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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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FDA/NIH JOINT WORKSHOP – DEVELOPING IMPLANTED BRAIN-COMPUTER INTERFACE CLINICAL OUTCOME ASSESSMENTS TO DEMONSTRATE BENEFIT

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M E E T I N G

(8:32 a.m.)

DR. MCMULLEN: Good morning, everybody. Thank you for joining us. My name is David McMullen. I'm the Director for Office of Neurological and Physical Medicine Devices. If that doesn't make sense, I will have plenty of org charts to show you tomorrow so don't worry. I'm delighted to welcome you to the Joint FDA and NIH Workshop on Developing Implanted Brain-Computer Interface Clinical Outcome Assessments to Demonstrate Benefit.

As you all are all well aware we are in an exciting time for implanted brain computer interface research. We are at a turning point where breakthroughs made from decades of painstaking work in the lab funded in large part by NIH and DARPA, NSF, and others, and including intense patient dedication are now at a turning point, and commercializeable device ecosystem for BCIs may soon one day exist.

However, there are still many hurdles remaining before that vision can become reality. The FDA is actively involved in working collaboratively to overcome these hurdles through a variety of stakeholder engagements from conferences, guidance development, listening sessions, and recently participation in the implanted brain-computer interface collaborative community. This Workshop continues these efforts with a focus on developing clinical outcome assessments to enable regulators and all stakeholders including patients, providers, and payers the ability to assess both benefit and risk in order to make informed decisions. Implanted brain-computer interface devices may provide a paradigm

shifting approach to restore function to patients with great potential comes the need to be able to clearly demonstrate the benefit for all patients. We hope this Workshop will continue to develop the evolution of BCI clinical outcome assessments that can demonstrate a functional benefit to patients.

We have an action-packed agenda. We will start both days with level-setting talks from stakeholders across the BCI ecosystem including patients, clinical researchers, outcome development experts, funders, and regulators. These talks are meant to prepare you all for the most important part of this meeting, your involvement.

This afternoon, and tomorrow morning, will be focused on breakout rooms where you can bring your perspective to active discussion helping to develop the next generation of clinical outcome assessments to drive forward the development of implanted brain-computer interfaces.

What you all contribute in the next few days could help lay the foundation of an exciting new field of clinical research and treatments for patients truly in need.

A brief note on logistics. The morning talks will be held in this auditorium and include a scheduled break at 10:15. After lunch, we will hear from a patient -- from a panel of patients, and then join the breakout rooms. We'll reconvene here to report out after and rejoin tomorrow in the same room.

For those online, you will be able to watch the lectures, and post breakout discussions both today and tomorrow, but will, unfortunately, not be able to actively participate in the breakout rooms.

Before handing off the microphone, I'd like to thank the FDA and NIH staff who have contributed to putting together this Workshop.

Dr. Molly Keszler and Guangying Wu, along with many NIH and FDA staff have spent many months coordinating across multiple government agencies and externally to ensure that we've brought together a diverse set of stakeholders in an environment conductive to active discussions.

I'd now like to hand over the microphone to Dr. John Ngai, Director of the NIH Brain Initiative.

(Applause.)

DR. NGAI: Thanks David. Thanks to the organizers, for putting together what I'm sure is going to be a great workshop, and thank you all for being here. As David said, I oversee the NIH Brain Initiative, a real privilege. 2024, this year marks 10 years of incredible innovation that have been fueled by BRAIN. The initiative was started in 2014. And over these last 10 years, we've supported really paradigm shifting science that's both -- that's innovative, inclusive, open and ethical. We've provided -- developed and provided tools and technologies, and resources that have truly revolutionized, transformed the study of neurocircuits. This is our big goal to, to revolutionize our understanding of neurocircuits in the human brain both in health and disease with the ultimate goal of accelerating these discoveries toward cures.

Now, just to give you a feel for how, how many tools you kind of put out there. We've established with Addgene, the company that disseminates many of these genetically encoded molecular tools, and they've set up a brain-specific page on their website. There's over 2,900 entries. That means, over 10 years BRAIN-funded investigators have put out almost 3,000 tools for everybody to use which is really quite incredible.

In addition, we've launched somewhat, I would call, big science projects to create

resources that could only be done at scale. So, for example, the BRAIN Initiative Cell Census Network last year published a series of amazing papers. One providing a complete Brain Census -- Cell Census and Atlas of all the cell types in the mouse brain, and draft cell atlases of cell types in non-human primate, and human brains. That was really amazing. The FlyWire Group this is the group, an international consortium of investigators who created a -- the first whole-brain connectivity map synapse-resolution of Drosophila. And this -- these kinds of research give us ground truth for the neurocircuits, and allow people to develop and test better hypotheses about how these, the hardware, underlies the computations of all the amazing things that the brain does. And these really represent a triumph of science. These projects could not be done in another way. The cell census projects for the mouse and human efforts, it encompassed over 250 investigators over three continents. And BRAIN is very proud that we played a role in bringing these people together, and getting them to work collaboratively to make these resources that otherwise could never be done.

And this sets the stage for other ongoing big projects that we have going on. The so-called BRAIN Transformative Projects. The Cell Census Project is now moving into creating complete atlases of nonhuman primate and human brains which, again, is really critical for understanding of what occurs over normal development or a lifetime, but also very critically in terms of disease.

We've also launched the BRAIN Connects Project, which is to develop the tools and technologies to provide, like in the Drosophila Connectome Project, a full connectome of the mouse brain at synapse-resolution, and a projectome or micron map of the human brain ultimately. And this is going to create a huge challenge, and drive for the next generation of AI technologies because one mouse whole-brain connectome is expected to

occupy one exabyte. That's a thousand petabytes of data. If you were -- if you were to be crazy enough to think can we do that for a human brain, which we're not that crazy yet, be another thousand fold to a zettabyte, which is roughly equivalent to the world's internet traffic over one year.

So we're really trying to push the boundaries, but I think necessity will be the mother of invention, and we're really going to drive these projects forward.

And the third big project that we launched back in 2022, is the so-called Armamentarium for Precision Brain Cell Access. And that's using the information from these large atlas'ing projects to now, develop better tools to more precisely target these cell types in specific circuits that will allow researchers to better test hypotheses about how circuits underly behavior, but ultimately to set the stage for a future precision circuit therapies which I think many of you here will be very interested in.

And then, more recently, we launched this what we call the Brain Behavior Quantification and Synchronization Project which is to develop high-precision behavioral measures, and to sync these with brain activity measures so that we can get, get closer to understanding causal relationships between neurocircuits and behavior ultimately to inform close-loop applications for treating behavioral disorders.

So very, very exciting times. Again, we're going to be generating a lot of data. This is going to be a great training set for future AI algorithms, and hopefully as we better understand how neurocircuits process information, we can use that to drive the next generation artificial intelligence paradigms.

So, that's all exciting. But, of course, I think all of you folks here know that there's been a huge explosion over the last 10 years in deep brain stimulation technologies, brain computer interface technologies that, that have been driven by a number of advances. One, is precision circuit mapping. Another, is better recording technologies. And, of

course, AI technologies to deconvolve these complex activity patterns, and use these either to drive neuroprotheses or to help us develop better closed-loop or adaptive stimulation protocols. And this was literally from where I was sitting the stuff of science fiction 10 years ago. But the thought that we could actually apply some of these technologies to help a locked-in person communicate, or to treat these devastating neuropsychiatric disorders, to me, is just mind-blowing. And we're very, very excited to see what's coming in the next 10 years which I think gets us to the topic of today, of today and tomorrow's workshop which is given all these amazing advances the next set of big challenges will have to do with validating them in larger populations, and scaling them for the benefit of all. We need to democratize these technologies. And I would -- I think it's probably preaching to the converted here, and while you're here is that we cannot do this unless we understand what, what we're trying to achieve and how to measure it. So, hence, the critical importance of understanding, gaining a good, a consensus over a framework for how we're going to assess the outcomes so that we can move this forward, and truly get this out into the clinic for all the millions of people who are relying on us t help them live a better life.

So with that, I'll turn it over to the next speaker, and just look forward to some great discussions over the next two days.

DR. WU: Thank you very much, John and David, for welcoming our attendees this morning. Our first speaker of the Workshop is Dr. Leigh Hochberg. And the subject of his talk is Emerging BCI Technology State of Development.

DR. HOCHBERG: All right. Elliot's happy, Adam's happy in back.

Okay, all right.

Molly's happy. Good.

Good morning. It is great to see everybody, and thanks so much colleagues at FDA

and NIH for putting together this incredibly timely, important, and exciting two-day workshop on Clinical Outcomes Assessments for Brain Computer Interfaces. Just hand full of disclosures; none personal much to my dismay, but really continue to be very grateful for the continuous support from the NIH, the U.S. Department of Veterans' Affairs, and philanthropies, and some other disclosures that are all listed up there.

