Which trends in CNS research are having the greatest impact on protocol design and trial execution? How is the industry keeping up with the pace of scientific innovation?

In conversation with... Sofija Jovic

wcg™

Q

Which trends in CNS research--and drug development in general--are having the greatest impact on how protocols are designed and trials executed?

A

Dr. Sofija Jovic: We now have an unbelievable amount of heterogeneity in data. More data from more sources than you can imagine. That's nothing new in our daily lives; we've been living with this for several years. But for clinical trials it's only really been in the last couple of years that we've had that kind of explosion of data.

That sounds like a good thing--in many respects, it is--but it is very hard for researchers to wrap their heads around how to use all this newly available data.

For example, "Are we going to be using any wearables?" is now a routine question. But what will it mean? There are all these very cool and interesting approaches, but the question becomes, how do you weave that into the protocol? Which endpoints are prime-time ready and which are exploratory?

How do you understand continuous data collection which, until recently, was never an option? Not so long ago, a patient would come in, talk to the clinician, go away, take medication daily, come back in a week, and the clinician would ask, "Are you better or are you worse?"

We still do that, but we are also sending them home with a smart phone app or a wearable that is tracking all sorts of metrics. There are clear threats to your ability to detect signal. The more variables you have, the more statistical cuts you have to take to allow for the analysis.

There are very complex questions around how you use this data, not the least of which is how did the wearable change the conduct of the trial beyond the data collected? We know placebo response is a huge and growing problem. Part of it is that the more you do to a research subject the more likely they are to think they are experiencing effect.

Continued >

Increasingly, sponsors are turning to experts who have "been there, done that" to help them develop protocols for their CNS trials. In this wide-ranging interview, ***Sofija Jovic, PhD, MBA,*** *of WCG MedAvante-ProPhase, explains why this is the case. She also discusses, among other topics, how clinical trial metrics haven't always kept pace with scientific innovation*

The interview has been edited for clarity and length.

Think about it. If I put you into an MRI every day, you'll think you feel better because so much was done to you. A wearable constantly reminds you that you are in a research trial, and that has been shown to increase placebo response.

So a seemingly simple idea such as, "Hey, why don't we just throw in a wearable?" opens up a can of worms because now you have new questions to consider: What hardware is the right choice? How are you getting that data? What are the clinical decisions you are making based on that data? We're now in this moment where we have a lot of data, but the science lags a little bit behind, making that data actually mean something.

Q

It sounds like you advise on both the scientific and clinical ops sides.

A

Dr. Sofija Jovic: Exactly. We bridge the gap between the two. Typically, choices about the protocol are made by the therapeutic area leads or doctors in one silo, and choices about execution are made by clinical operations people over in the other silo. We sit at the nexus of the two.

Let's use the example of whether patients in a trial will be allowed to stay on their current medications. That's usually a scientific question. There's no clin-ops person in the room when that issue is first being discussed. Then the clin-ops team sees the protocol and asks, "If you don't even allow an aspirin, how are you going to run the trial?" But because the issue is raised by the operations team, the medical people may dismiss it and say, "Well, you guys are not doctors; what do you know?"

But if one of our external experts is at the table, they can say, "You're unnecessarily tying your own hands here." That carries more weight because it comes from a peer. Moreover, the outside expert doesn't have a stake in speeding up enrollment as the clin-ops people do. The advice is strictly based on what has worked--and not worked--in prior trials. That just brings the temperature down in the room, and we can have a reasonable conversation about what's feasible and what's not.

It's not just about what is the scientifically pure way to write this protocol, but what works operationally. We can help the medical lead think through that in a way that's more operational.

That's particularly important in global trials.

Let me give you an example. We've worked on several trials looking at agitation in dementia. This is a very difficult set of symptoms to deal with both for the caregiver and for the patient. We've done a number of those trials.

During a protocol advisory meeting, a sponsor may be grappling with how to define the population—as people living in the nursing home, or in assisted living facilities, or independently at home.

Continued >

But if they plan to run an international trial, they have to figure out who is the equivalent of a U.S. nursing home patient, assisted living patient, etc., in, say, Russia, or in India, or in Japan.

The sponsor is unlikely to bring up that issue. We will, because we've seen it in other trials. So we can say, "In the U.S., people go to a nursing home much earlier in the disease compared to most of the rest of the world. Because many of those care facilities are, well, not so great; families avoid them until the very last moment."

