or not worked, we're going to be looking at the data very regularly at scheduled interim analysis points and we can make changes along the way based on the learning that we find along the way, which means that in the end we're much more efficient, we'll be doing this in much less time than normal, and hopefully picking up lots of new techniques as we move along.

- Yeah, I think it's just the flexibility of the design of OCTOPUS and PLATYPUS is just really key to what makes this so special for the MS community, and it really, it hasn't been done in MS before now, so to be able to bring this kind of flexible design to the fore is amazing. And I think we talk a lot about how well we've done with the relapsing MS medications, and that's because it has been quite easy in clinical trials to potentially measure relapses or changes in MRI on people that are participating in traditional clinical trials. But progression can be much slower, people can plateau, it can take a very long time for people to move through that. So the other thing that we're very excited about for this particular clinical trial is we're overlaying ways of measuring progression and learning from that as we go. So when Therese says we'll be able to learn and adapt and change as we go, if we can find some really great robust ways to measure progression, that will also allow us to have a tool that we can use in a whole bunch of other clinical settings or clinical trials going into the future. So that again, in this project is layered over the testing of the medications that we'll be doing.

- It's almost a double whammy, isn't it, Julia? So we are going to be looking at the drugs and that's what everyone's hoping for, but then clinically for the researchers and scientists and neurologists will hopefully have some tools that they can put to practise when they see people clinically that will just improve everything along the way. So, and a way of assessing people as they're moving along. So I think that's really exciting. And like you said, we could potentially shave years off this process and people with progressive MS don't have years to wait around to find if something works. The other really great thing about this particular study, which also makes it unique is that there might be the option for people involved in the study to stay in the study, even if their study arms drop. So traditionally, if the study arm was stopped in the study, patients have to stop the study and that's the end of it. But for these patients, they may have the option to continue in this study on a different arm. And that's the beauty of this adaption.

- I think the other piece that we really wanted to talk about is the fact that it's repurposed drugs. So by repurposed drugs we mean medications that are already out in the world, being used for the treatment of conditions other than MS. And the beauty of using repurposed drugs in a clinical trial setting is we already know that they're safe for use in people because we're using them for other things. So we skip over that whole safety path that usually happens at the beginning of a traditional clinical trial process, and go straight into the part where we're looking to see if it will work in MS, so it's faster, it's more efficient, it's a flexible design, and it just speeds everything up for people in that progressive phase who, as you say,

don't have time to sit around and see if it's going to work. So I think the efficiency and the speed at which we'll hopefully be able to get answers is really so exciting.

- Yeah, and even the process behind that, Julia, I mean, these drugs were really carefully looked at by a group of very experienced scientists and clinicians, not just in MS, but from other disciplines where these have been used. So they've all met and very carefully considered all of these drugs that did show some promise in remyelination and neuroprotection. And they've gotten together as a, it was actually quite a large group and they've looked at every drug, the pluses, the minuses, how it might work, and they've made a list in order of what they think might be potentially the best medications to use in MS. And as you mentioned, we already know that safety is not likely to be an issue. So it just helps us shave years off these studies and that's what we mean by getting to a faster answer quicker.

- Yeah, and it's a good list, which means that we can move through this and as potentially some medications drop off, we have others ready to go. So it's all mapped out, and it's just a beautiful design that we are so thrilled to be part of.

- So glad you said mapped out too, because I should have said that earlier, these studies are really carefully planned. So, and that's what's made them so difficult to plan because they had to put so much thought into all the possible scenarios that could happen and how they would handle that before the study starts. And so everything is very carefully planned.

- Right, so we've talked about OCTOPUS, we've talked about PLATYPUS, it's happening in Australia. We're going to have various sites around the country hopefully involved with this, multiple sites. How can people find more information?

- Okay, well firstly I will say that the process to get this set up in Australia is not insignificant. We've learned from Modules 1 and 2 that it can take a very long time to get all of the regulatory ethics and governance frameworks set up. So that needs to happen first. So once that's all properly assessed and ready to go, that's when we'll be approaching the MS community to let them know that the study is just about to get started. MS Australia will have loads of resources available on our website. We'll be advertising very, very much through all the social channels that we use. So make sure that you're hooked up to all of those. Check our website regularly for updates, but also importantly, talk to your neurologist and your MS nurse and your care team about the potential of being involved in the study. First and foremost, your treating neurologist needs to know what you're thinking about and be able to advise about whether this might be suitable for you.

- You won't be able to miss it if you're connected to MS Australia. I think it's safe to say to say so we are just so thrilled to be part of this. We are so excited to be able to offer this for the progressive MS community in Australia. I think we can safely say they've been waiting for this day, and really think this is going to be a way that we could close the gap on that unmet need of medications for people with progressive disease. MS Australia, thrilled to be part of it. Thank you so much.

- Thank you, thanks Julia. We have made it to the end of Module 9. Congratulations. This is the final instalment in this series. We hope to add other topics to these modules in the

future. Don't forget to take our final quiz to check your knowledge of adaptive clinical trials. It's been an absolute pleasure to take you on this journey about research and clinical trials, and I hope that we can all reconnect again in the future. Bye for now.