To begin, I was given some very specific instructions about what to achieve today, level set, was the phrase that was used. And since so many people in this room are so familiar with brain-computer interfaces, I'm really going to do my best to focus my thoughts on comments that are related to clinical outcomes assessments. BDIs in linear block diagram form are as presented on the board. Every BCI has a neurosensor, has a decoder, and then does something. There's some action that's associated with it. As we begin to think about, what are we going to measure, and where are we going to measure, and what is a clinical outcomes assessment, there are three opportunities to kind of ping the system.

One, is the output of the neurosensor itself. Generally, we're recording a signal, it's related to the intent of somebody who may be unable to move their limb or perhaps unable to speak. If we capture that signal, is there an output, is there an assessment there that we should be measuring?

That signal working, the way that we want our systems to work, finds its way into a black box labeled up there as Magic. That's sufficient for today. But that unbelievable, computational neuroscience machine learning is responsible for taking that intent, and then converting it a moment to the action. And perhaps, it is the output of that decoder that may be one of the places that we can again pull in the system, find out whether there's an assessment that we should actually be measuring, and asking ourselves the question is it

clinically meaningful.

The output of that subsequent decoder does something. There's a long list of what it could do. I'll show you some movies, in a moment, of some demonstrations of what an implantable BCI can achieve. We certainly can measure, although as a team, as a group, we're all going to figure out exactly what those outcome assessments should be hopefully in the next few days. One of the ways to think about those outcomes are, do they affect the way our participants in the clinical trial, and more importantly, in the next stage the people who we identify for these technologies, how do they feel, how do they function, how well, and for how long do they survive.

So these are all some of the themes that are kind of resonating in my head as, as I think about what we're focused on here.

There are plenty of sensors available for brain-computer interfaces. They can be on top of the head. They can be under the scalp or under the skull, or they can be on the brain, or they can be in the brain. Again, we can record signals from any of these locations, and some of those have opportunities to be of course measured, and to potentially be candidates for a clinical outcome assessment.

So, what do we really want in terms of validated -- and I did put a question mark up there because I think whether they need to be validated is a legitimate question for us to debate over the next couple of days. But what could these outcome assessments look like? Well, what do we want from them? They need to inform pivotal clinical trial design. If they don't, we can't really have a meaningful pivotal clinical trial.

That COA, which I'll start calling it that just to save a few syllables, needs to be sufficient to lead, hopefully, to pre-market authorization. Needs to enable both public and

private reimbursement. And I'm a full-blooded academic, but that reimbursement needs to be sufficient so that the companies that are actually creating these technologies, will become available to the people who will benefit are at least solvent. Whether I make a profit is their problem, not mine. But we -- those companies need to exist or our field stops.

They need to establish a threshold, or we need to establish a threshold, for a minimally clinically relevant difference perhaps thinking again about how people feel, function or survive. These COAs need to satisfy the clinicians, who if they don't think the outcomes assessments are terribly relevant, they're not going to refer their patients. They're not going to prescribe the device. They need to be relevant to the people who are going to use these devices. They might be amongst these COAs are ones that are selected by the people who will use the devices themselves perhaps from a pallet of options. Patient-reported outcomes measures, patient-determined outcomes assessments prior to the start of a trial, an option for us to consider.

A really good COA will drive innovation. It will allow for comparison between product one, version one, and what we all hope happens which is product one, version two, and hopefully, being able to compare either of those to somebody else's product one.

And then, finally, we want to make sure that these outcome assessments are actually capturing the contribution of the implanted or the other BCI itself as opposed to some other component that may not actually be the BCI. It's a hard list to achieve so it's an ideal.

Just ones slide on safety assessments. Purposely illegible. The text far too small. We kind of have a sense for what safety assessments look like. We can get very detailed

about this. They are important. I don't think they're the focus of our next few days, but clearly without demonstrations of safety the demonstrations of efficacy won't get us very far.

This represents the next two days, I believe. And certainly all the videos that I'm about to show. I want to thank, before I show these videos, the incredible participants across any number of trials they continue to roll in these trials. Without their eager participation, without their constant feedback, none of this would be possible.

And I'm now going to congratulate, in advance, all the authors and teams who made the videos happen. Breaking with all kind of scholarly custom all videos as best as I could have no citations. They have no evidence of who did them. If you did them, thank you in advance. But the real purpose here, is to focus on what the BCI itself is contributing to the users their life that they feel, function, or survive. And what do we collectively, think would be an effective clinical outcome assessment for what's being demonstrated.

So let's start here. One thing that could occur with the BCI is to provide an opportunity for entertainment or perhaps the ability to control multiple devices. So this is going to be the beginning of seeing how our videos are working.

The gentleman you're looking at, has a cervical spinal cord injury. He is using what happens to be a percutaneously wirelessly transmitting neural activity to control first, the Kindle reader on his own PC, and then to launch Garage Band. I don't think there's yet a Garage Band clinical outcome assessment. Perhaps, there should be. But there's something about entertainment and multiple device control that perhaps we want to capture. Playing chess. Don't know how many chess players there are in the room. People, some people like to play chess. Exactly half of my family like to play chess.

There's something about this that probably gets captured in some sort of quality adjusted, adjusted life here or quality. But is this important? Is it important to the individual? If it is, how do we capture it? Because it may in fact be an important outcome assessment.

Now, focus on communication, handful of videos. Here's one version of how a BCI could enable communication. The BCI here, the output is a click. What's being selected automatically on the screen, or what's being toggled is the serial selection of groups of letters, and then rows. When a click is issued by the person, who then is generating neural activity that allows that click to be converted to control the -- or at least selection of the noncom on the screen, that provides for a slow but certain method of communication. And we'll let this continue for awhile, but eventually the letter gets selected. So, where exactly in the system are we measuring the output of communication? Here's a similar, slightly different, but here's another implanted BCI different signal. Not going to really focus on how any of these are being collected, but again, there's a click or version of a click that's voluntarily being generated by the user who is locked in, in order to select first a column, and then a row in order to get a letter out to the computer which can then slowly but surely be converted to any number of sentences.

So an example of communication via click, how do we capture that? Here's a point and click being generated as a result of the implanted BCI using a particular optimized keyboard. Letters in the middle. More commonly used, letters in the English alphabet. That's why t-h-e is kind of the center box, and woman with ALS who is, who is typing here is just pointing and clicking, and copying the phrase that's on the top of the screen. How do we capture the speed and the accuracy of this out? There are engineering answers to that

question. Are they clinically relevant outcomes assessments that meet all those other criteria? That's part of what as a team we should be discussing over the next coupe of days.

Another method for communication is handwriting. Some people have tablets open that are in the room, and are taking notes via tablet. In the upper left-hand corner are the, what we could consider the neural trajectories being decoded from an implanted BCI to make some green squiggles on the screen. The handwriting up there is better than mine. So that is an outcomes measure. But the gentleman with cervical spinal cord injury, using an implanted BCI is intending to write those letters. Neural activity is being decoded in real time, into what you see is the real time, free form full vocabulary answer to the question that was posed. Again, watch the right clinical outcomes assessment for the intuitive ease and speed and accuracy of being able to communicate in that method.

One more in the communication realm. Two people that you're seeing on the top, same two people on the bottom, are both using an implanted BCI. They're using an unmodified tablet computer to point and to click on the left to send an e-mail, on the right to do some looking on the YouTube to learn a little bit more about ALS. They both have ALS. They both have an implanted BCI. And in the bottom, they're chatting with each other using that implanted BCI. So there's text messaging. There's e-mail. There's additional education available from the web. There are components of clinical outcome assessments that somehow need to capture the joy that they reported that -- to us that they had from being able to do this, and being able to do it so intuitively and so quickly.

I thought there was one more on communication. Here, again, is another version of communication. Here we have a combination of visually-guided selection, and a couple of versions of neural clicks that allow for rapid control over here in this laptop computer for

directing of one's eyes, and then clicking in a number of ways. Powerful, intuitive, rapid, fully implanted system. How do we correctly distinguish is this one BCI, is it a BCI plus? What's the right outcomes assessment? From the user's perspective he can do this. He might not have been able to do this before. How do we scientifically and clinically capture that outcome in a way that is either validated or not, that is reportable and comparable to others?

All right. Moving away from communication, prosthetic arm control. Here's an example of somebody who has very limited control over their own dominant hand, is thinking about using her own dominant hand, and is doing a actually clinically validated task. This is a sort of I'll call the ARATs that she's using. I think these may be the official blocks from that, and picking up a block, moving it to another location. There's PTs and OTs in this room who are trained, and skilled, and licensed unofficially to perform this task, and to report it appropriately. Here's a very similar task. Press click. With and without ICMS, intracortical microstimulation feedback. So, again, we're seeing different versions of the same task, picking up an object, moving it to a different location. Objects of different weight, different size, different geometry. And it's happening at different speeds. And also there's some sense of perhaps additional embodiment because there is Intracortical microstimulation to the postcentral gyrus. So that the person who is doing that can sort of feel the moment of contact of that object as it's being moved from one place to another. How do we capture that as a COA?