Without accounting for such differences, you will not be able to compare the drug and placebo conditions because the difference will be greater across the border than it will be in the two groups you're looking at. That could torpedo a study.

Q

It sounds as though you ask as many questions as you answer.

A

Dr. Sofija Jovic: We're giving them answers to questions, but yes, we're also helping them reframe and contextualize questions.

We don't ask questions to which we already have an answer (or to which the answer is a purchase order). We sit beside the client and approach them as a thought partner. We will figure out the services on the back end, but we want to get in there and talk to them about the choices they are facing. How this is going to affect the trial, how it's going to affect reimbursement, approval, access to various markets, etc.

We've often been in a situation where we say, "Yes, but have you thought about how that affects placebo response?" The initial response is typically, "That has nothing to do with placebo response." Then you see their brain working through the idea, and then they say "Oh, okay, I actually see it." We take them down that path. We look around corners.

Q

How do you know which questions to ask? How do you know the answers?

A

Dr. Sofija Jovic: That comes from having done trials where each of those choices was made. So when they're facing choices A and B, we'll say, "Well, let us tell you what happened in trials we've been in when A was chosen and what happened when B was chosen." That's a very valuable perspective to bring to the table for them.

It is science, but it's science married with deep experience. The question isn't who has more expertise, but who has the broadest experience. The view that we have to the market is horizontal; the view the clients have is vertical.

Continued >

Q

For the first time since the '90s, there are new mechanisms of action in CNS drugs. How is that affecting clinical trials?

A

Dr. Sofija Jovic: One challenge is that we're testing new therapies using old outcome measures.

Rapid-acting antidepressants act in a matter of hours. That completely changes the paradigm, and it sounds amazing, except for the fact that all the outcome measures we have designed are designed for standard, old school medications.

Consider the Ham-D. It was developed in 1960, but it's still in use today. The questions, such as, "How has your sleep been the last week? How has your appetite been in the last week?", do have some value today. But it was designed to be administered once every two weeks, maybe six times over the course of the trial, and so in 12 weeks I should be able to determine if a patient is becoming any less depressed.

But now, we're using a set of questions designed to detect changes over a two-week period to detect changes over a few hours.

Imagine if I'm asking a woman who's just given birth, "How's your sleep been over the last week?" She'll probably be annoyed and say something like, "I don't know, I just gave birth, so not that great." And then I come back four hours later and say, "Okay, what about now? How has your sleep been over the last week?" You get the picture.

The science has changed so much from when the Ham-D was first published; it would be like using one of those huge Nokia mobile phones from the 1990s and trying to get service now. You'd say, "I'm getting nothing. I have no signal." Well, of course you have no signal because you're using the phone from Back to The Future."

It may sound absurd, but no one wants to be the first to change an outcome measure. Because when we do, we have to go to the FDA; we have to go through this very painful 18-month approval process.

Q

With so much exciting innovation going on in CNS research, how does one make sense of it?

A

Dr. Sofija Jovic: How do you understand the risk of something that's new? Unfortunately, the only way is to do it and then look back and say, "This is what I should have done."

To use an earlier example, when you're designing inclusion and exclusion criteria, do you require that the patient be on no other medication? If not, then which medications are allowed?

Continued >

That seems like a simple question, but it opens up so many other questions. For example, if you're doing a treatment-resistant depression trial, it's likely the volunteers are already on some psychotropic medication. If the investigator wants them to be "washed out," a lot of doctors will refuse because these patients are fragile. So now something that seems scientifically pure to do--to say we just want to compare drug to placebo, and we don't want the patient to be on anything else--is actually not practical.

That's where our outside experts can play a role; many of them have been running similar trials as investigators.

They have the experience and the influence to be able to say, "If you disallow benzodiazepines, you're not going to be able to run this trial." They'll also explain that, based on the mechanism of action, allowing participants to continue taking benzodiazepines won't affect their response to the therapeutic being tested.

Why stack the odds against your ability to enroll when it doesn't matter scientifically?

We help find the gray area between some of these very stark choices of, "Okay, they can't be on any medication while they're taking our investigational drug" and allowing everything. We look at what's in the middle and talk about how to make that choice.

Q

A

So you and your team focus on answering the big questions?

Dr. Sofija Jovic: And the small ones. Each decision matters. The cascading effect of those small scientific decisions that are taken at the outset have a huge impact on data quality, on feasibility of doing the study, and on outcomes.