This particular task, I like to refer to as coffee, chocolate, or beer. Those are the three that are going to be consumed here. I'm sure three of the four major food groups captured by IBCS. So we somehow we needed this as a COA. What are we actually measuring? Are we

measuring the speed of the robotic or the assistive arm control? Are we counting calories? Probably not. But each of their ability to do this, was incredibly meaningful to them. And how do we make sure that that somehow is captured as part of the COA?

That was an example of three people who had lost their ability to use their dominant hand using an external device to regain some of that function. Here are two people -- making sure that the videos are playing.

UNIDENTIFIED SPEAKER: Yes.

DR. HOCHBERG: Who are both using their own limb again. One with external functional electrical stimulation system. Somebody who has very limited ability to open and close their hand. And on the right, somebody who has no ability to flex, or extend their elbow, or to elevate their arm. On the right, the ability to do those tasks enabled by an implanted brain-computer interface controlled functional electrical stimulation. And then on the right, they are both the elevation through a mobile arm support, and the flexion extension of the arm, enabled by an IBCI plus an FES. How do we capture that? What's the right outcome assessment?

Another way to reanimate limbs, is to use soft robotics. Here's an example of somebody who is unable to open and close their hand who is thinking about doing so, and is opening and closing their hand with a wearable robotic on top of their hand making a few different grasps on the top, in the bottom, does have the ability to externally rotate it by their shoulder, and a little bit of that is elbow. Can't open and close his hand. So his ability to move that object, again, enabled by a BCI plus something else. Is that one system? Is it two systems? How do we measure it?

We've been talking about communication and upper extremity. Also, an example the lower extremity. There's somebody -- there's brain recording. That brain BCI is sending a signal

to a spinal stimulator, and with that somebody has a greater ability to stand with assistance, and to, to ambulate again with that, with that rolling wheelchair. Early days of a brain-spine interface. And the lower-right, eating French fries, completing the four major food groups.

Just to finish a couple options for speech. Woman with profound -- with brainstem stroke with profound dysarthria, presented with a phrase on the screen, and she will then attempt to say that phrase, and volume might have been a little bit soft, but the decoded phrase is spoken aloud from the computer. And there's an avatar that's associated with it. That avatar may have additional value in supporting the fluid communication between her and, and the person with whom she's speaking.

And one last quick video. Gentleman with ALS, advanced ALS, with substantially, as you'll hear in a second a substantial dysarthria. On the second day of use with 125,000 words available to select from speaking freeform, and while I'll let this play in the background the videos are edited, so we skipped a few phrases. But that second phrase was, I'm looking for a cheetah. And I'll just note that I'll -- may turn down the sound a little bit, but that phrase I'm looking for, a cheetah, believed by many including me, when I first saw it to be a decoding error because there's no way that on the second day of decoding anybody would have ever said, I'm looking for a cheetah. That's obviously a decoding error, except for the fact that his four-year-old daughter had just walked into the room dressed as a cheetah.

That moment, and the rest of the discussion that he had with his daughter, who likely doesn't have a memory of the -- his pre-ALS voice, how do we capture that, not only for the speed, the intuition, the accuracy of the decoding, but how do we capture that reconnection between father and daughter using an implanted BCI technology on day two of use?

Somehow that should be part of some clinical outcomes assessment.

Anybody else put off, a little bit, by the data request thing that's there at the bottom? Just to finish, yesterday thank you to all of you who were able to join. There's been launched an implantable BCI collaborative community. One of its interests, as well, together with folks in here are trying to figure out, what are the, what are the outcomes assessments that again, will be perhaps valid, certainly informative, will enable pre-market authorization, will permit actual clinical trials to be launched, will allow for sufficient reimbursement, will be meaningful to the people who use these technologies, will be meaningful to the clinicians who are thinking about referring these technologies. That's a lot to ask. And we've got about a day and a half to figure it out.

So I look forward to that happening. And just to finish off, communication mobility will be restored by implanted brain-computer interfaces. I have no doubt about that. It's going to positively impact how people with a wide variety of neurologic diseases, or injuries feel, function, and survive. We need outcomes assessments as starting points. They're going to need room to grow. Perhaps, they're going to be valid. We want them to be generalizable. They need to be specific enough to be meaningful. And we may need some creativity to perhaps, even create additional outcomes assessments that really capture some of what's been shown. There's all kinds of ways to really rely upon the users to tell us what is meaningful to them as an outcome assessment. And, as some people heard yesterday, there may be other models in neurologic disease for how we take baby steps. How we start small, and think about them with proximal outcome measure that is informative in order to keep this field moving, and to enable the innovation that's required so it can achieve all that we hope that it achieves.

And with that, just want to thank again, FDA, NIH for bringing us all together on this important topic, and look forward to the future discussions.

Thanks so much.

(Applause.)

DR. WU: Thank you so much Dr. Leigh Hochberg.

And our next speaker is Dr. Fraser Bocell, and also Dr. Erin O'Brien, to give us introduction to Clinical Outcome Assessments.

Dr. O'Brien.

DR. O'BRIEN: Good morning everyone. Thank you for coming. I'm Erin O'Brien. I'm a psychometrician for the Division of Patient Center and Development in the Office of Equity and Innovative Development at CDRH. And today, I'm going to give you a very high-level overview of clinical outcome assessments from a regulatory perspective.

Here's our FDA disclaimer. And here is our agenda.

I'll start by discussing what COAs are, and how they're used in clinical studies. Then, we'll talk about exactly how one goes about identifying or modifying a COA. Then, we'll talk about what FDA considers when evaluating whether COA is fit for purpose, and share resources where you can learn more about COAs from the FDA regulatory perspective.

A quick, exciting, regulatory note on some context before we dive in. This presentation references that patient-focused drug development draft guidance number three on selecting, developing, or modifying fit for purpose clinical outcome assessments. And I wanted to note that this is still a draft guidance. It is in the process of being finalized, and it's not yet final. When it is final, it will reflect FDA's current thinking on the topic.

A current final guidance on this topic is the 2009 Guidance for Industry Patient Report Outcome Measures Used in Medical Products Study, Design, and Development to Support Labeling Claims.

I note that the 2009 Guidance only pertains to PROs and not all clinical outcome assessments. And this new draft guidance is expanded to apply these same concepts to all clinical outcome assessments.

Okay. So what are clinical outcome assessments? So I think they've already been defined, but let's jump into the four types. These four types differ depending on who is doing the reporting, and what type of report is being made.

So the first type of clinician-reported outcomes or ClinROs, these involve an observation using clinical judgment, and are reported by a trained healthcare professional. For example, and some of FDA's dermal photo submissions we see the wrinkle severity rating scale where a dermatologist will rate the severity of a wrinkle on the face. A patient reported outcome, or PRO, involves a report directly from the patient without interpretation by anyone else. For example, the numeric pain rating scale. The patient is the one reporting the pain. Observer-reported outcomes, or ObsROs, are a measure based on observable signs, symptoms, or behaviors, and should involve minimal judgment that are reported by an observer, such as, a caregiver. For example, the FLACC pain scale. This is a behavioral pain assessment used for patients who are unable to self-report, such as infants. An observer rates behavior to derive the pain level.

Finally, a performance, performance outcomes, or PerfOs are based on the performance of standardized tasks. For example, the six-minute walk test evaluates functional exercise capacity. It's a supervised test that measures the distance the patient can walk over a six-minute period.

Want to talk a little bit about terminology related to COAs. So we've already defined the COA, but I wanted to note that this definition includes any instructions, administration

materials, content, formatting and scoring rolls. The COA score is the numeric value generated by a COA instrument through a standardized process. And the end point is a precisely defined variable intended to reflect an outcome of interest that's statistically analyzed to address a particular research question. So, for example, COA score at 12 weeks post-procedure.

So, now that we know what COAs are -- and let's talk about how they're used in clinical studies. How can COAs be used in clinical studies? Well, to make a long answer short, they can be used in pretty much all the ways. They can be effective end points, or safety end points. They can be primary, secondary, or additional end points, and they can also be used to determine trial eligibility.

I also wanted to note that the inclusion of a COA, is voluntary. They don't replace other types of evidence, and they may use -- you may use other means to assess an outcome instead of a COA that's available, well-defined, and reliable. CRH encourages the appropriate inclusion of the COA.

So now that we know what COAs are, and how they can be used, how do we identify, adapt, or modify them?

So this is a very busy slide that we're going to walk through step-by-step to unpack. Here you can see the bigger picture of how each step builds on one another to obtain a particular COA that's appropriate for measuring a specific concept of interest and the specific context of use.

The three main parts that we're going to walk through are number one, understanding the condition or the red text; number two, conceptualizing the clinical benefits and risks or the TL text; and number three, selecting or developing the outcome measure, the dark blue text.

Number one, understanding the disease or condition. The first step to identifying the

concept of interest or things that you want to measure is to understand the disease or condition, understand the perspectives of patients and caregivers. How does the disease impact them? This can help identify the most important concepts to measure. It's also helpful to understand the natural history of the disease and range of manifestations.

You also want to understand any potential patient subpopulations to ensure that your COA works for the full range of people it will be used with.

Finally, it's helpful to understand the healthcare environment, the clinical standard of care, and treatment alternatives, and other expert input such as clinical expert input may be helpful. And all this information coming can be collected through literature reviews, interviews with clinical experts, and patients and caregivers.

The next phase is conceptualized in the clinical risk and benefits. So the concept of interest is the aspect of the patient's experience or clinical, biological, or physical functional state that is assessed -- the assessment is intended to capture. So the very specific thing that the assessment is intended to capture.

And in a clinical trial, it's important to carefully select concepts that when measured adequately reflect an aspect of health that is important to patients, has the ability to be modified by the treatment, and could demonstrate a clinically meaningful difference between study arms within the timeframe of the clinical study.

You'll also need to define the specific context of use. This includes the patient population, the clinical trial design, administration method, and end point definition.

A conceptual model can be useful for representing patients' specific health experiences that result in their disease or condition, the health concepts that describe those experiences, and concepts of interest. For example, this model depicts how different activities relate to

different health concepts that ladder up to activities of daily living as a concept of interest.

Lastly, once you understand the condition, and you've determined the specific concept of interest that you want to use, that you want to measure, and the context of use, it's time to figure out how to measure it.

So here's an outline of steps involved to doing this. First, you should determine what type of COA to use, and have a rationale for this. For example, if you're measuring pain in adults getting Lasik surgery, a patient-reported outcome makes sense since the patients can report on this, and it's only known to them.

Next, you can search for a COA measuring the concept of interest in the literature. It's possible that one already exists, and is appropriate for your context of use. For example, its validity has been demonstrated in the same patient population. It's also possible that one exists, but it needs to be modified. For example, if a measure has been developed for one patient population, but some of the items don't quite make sense for your patient population, and it needs modification. Additionally, there may be cases where COAs exist, and they are being used, but the reliability and validity hasn't been formally assessed.

It's also possible that an entirely new COA is needed. If you do decide to develop a new COA, generally you have to do an empirical evaluation of it to support its interpretation and use in your clinical study.

I also wanted to note that the least burdensome principle, applies to COA development here at CDRH. Least burdensome is defined as, the minimum amount of information necessary to adequately assess a regulatory question through the most efficient manner at the right time. Applied to COAs, this means that we encourage the use of publicly available COAs when they're fit for purpose; i.e., you don't need to reinvent the wheel.

Also, we note that validity evidence may be generated from real-world evidence, early feasibility studies, phased clinical studies, the pivotal clinical study or post-approval studies. So you don't necessarily need a separate validity study.

And when we say that we need evidence to support the use and interpretation of a COA, we mean the evidence should be applicable to the context of use. This means, for example, validity evidence should have been generated in the same patient population, and in a study where it was administered in the same way as the clinical study will administer it. And at the end of the day, the evidence should show that the construct of interest is fit for purpose to measure the -- the construct of interest and the context of use.

And that brings us to an important question. What does FDA consider when deciding if a measure is fit for purpose? Big picture decisions about whether a COA is fit for purpose are based on two main considerations. First, is that the concept of interest and context of use are clearly described. We need to know what we're evaluating. And second, whether there is sufficient evidence to support a clear rationale for the proposed interpretation of the COA. So in the 2009 guidance focused on PROs, this meant evaluating the measurement properties of the, of the instrument in the context of use. But to expand it more broadly to other COAs, I'm going to reference the framework from the PFDD Draft Guidance Number Three, and when final that will represent the Agency's thinking on this topic. I'm going to describe eight components that can be used to make an evidence-based rationale for proposing a COA as fit for purpose, explaining how and why the specific COA is expected or intended to work. And this may -- applications may contain fewer or more of these components and submissions.

So, the first component, is the reason for your choice, type of COA, PRO, ObsRO, ClinRo, PerfO. The reason that you're selecting it to assess your concept of interest is clear. So why is

the particular type of COA appropriate for measuring the concept of interest? So for example, a rationale for using a PRO to assess pain is because patient is able to self-report pain, and pain is only known to the patients.

B, is that all important aspects of the concept of interest are covered by the chosen COA. This corresponds to content validity to ensure the measure is comprehensive.

C, evidence should -- respondents should understand the instructions, and items or tasks of the measures as intended by the measure's developer. So for the measure to work, respondents need to understand the instructions in the items or tasks.

For Component D, scores the COA are not overly influenced by processes or concepts that are not part of the concepts of interest.

So this is acknowledging that no COA score is a perfect reflect of the concept of interest, but scores should mostly reflect the concept of interest. And evidence supporting this could include evidence related to responses being consistent across demographic characteristics, evidence supporting the recall period, or evidence supporting the mode of assessment.

E, the method of scoring responses to the COA is appropriate for assessing the concept of interest. So big picture the rules for generating a score makes sense. And for this component the rationale for combining responses to multiple items or tasks should be supported by the measurement model.

F, scores from the COA correspond to the specific health experiences the patient has related to the concept of interest. So the scores should tell us how a patient feels or functions in their daily lives. Once it's all boiled down it's meaningful to describe how the patient is doing.

And this evidence could include known groups' validity or convergent validity. So scores

correlate with other related measures as expected, and scores differ between groups of people known to be clinically different in the concept of interest.

G, and the scores are sufficiently sensitive to reflect clinically meaningful changes within a patient over time in the concept of interest within the context of use. So when the patient's health changes in response to an investigational treatment scores should also change. And there are two main ways to show this. One is responsiveness to change. So if the COA changes as expected over time along with measures of the same or a similar concept, this would provide support. So if the score is changed in response to natural disease progression, or response to an intervention. The second way to show this more indirectly is by assessing the reliability or the precision of a tool. Showing there's minimum measurement areas in scores, and the types of reliability that are needed will depend on the type of COA.

And, lastly, differences in COA scores are interpreted and communicated clearly in terms of the expected impact on patient experiences. So scores should be interpretable. And one should be able to discuss changes or differences in the scores in a way that's clearly tied to how the patient feels or functions.

So for this component, we can explain how differences in COA scores translate to differences in people's lives. Draft Guidance -- PFDD Draft Guidance Four discusses different empirical approaches to this.

Okay. Let's start to wrap up. So this is a very high-level overview. How can you learn more? So I know there's a lot of information on this slide, but at a high level CDRH currently has two final guidances; one from 2009, and one from 2022. Both of these guidances are limited to PROs only, and not other COAs even though the same concepts can apply to other COAs. However, PFDD Draft Guidances Three and Four are in the process of being finalized,

and number three provides an update and expansion to the 2009 Guidance to the other types of COAs. Draft Guidance Four, is building on the foundation of some of the concepts described in the 2009 Guidance, but it's necessarily different, and it's focused on incorporating clinical outcome assessments into end points for regulatory decision making. And when we final these guidances, will represent the Agency's current thinking on COAs.

The 2022 CDRH specific guidance on PROs will remain complementary to the PFDD Guidances.

Here are some key links to our current final and draft guidances and our Q-sub process.

And to summarize, COAs are assessments of outcomes that describe or reflect how an individual feels, functions or survives. They can be PROs, ClinROs, ObsROs, or PerOs. COAs can be used to determine eligibility or create a primary, secondary, or additional safety or effectiveness end point. COAs can be identified in the literature adapted or newly developed. FDA can evaluate whether a COA is fit for purpose for the proposed context of use based on an evidence-based rationale. Those eight components I walked through. And you can learn more by reading the FDA CRH final PRO Guidances and draft PFDD Guidances Three and four.

And instead of questions I'm going to turn it over to my former colleague, Dr. Fraser Bocell.

(Applause.)

DR. BOCELL: Thank you, Dr. O'Brien. See if we can get my slides up. So while it's going, my name is Fraser Bocell. I'm a psychometrician, and a senior COA scientist with the Critical Path Institute. As Erin mentioned, I'm a former colleague of hers. I was a COA reviewer at CDRH for seven and a half years before leaving to join C-Path.

So those aren't mine. Mine has lots of yellow in it. As I like to say a social scientist. So

that one I think it is Erin's. There we go. I tend to put my name in the title. There we go. Okay.

So I'm going to talk a little bit about how to move forward with this. I think Dr. O'Brien gave you great level setting on what COAs are, and what the FDA kind of expects. I want to talk a little bit about how to accomplish that. Because it -- she makes it seem very easy, and it's nice to know a few key points that will help you move forward with that.

So, first of all, I'm going to talk a little bit about the Critical Path Institute where I'm at now. So we lead collaborations to accelerate drug development, advancing better treatments for people worldwide. We form collaborative workgroups comprised of diverse stakeholders to identify specific barriers to develop safe and effective therapies for a given disease, and then create tools and solutions that help product developers overcome these barriers.

So the key here, and I'm going to talk about this throughout, is that we bring different stakeholders together to work on this.