Sponsors spend billions of dollars in CNS programs over the lifetime of a drug. They should be doing everything they can to maximize the likelihood of a positive outcome. They have access to the best science and the best expertise within their organization, within that drug, within that compound. They are forbidden to access that kind of expertise from their competitors. The don't have a global view. Part of the problem in drug development is that there isn't that kind of sharing of information.

What we bring to the table is having lived through those different trials. If I were them and I'm running these huge budgets trying to get these studies across the finish line, why wouldn't I want to avail myself of absolutely everything that's potentially out there? I would want to know, that the expert sitting across from me who has done those trials will be using that experience to give me advice. That's really what we bring to the table—not just another piece of technology or another set of services.

Continued >

Q A Who do you bring to the table?

Dr. Sofija Jovic: Usually we bring in a team. We have subject matter experts and key opinion leaders who are both internal and external. The external ones are exclusive to us. They are sometimes researchers in academic institutions. A lot of the time they are running their own clinical trial sites.

It largely depends on the therapeutic area. For Alzheimer's, we have a specific team, for psychiatry we have a different team, neurodevelopmental disorders a different team.

I think it speaks to our depth of experience in this therapeutic area. CNS is all we do and measurement science in CNS is specifically all we do. There isn't really another organization that can say that.

Q A Does using in-house and outside experts make it more complicated?

Dr. Sofija Jovic: Absolutely. As an organization, WCG MedAvante-ProPhase consciously chooses not to solely rely on internal experts. We have those people, but we supplement them with, most recently, the team of eight experts in the field--professors who lead research programs--and we have made them a part of our internal team.

It's much easier to just have your own people who are employees whom you control.

We have chosen the messier--and what I believe to be the more valuable --approach. We are bringing in our internal experts and the scientists who are living and breathing CNS research every day who have up-to-the-minute experience with it.

Q A We've talked about the talent. What about the data you bring to the client?

Dr. Sofija Jovic: WCG MedAvante-Prophase is in a unique position in CNS. Because we work with so many sponsors, we have a view into all the data for well over 2,000 CNS trials over a combined 25 years.

We're able to draw on 95% of all industry-sponsored protocols and associated study details through WCG Predict. We have the only data that can tell you, not only what investigators said they'd be able to do in terms of enrollment, but how quickly they enrolled those patients, what the dropout rate was, and all those other variables.

Continued >

That data set is very powerful in terms of selecting not only the sites that are going to enroll faster but, historically at least, those that have been better able to separate drug from placebo--that have fewer errors in administration of these instruments.

We're looking at quality, quantity and speed. As a result, we're able to model an enrollment curve based on their current site. And then we say, "If you use a site that we recommend, we can cut that in half, in two-thirds"—basically it ends up being a very dramatic difference to how quickly they can enroll and how many patients they need to find the signal.

Q

How do you think potential clients view WCG MedAvante-ProPhase?

A

Dr. Sofija Jovic: The reputation we have in the market is such that if sponsors have complex questions, if it's something they're doing for the first time, or if it involves a lot of moving parts, they're coming to us because they're getting all of the upfront consultation, the thinking-together aspect, and the design.

Interviewee

Dr. Sofija Jovic joined WCG in 2017 when WCG acquired ProPhase, a leading global provider of specialized tools to support measurement-related activities in clinical trials. She now serves as a member of WCG's MedAvante-ProPhase executive team. Dr. Jovic led ProPhase as co-founder, CEO and managing board member for more than 10 years, transforming it from a start up to a market leader. ProPhase's portfolio includes electronic clinical outcome assessments and endpoint surveillance solutions, rater training and certification, and study start-up support. Keen to share her knowledge, Dr. Jovic serves as a member of the board at Inflexxion Inc., CRA Assessments, and Gilda's Club of New York City.

An active supporter of both CNS-related organizations and women entrepreneurs, Dr. Jovic is a member of CNS Summit, The International Society for CNS Drug Development, Women in BIO, Women Entrepreneurs in Science and Technology, and the Healthcare Businesswomen's Association. Dr. Jovic was recently named a National Association of Corporate Directors Board Leadership™ Fellow and one of the top 20 life science executives poised for board service by the Women in BIO Boardroom Ready program. She also serves on Springboard's Life Science Council, an invitation-only group of professionals who support women entrepreneurs seeking resources to grow companies they lead.

Dr. Jovic received her PhD in clinical psychology from Long Island University and her MBA from MIT.