Now, my version of the roadmap is a little bit different than Erin's because I'm pulling it from the draft guidance. I think hers is a little bit more updated. And all of this, choosing an outcome measure, really needs to be grounded in your understanding of the disease or condition, and in conceptualizing how you're going to change that meaningful aspect of health into a concept of interest. How you're going to define that, and then, how you're going to measure that concept of interest.

So when you're going about understanding the disease and condition, make sure you're using any, and all available, publicly available information, right. Do your literature reviews. Find out what's out there. Find out what's useful. And don't go it alone. I'm willing to bet, you don't have a psychometrician on staff. So there's lots of companies out there that have built their strategy around helping you with this; contract research organizations, consultants. Make

sure you've got the right people helping you with the right topics. Involve patients and caregivers as research partners so they're not always research subjects. They can be your partners in this research helping you think about how you're talking to patients, how you're going about your research, how you're meeting your research subjects where they are. And to that end do what works for your patients. Don't make them come in to an office if you can do something remotely. It may not be possible in this case, but really think about how you're working with your patients, and think creatively in terms of measuring outcomes. This is a very challenging field, and we don't have all the answers. So that's why we're here, right? So you've got to think about it creatively.

When you're conceptualizing benefits and risks, and identifying the concept of interest, I'm going to reiterate it's important to talk to patients. Sometimes patients are unable to speak for themselves. So, oftentimes, you have to include caregivers in those conversations. They are a good source of information as well.

When you're thinking about the concept of interest, I mean, I'm assuming there's a lot of engineers in the room, make sure that we can talk to other people about what we're measuring, keep it in plain language. And, once again, did you talk to patients?

Defining the context of use. This is not a typo. This is the most important thing in some respects. I have colleagues at the Center for Drugs who actually have t-shirts printed up that say what is your COA, COU? So define your context of use, and talk to the FDA about your context of use. Make sure that you're getting the right information, and that you all can come to an agreement as to what that's going to be.

So, then, as we've already said, selecting, developing outcome measure, explore what already exists, but be mindful of who owns the rights to the tool. You may have to license it. If

it's not fit for purpose, and you need to modify it, you need to get their agreement that you're allowed to modify it. And be aware of the original concept or context of use that the tool was originally developed for. If you're working with pediatrics, you can't use a tool necessarily that was developed for adults. You've got to make sure it's going to work with that group that you're working with.

Make sure you're engaging with the appropriate experts, explore opportunities to collaborate. The pre-competitive space where you can share information is a great opportunity for this. And it feels weird not being with the FDA and saying this, but consult with the FDA early and often. They are there to help you. They are there to get -- help you get your product to patients. And I'm going to just keep saying this. Always keep your context of use in mind.

Now, for a fit of purpose COA the evidence should support the use and interpretation of the COA for its intended context of use. It's not the COA itself that you're collecting evidence to support. You're collecting evidence to support that score, how we're interpreting that score, and then how we're conveying that information once we've collected it.

So the evidence should demonstrate that the resulting score and the associated end point definition are meaningful and interpretable. Remember, this is going to have to end up in labeling. This is going to end up in public summaries. This is going to have to end up with payers, and they've got to be able to interpret that, make sense of it, and draw meaning from it

The COI and the COA determine the types and strengths of evidence needed to support the interpretation of the score. If you're proposing a COA as a primary end point, you're going to need a lot more evidence to show that it's an appropriate end point than if you're using it as an additional, or an exploratory end point because the inferences you're drawing from it are much stronger in that case. So we need to have more evidence.

And, finally, I know that Dr. O'Brien provided a link to the Q-sub guidance. I do encourage you to submit a Q-sub to get feedback before implementing your PO, your COA in your pivotal trial. Don't go this alone. Make sure that you're involving the FDA, and appropriate experts whenever possible.

Thank you for your attention today. And I don't think we're doing questions. So I'll pass it back to Molly.

(Applause.)

DR. WU: Thank you Dr. Bocell and Dr. O'Brien.

So our next session is the Current State of COA in Payor's Coverage Decision making. It will be moderated by Dr. April Marrone with speakers Dr. Lea Drye, T.J. Sutphin on the panel in person, and Dr. Sharyl Martini, joining virtually.

DR. MARRONE: Good morning. Can you hear me now? Interesting. It's red instead of green. Okay.

So, good morning. My name is April Marrone, and I am an advisor with the Total Product Life Cycle Advisory Program and CDRH. It's really great that -- to be invited to be here as a moderator of this very important session.

We are joined today by three guests. Dr. Martini is online, right? So I will introduce our guests who have joined us in order of, alphabetical order of the organizations they're here representing.

So, first of all, I'd like to say welcome to Dr. Lea Drye. She is with the Blue Cross Blue Shield association which is a national federation of independent community-based and locally operated Blue Cross and Blue Shield Companies that collectively provide healthcare coverage for nearly 118 million people or 1 in 3 Americans. Blue Cross Blue Shield Companies are nearly

-- are in nearly every ZIP code in the U.S., the District of Columbia, and Puerto Rico. Dr. Drye is Director of Clinical Science Services with the Office of Clinical Affairs at Blue Cross Blue Shield Association. Dr. Drye is the lead methodologist for health technology assessments, and serves as the Blue Cross Blue Shield Association liaison in collaborations with regulatory agencies and industry stakeholders.

Prior, to coming to Blue Cross Blue Shield Association, Dr. Drye was faculty at Johns Hopkins in the Epidemiology Department, in the Center for Clinical Trials. She has over 15 years of experience in the design, implementation, and data analysis of clinical trials and observational studies.

Dr. Drye has received graduate degrees in statistics from the University of Wisconsin, Madison, and epidemiology from John Hopkins University.

So thank you for joining us this morning.

So next here, in person, is Mr. Anthony Sutphin, who serves as the acting Medicare pharmaceutical and technology ombudsman or PTO within the Centers for Medicare and Medicaid Services for CMS, Office of Hearings and Inquiries. In this capacity, he also serves as a new technology liaison working closely with colleagues in the Technology Coding and Pricing Group, and other CMS groups to support engagement with medical device, pharmaceutical, and biotechnology manufacturers and other stakeholders. He has experience with the works to assist medical technology and avers with engaging CMS and addressing coding, payment, and coverage matters, concerns and inquiries. Prior to taking on this role, Anthony worked as an associate ombudsman, providing key support to a Medicare beneficiary ombudsman, competitive acquisition ombudsman, and PTO in assisting Medicare beneficiaries and other stakeholders.

So welcome. Thank you for joining us today.

And last, but definitely not least, joining us virtually is Dr. Sharyl Martini, who is with the Veterans Health Administration. The Veterans Health Administration, or VHA, provides healthcare to more than 9 million veterans each year. She will be sharing her experience as the Executive Director of the National Neurology Program, and in that role she serves as the principal advisor to Veterans Health Administration and all policies and procedures related to delivery and assessment of neurology services. Dr. Martini is also an associate professor in Baylor College of Medicine's Department of Neurology, and her research has focused primarily on ischemic stroke and intracerebral hemorrhage.

So thank you, Dr. Martini, for joining us virtually today.

Okay. So I do have some questions I'd like to start to engage our panel. And the first one is, how do clinical outcome assessments or COAs play a role in coverage policy development made by your organization? And I'll also add to that question assuming that they do play a role, what are the characteristics you consider when looking at clinical outcomes for novel technology when making your policy decisions? And if you can include in your answer how you think of validity, and what type or level of validity is helpful to you.

So let me start with you, Dr. Drye.

DR. DRYE: Thank you. And thank you for the invitation to be here today.

DR. MARRONE: You have to push your button. Okay.

DR. DRYE: So we include clinical outcome assessments directly in our evaluation criteria. So let me start by explaining a little bit about how it works. So you went through that I am with the Blue Cross Blue Shield Association, and we are the trade association for the Blue Cross Blue Shield companies. The Blue Cross Blue Shield companies are all independently

owned and operated.

One of the services that we provide at the Association is that we do help technology assessment for the Blue Cross Blue Shield companies so they can use that assessment when they're making determinations about eligibility for coverage for new and emerging technologies. So my comments are going to be focused mostly on technology assessment because the coverage decisions are made at the plans themselves.

So we -- a lot of what we consider though, in our health technology assessment, is similar to what we heard in the previous talk about clinical outcome assessments. We have evaluation criteria, our technology evaluation criteria which are published, and you can look them up. I won't go through all of them in detail, but in grief when we evaluate a technology we are looking first to see whether the evidence is sufficient that we can evaluate what we call help outcomes. And second do those -- for those help outcomes is there a net improvement in the outcomes compared to available alternatives.

So we define help outcomes here, very similarly, to what we've already heard with clinical outcome assessments. They are outcomes related to length of life, quality of life, and the ability to function. So they really do parallel the feels, functions, and survives.

So those are the primary outcomes that we are looking for in our assessments. And we are, again, when we're looking at outcome assessment tools we're looking for ones that are, have been validated, and that have been -- have a pedigree preferably in the target population, and that target population should be one with the condition of interest, and it should reflect the relevant diversity of that population. We're also looking for things that are important to patients because, again, our help outcomes definition includes function and quality of life. So we're looking for things that are important to patients. We're looking for outcomes that are --

that have been shown to be able to detect change, and we're looking for things, again, that have preferably been validated in the, in the target population.

We think that those many different levels of validity are important. It should measure what it's supposed to measure. It should also capture the range, the scope of the lived experience of the people who have that condition.

DR. MARRONE: Great. Thank you very much.

So Mr. Sutphin let me give you the, the same question, please.

MR. SUTPHIN: So, well, thank you very much for the opportunity. But I would double-down on what Dr. Drye said. A lot of what CMS is looking at is the functional outcomes, what the beneficiary is experiencing, how -- the causal relationship of your product or item of service --

Better? Do I need to yell?

Okay, here we go. So I, again, I will agree with Dr. Drye. What CMS is looking for are the functional outcomes, the experience of the patient. How does that patient's life improve? How do their activities of daily living improve based on what the product may be doing? We're certainly looking at viability, durability, the length of the disability, and sorry, I keep scooting away, and as well as mortality. And so essentially how does this make the beneficiary's life better? Not just what the product can do, but that that adjustment increased the quality of life for the beneficiary. And that's really one of the main focuses for CMS.

DR. MARRONE: Great. Thank you.

And Dr. Martini, let me turn the question to you, please.

DR. MARTINI: Thank you. I would just like to go with our prior two panelists said. I will start by telling you all a little bit about how coverage decisions are made at VA. And you're

getting my experience leading VHA neurology. As you can imagine, there are a lot of different players that go into policy development, of internal capacity, as well as, payment procured outside the VA. All of those decisions are based on published evidence. We have a group of subject matter experts that obviously, are put together based on the specific coverage decision that is desired, and those subject matter experts consider the degree of meaningful clinical improvement as well as between groups statistical significance overall.

I will say that for prosthetics, for the prosthetic portion of VA, VA does not make general coverage decisions about medical devices. If a device has received FDA clearance, and the prescribing clinical provides the requisite justification, VA is authorized to purchase the device, and issue it to the veteran. However, program offices staffed by subject matter experts will make recommendations to the field that are again based on the published evidence. And in the published evidence the things that matter most to patients are the things that matter most to us.

You also asked about types of, of validity. I would agree that outcomes that measure what they aim to measure, and capture as many factors of what they're purported to measure as possible are the most important to us as well.

DR. MARRONE: Thank you, Dr. Martini.

So let me move to our next question then, and I'm going to start with you, Mr. Sutphin. So when considering medical necessity, or reasonable and necessary, being able to measure clinically significant improvement that a patient considers important and will lead to a change in their care management, is important as, I think all of our panelists just mentioned. So for BCI technologies, what do you consider may be an appropriate clinical outcome assessment that may support that clinically significant change? And to add onto that could the ability to connect

say to the modern world such as e-mailing, texting, using health apps, performing instrumental activities of daily living, and by a computer be considered reasonable and necessary or medical necessity?

MR. SUTPHIN: Make sure I can be heard now. All right. Thank you for that. And I think yesterday I had the honor to join a couple of the working panels. So some of this may be a little bit reiterated. Because the technologies are so new so many of these will need to be separate and private conversations. All of your end points are going to vary. All of your, your approach. The populations you're looking at are going to vary. But when it comes to other applications that may even already exist, it's a good and safe bet for you to take a moment, and take a look at through some of the national coverage and local coverage determinations. I know many of you are working towards speech devices or speech-generating technologies. CMS has NCVs, LCVs, and local coverage articles that should provide information on what -- how those contexts are covered, and what evidence is available for that to be covered.

Additionally, I would add most recently there was NCD for a wheelchair seat lift mechanisms, I believe, for a Class II, Class III, and as you are all are looking at evidence, an what CMS may be looking at it's a -- that's another NCD to take a look at. It's one of the more fresh ones. And then, I guess, the, the next thing to certainly take a look at is on August 7th, the Coverage and Analysis Group released an updated information article around the evidence for coverage and review. And so, it lays out some pretty good information for everybody to take a look at. And, again, as you have questions as you're going through all of that we remain available.

DR. MARRONE: Thank you.

Dr. Martini, let me turn this question to you next, please.

DR. MARTINI: Sure. Again, the -- these COAs should focus on functional gains that are meaningful and increase independence. Does the device prescribed in the case of prosthetics serve a direct and active component of the treatment or rehab for which it's prescribed? I'm most familiar with ALS so, obviously, respiratory function is absolutely key. Muscle strength and motor function. But obviously, as we're going to talk about next, there are other aspects like communication as well, that are important.

DR. MARRONE: Thank you. And, Dr. Drye, can you also take this question, please?

DR. DRYE: Thank you. So I agree with what has been said. We do frequently consider activities of daily living in our reviews. And the specific, the specific components of the assessment are very context-specific. So like in the previous discussion, we also are always telling manufacturers when they come to us to be very clear about the context, and it's so important. And I think that the context is important here because the -- what you should measure will depend on the patient, the participant's characteristics, and what can you feasibly measure. What is the level of functioning? What is the level of communication? And then it will also matter depending on what's the target of the BCI. So what type of functioning is that tool supposed to facilitate?

But because these are designed to increase independence, instrumental activities of daily living will be very important in our assessments.

MR. SUTPHIN: And I would, I would just add, since you mentioned the characteristics, it would be important as well, to understand the characteristics of the patient group that you're looking at. Because some of -- as you're going through this, there may be -- you may identify folks that are unable or would not qualify for these types of devices as well. So that information, is still data that's important.

DR. MARRONE: Thank you.

Okay. So we've talked a lot about the clinical characteristics. So our next question focuses maybe, a little bit more on the technology. So when considering advanced technology and future coverage policy decisions, to what extent do you think that those decisions may be kind of more focused on technological parameters? And would they, on their own, be considered? So like, how might you imagine building evidence that translates those technological parameters into then clinically meaningful health outcomes?

And Dr. Martini let me start with you, please.

DR. MARTINI: Sure. I think clinically, obviously, we've talked about clinically meaningful function is what's important, and would supersede technological parameters. So the VA technological parameters are very important about whether to issue a device to veterans. VA is subject to a number of privacy information security and cyber security laws that are more stringent than typical healthcare laws. And so, any devices that can capture or transmit patient data would, would have to consider that in the VA as well.

DR. MARRONE: Thank you. And Dr. Drye, can I turn the question to you, please?

DR. DRYE: Sure. So technological parameters I think they've been very important in driving innovation and development in the evolution of these technologies so far. For our purposes and our reviews we will be looking for, again, the functional, and the quality of life outcomes more than the technological outcomes. But that doesn't mean that they're not important anymore. Because they still give us information about how the patient's interacting with their device, and what the user experiences. And I think they can also give us information that might help us to understand any variability that we're seeing in function, or they can help us understand differences in adherence and uptake.

DR. MARRONE: Great. Thank you. And Mr. Sutphin would you like to take a stab at this one, please?

MR. SUTPHIN: I assumed I was next, but it's really hard to add on to what has already been said. As kind of been mentioned, the technological advancements certainly matters, but it's, it's that function. It's what it does for the beneficiary. That's going to be the largest measure if the beneficiary can now get up out of bed by themselves. Can they feed themselves? Like what your product does for that beneficiary's quality of life is certainly going to be one of the higher tiers that we look at.

DR. MARRONE: Great. Thank you very much.

So I'm going to jump a little bit ahead on the questions here. So we do have several scales or measures, such as, the Functional Independence Measure, the Functional Assessment Measure, or Section GG Functional Abilities and Goals as defined by CMS. Are there any other scales or measures that you think could be used as a model?

And Dr. Drye I think we're back to you in my, my circular pattern here.

DR. DRYE: Thank you. So the FIM and the FAM they're very global scales. They capture a lot of different functions. There's a lot of different functions in them, and I think that the positive is that they have been validated across many different groups, and so they could potentially be used with a heterogeneous population. But the, the disadvantage is that they have items on them that will not be applicable to all of the people that are potentially in the patient population of interest. So if you have patients that have severe disabilities, severe physical limitations, and you are asking questions about physical function, then you wouldn't expect that scale to be able to detect change when it's used over time.

So I think that it's, it's going to be difficult to use very generic scales like that. But there

might be subcomponents of those scales that you could pull out and use for particular patient populations. But again, I come back to, it really is depending on the context, and what the patient group is, and what the tool is, and what the device is supposed to address.

DR. MARRONE: Thank you. Yes. I've heard somewhere the context of uses is very important.

DR. DRYE: It's very important.

DR. MARRONE: Mr. Sutphin could you respond to that question, please?

MR. SUTPHIN: Oh, absolutely. So CMS will certainly never tell you which tool you should be using, and each tool really is going to be dependent on the outcomes and the goals that you're trying to achieve. CMS really is looking for valid and reliable outcomes, responsive to change, and that can provide meaningful change to the patient's life. So I wouldn't necessarily have any advice or guidance on what else could be used. Just more that what you're using is applicable to your product.

DR. MARRONE: Thank you. And Dr. Martini, I'll turn this question to you, please.

DR. MARTINI: Sure. Thank you. The VA doesn't have any ideas about additional assessments, and we don't endorse any specific scales or measures. However, clinically VHA currently uses Section GG to monitor functional gains during --

DR. MARRONE: Great. Thank you very much. Okay. So let's shift a little bit now to, to patients.

And Mr. Sutphin I'm going to start with you please. Should clinical outcome assessments and therefore studies be focused on specific patient populations? How has this been approached in previous coverage policy decisions for treatments targeting a population with a broad range of functional presentations and goals? And what information may be

helpful in identifying the patient population for a coverage policy?

MR. SUTPHIN: So that's, that's really helpful.

I turned it off so I wouldn't make any noise, and then here I am.

So that's really helpful. So when CMS is looking the quality of evidence is going to matter. Again generalization to the Medicare population, and kind of the overarching conclusions that can be drawn from your study, and the effects that it may have on that population. Really we want to make sure that any questions that are, that are -- that may be, that may exist can be addressed conclusively that if we have a question that, that -- I'm sorry. If we do have a question that you are able to, able to provide a logical and succinct response without gaps in information or knowledge.

DR. MARRONE: Dr. Martini, I'll turn this to you, please.

DR. MARTINI: Thanks. Of course for the VA, ALS, traumatic brain injury, and spinal cord injury are of special interest. In terms of targeting a population with a broad range of functional presentations and goals most of the published items that we base our coverage decisions on are relatively narrow. I'm not aware of any coverage decisions that have been based on a study that's, for example, combined variety of different populations.

DR. MARRONE: Thank you. And, Dr. Drye can you please respond to this question?

DR. DRYE: I think it would be very challenging to design a study that was applicable to a very heterogeneous population because the population itself, they're going to vary with respect to their physical and communication functionality. But also, the tool itself, what the BCI is supposed to address, is going to vary. And so when you're measuring the outcome, what you, what is actually measurable, but also what is clinically meaningful is going to vary across those populations as well. So I think it would be difficult, challenging to, to lump all of those into a

single study.

DR. MARTINI: If I could add something else to that. I think what I've seen in the scientific literature, as I'm sure most other folks have, you can have a treatment that works really well for a particular population, and if you lump a big group of people, that signal can be reduced, and you can end up with a negative study.

DR. MARRONE: Thank you. Thank you for that additional input.

So let's think about now the duration of studies, and the differences in population. So what kind of duration would be expected for participants with chronic nondegenerative diseases versus degenerative or terminal conditions based on current coverage policy decisions? So should the natural course of the condition impact the timing of outcome assessments in a clinical trial?

And, Dr. Martini, I'll turn this question to you first, please.

DR. MARTINI: Sure. Obviously, coverage decisions again are based on the impact not the prognosis of the patient. I think we know that, for example, ALS has a pretty rough diagnosis, and I don't think there's anyone that would claim that it's not valid to, to focus on that because of the poor prognosis. The natural course, obviously, is going to impact the timing of the outcome measure. If there is a condition where you expect stability or improvement, for example, stroke, that would have different timing, and different expectations than for example something like ALS.

DR. MARRONE: Thank you. And Dr. Drye.

DR. DRYE: Yes. So we, we do get asked a lot about duration of follow-up. This is a tough question in all of our evaluations. So it depends, again, on the context. It depends on how long you expect the benefits to take to accrue. It depends on how long you expect the

harms to accrue. And it depends on what you think the durability of the effect will be. So do you think that there's going to be problems with the -- potentially with the device? Does the device use wane over time? But then also with the patients themselves is the disease going to progress so that the effect of the treatment might, might be less over time? And it does depend on the natural history of the disease as well. Is this a chronic disease or is it progressive? And if it's progressive, what is the variability around that progression over time?

DR. MARRONE: Thank you. And Mr. Sutphin.

MR. SUTPHIN: So there's very little to repeat off of what's already been said. Really, the easiest answer for CMS is, as you're developing and having these conversations, the earlier that you can reach out to myself and -- we can organize conversation with my colleagues the better. As you've heard every -- each one is going to be different. Each variable, or each project, is going to have different variables, different outcomes, and different impacts. And so it's one of those things where it's better for you to meet one-on-one with us so that we can ask more direct questions. It's easy to give broad, vague information up here, but knowing that the questions you have are very detailed it's a lot easier on a one-on-one occasion. So I'll use this opportunity to welcome any of you, to shoot me an e-mail, or give me a call so that we can figure out, you know, more internal CMS conversations to help address your questions.

DR. MARRONE: Great. Thank you very much.

Okay. So we're going to shift gears a little bit. I apologize. This question I wrote it so it is a little wordy. Professional society input is likely crucial for assessment of novel technology. Societies may offer recommendations on conditions to optimize patient outcomes, facility volume, training, et cetera. However, for emerging technology this can be challenging since there may not yet be society guidance. Society guidance may take years making it very

important to start early in the device development process to sensitize relevant to societies to technology and the procedures for using the technology, and to develop a comprehensive publication plan to garner that support, support common procedural terminology coding if applicable, and generate the publicly available information that is critical for reimbursement policy decisions. So how do you see your organization coordinating with professional societies to further evidence development such as clinical outcome assessments for brain-computer interface technologies?

Dr. Drye I think it's your turn to go first.

DR. DRYE: Okay. So we do very much value input from professional societies. We use it in all stages of our developing of a technology assessment. We have a process where we also will reach out to societies, and to academic medical centers to get expert opinion so that that gives their experts an opportunity to make sure that their opinion is heard, and we document it in our assessments. And we, like I said, we, we interface within multiple spots in the review. But in particular, for this question, we talk to them early in the process when we're still developing, and thinking about the, the review itself. We ask the questions about, what is the current management pathway to make sure we understand how this technology would fit in. What is guidelines-based care? What is the appropriate population? What are some features of the intervention that we need to be looking for? And what are important outcomes of interest? And it is very helpful to us, but rarely available when there are professional guidance on the appropriate outcomes of interest, what are clinically meaningful differences, what is the appropriate duration of follow-up? So on rare occasions we have that, and it's very helpful.

DR. MARRONE: Thank you. And Mr. Sutphin.

MR. SUTPHIN: So I'll say we work with a number of organizations kind of across the

board through medical device and drug industry. The feedback is important. It's certainly helpful. It kind of like signed on peer review we've received. A lot of what we do goes through public notification and comments, and that's really where we get that information anyways through new products and codes that are being recommended for coding our coverage payment. And so that gives the, the public the opportunity. But a number of that, those comments, also come from professional organizations who may also reach out separately outside of those public comment periods to provide nuanced information, perhaps additional background. I would also say sometimes that comes with a professional organization that might be maybe against a new technology. So we understand we have to hear both sides, and we're open to taking in all of the information to make sure that we're making an appropriate decision.

DR. MARRONE: Thank you. And Dr. Martini.

DR. MARTINI: As a government entity, VA has to be very careful about endorsing things that may have a commercial component. So it's unlikely that VA would work with professional societies to endorse something in particular. On the other hand, VA does support research that is relevant to veterans. So VHA researchers can certainly participate in these types of discussions with their professional societies, but it wouldn't be an organized effort per se.

DR. MARRONE: That is helpful. Thank you very much.

Okay. So I will move on to our last question, and that is general note peers are reliant on what is available in the peer reviewed literature which underscores the importance of a well thought out evidence collection strategy. It includes sufficient publication of trials that leads to a high degree of confidence in the outcome data. With the opportunity to consider the future of BCI technologies in this early stage what would be your word of advice to this industry as a

whole to work together to promote patient access to these groundbreaking technologies?

And Mr. Sutphin, I will give you the opportunity to respond to that first, please.

MR. SUTPHIN: Well, so as I've already noted, you're all working on something different, different populations, different end points. And really, to start the conversation as early as possible, is certainly going to be helpful. Admittedly, early conversations with CMS will revolve around clinical trials, coverage development, evidence that you may need. I know there's hot topics of coding and payment, but a lot of that, until there's a product, it's all theoretical. So we have to be really, kind of, careful about what we're saying. And so, as you probably -- many of you, you here were there yesterday you probably heard me reference several ACD -- or LDCs, NCDs, or, you know, again, the coverage with evidence review policy that went up on T-set policy that's out. It's much easier to reference what already exists. But also, there's items I will reference are the HCPCS quarterly coding cycles. And if you take a look at that, the preliminary decision is posted. And then a few months later you see the final. So you can kind of see how decision making works.

Twice a year there are public meetings for durable medical equipment, prosthetics and orthotics, or really nondrugs and nonbiologics. And that's, that's a public meeting. Anybody can attend. But you can see how the questions, types of questions CMS is asking. So any of those opportunities to really be part of the process without being in the process I think will help, help you set up for the future you guys are looking for.

DR. MARRONE: Thank you. And, Dr. Martini, what would be your words of advice to our innovators?

DR. MARTINI: Well first thank you for doing this innovative work. Our veterans and special populations affected absolutely deserve the very best quality of life as to all the folks

affected by these conditions. So first of all just really appreciate this.

And second, again, focus on clinically meaningful functional improvements that, that matter to patients. And we're just eager to see what you all will come up with.

DR. MARRONE: Thank you.

And Dr. Drye what is your advice?

DR. DRYE: Thank you. So facilitating access to these treatments in a timely manner is a shared goal of all of us here today. And I think that these conversations that we're having over the next two days are really important for us to hear everybody's perspective, and everybody's expectations of what this will look like. And I think that now is the time while the feasibility studies, the early phase studies are ongoing to be working in parallel on developing these outcome measures, and validating them so that when we get to the pivotal studies they'll be ready for use in the pivotal studies.

DR. MARRONE: Thank you.

So I would like to take this opportunity to thank all of our guests who have agreed to take some time from their valuable schedules and participate in this panel today.

So we will, I believe, move into a break next. And our two participants that are here are more than happy to take some informal questions during our break. And I hope that's true. I didn't really double-check with them, but maybe get them before they run off too fast.

But with that thank you very much, and look forward to further discussions.

(Applause.)

DR. WU: Just a reminder we'll be back at 10:30.

(Off the record for break.)

DR. WU: So welcome back everybody. So our next session is the Current State of

Clinical Outcome Assessment in Evaluating People with Functional Impairments. And our speakers today are Dr. Catherine Lang, Dr. Kimberly Frey, and Dr. Carolyn BAUM.

DR. LANG: So thank you all for inviting me here. I'm glad that we finally get to go through these slides since they've been up here so many times.

I've put motor function in quotes. And so in the next couple of slides you're going to see why that term is in quotes.

Instead of giving you a list of funding and disclosures like I usually do, I thought I would give you some perspectives and biases before we go into the talk.

This is the brand new Neuroscience Building at Washington University, $670 million, mostly molecular and cellular labs. A few systems labs, and no direct patient labs in this building.

My building, and the building that Dr. Baum works in, are signified by the little white arrow next to this beautiful building.

I'm trained as a physical therapist, and I have a PhD in movement science. I have a colleague, who I met last April, who calls me a WWW which stands for a walking white woman. Sometimes I add onto that over educated, and a Midwestern and middle aged. So just so you know where I'm coming from.

My long-term research has been in the human model of stroke recovery and rehabilitation, and at my institution I always talk about the human model because we talk a lot about rodent, nonhuman primate, fish, et cetera, other models.

And I also want to just tell you that I don't do research in the BCI space, and nor do I have a lived experience of having or needing a BCI, at least so far.

So this seems incredibly obvious, but I just want to state that the target of the BCI

design needs to match what the user needs and wants to do.

You'll notice, by the way, throughout my slides that the main point I'm trying to communicate is on the top. So if you tune out because you're getting hungry for lunch, just reorient yourself to that slide.

This statement is obvious, but it's actually not trivial, and it's -- there's a high potential that for designing different systems that the users may not want or may not need. So I'm really happy to hear all of the discussions already talking about the importance of putting the user in front of the user-centered design.

The other thing I was thinking about as I was making this is, is that the devices that are going to need FDA approval are going to be in a space that can't be solved by the nonmedical commercial options. And so, thinking about as you're building your design, not to put yourself out of the market when Meta or Google, or someone else does something that's already in place.

And then the challenge for the motor system is that the motor options for BCI are going to need to control peripheral apparatus. They're going to need to control a human arm, a human leg, a human trunk, a human trunk and two legs if you're walking, plus arms, or a prosthetic or an exoskeleton or a wheelchair. So we have to think about those options, as well.

Okay. I'm going to make two main points today. And I'm going to first, make the point of now is the time to use more precise terms than motor function. And so motor function means a lot of different things to a lot of different people. I had the privilege of serving as to co-chair for the Motor Function Group in the Common Data Elements that was done by NINDS and NCMRR a few years ago. And we had a group of experts in motor function, and none of us could agree on what motor function meant.

And so, we can think about, to some people motor function might mean whether I can activate muscles. To a physical therapist, it might mean how much strength can I measure in a particular muscle. If I work in a research lab, maybe I'm measuring the kinematics of someone as they use those muscles to walk. Again, in a clinical setting I might be measuring how fast someone can walk. The clinical outcome assessment of the 10 Meter Walk Test is a very common tool in rehabilitation clinics. And then, of course, we might be measuring how much somebody walks in daily life. Maybe I want to measure walking based on someone's individual perspective which might involve more than just walking in a straight line. Might involve a dog or a stroller or something else. And then, of course, people have different means of mobility. And so looking at daily mobility performance from individual perspectives is incredibly important.

There's actually, already a framework for you to think about this. This is the International Classification of Functioning from the World Health Organization. How many in the room have seen this before?

Okay, good. So some, but not as many as I had hoped. This means that the FDA, and that your company, doesn't have to reinvent a measurement framework because one already exists. And so in this framework there's an interaction between the health condition of interest, and three different levels of measurement.

The first level of measurement is called body function and structure. You can think about this measuring different structures in the body, and different functions of those particular structures. So if I get an MRI, then that is a measure of body function or structure depending on whether it's FMRI or an anatomical FMRI. I might make a measure of grip strength. That would be a measure of the function of the muscle. Or I might collect a specific

angles of somebody as they're walking across a room with kinematics.

Before I get to activity, it takes a bunch of different body structures and functions to allow you to do activities. And if you can do a bunch of different activities, then you can participate in life goals. And I'm going to pass participation on to my colleague

Dr. Baum down here, and I'm going to stay in the activity level. And in the activity level we can actually split this into two levels. We can split it into the capacity for activity. What is somebody capable of doing in a structured setting? So think about, what can you do on a standardized clinical test. And then, what is someone capable of doing in their free-living environment? And we call that performance. And so we can measure motor capacity, or the capacity, for example, to walk with something like the 10 Meter Walk Test or the Timed Up and Go. We can measure someone's capacity to grasp objects with something called the Box and Block Test. And then we can measure their performance of that activity in everyday life as was mentioned earlier patient-reported outcomes. I've personally worked in the space of wearable sensing for the past 10 to 15 years. And so we can measure the integration of the limb into daily use or the number of steps that somebody might walk in a day, for example.

And so, as was mentioned earlier, any measurement that we're taking is just a sample of the construct of interest in any of these we can think about as COAs. So here's our measure of, of muscle strength, and any manual muscle test that we might do just fills up half of that part of that then diagram, right? It's not a comprehensive measure that collects everything about strength in that particular muscle of that particular person.

When we think about upper limb capacity or upper limb motor function, I mentioned earlier the Box and Block Test. This is a test where you see how long it takes you to move a whole bunch of blocks over a barrier with one hand. And so you can think about that measures

part of your ability to use your upper limb capacity.

Lea mentioned earlier, the action research arm test. This is a picture of that. That one has 19 items. So that one samples the capacity to ask those questions. And then as I mentioned before, if we want to think about something like walking performance in daily life, if we measure something like steps per day or minutes of moderate to vigorous physical activity or distance time walked, then we're getting part of their walking performance in daily life

So I want to encourage all of you to be thinking about where on that measurement model you might be wanting to measure. As was mentioned earlier, we might be thinking about a measurement strategy so that we're measuring at multiple levels, and at different phases of trials the end point or the primary outcome might shift so that it might be early in the measurement scheme in the early trials, but later in the evidence scheme in the later trials.

The next thing I'd like to just share with you is that the -- if the BCI is intended to target a particular function then your best option for measuring that as was kind of hidden in the messages earlier is going to be the appropriate standardized measure that already exists.

So on this slide, I'm going to share with you a bunch of different measures. You can see here for upper limb capacity, we've got the Box and Block Test. This is actually the test that was recommended by the Motor Function Common Data Elements Group in -- through NINDS. This is one the few upper limb capacity measures that has been used in multiple populations.

The Action Research Arm Test has been used primarily in stroke, but in a little bit in another population. And the Grasp and Release Test of course is a, is a test that's used for evaluating treatments after a spinal cord injury.

If we're talking about walking capacity, the most basic one of those that's used is the Functional Ambulation Category. This is a simple scale that goes from you can't walk at all to

you can walk on uneven surfaces, on inclines, and not need an assistive device. It's very definitive scale, but as you can imagine there's not a lot of range to it, and it takes a lot to move from one level to the next.

If someone can walk independently or can walk with an assistive device, your target is probably going to be the 10 Meter Walk Test. This is the most commonly used measure in your rehabilitation clinics for physical therapy. It's already used in the population. It's been well validated. It's not difficult to do. And there's actually a lot of good data out in the world suggesting that your walking speed is the sixth vital sign, and that decrements in walking speed also show you declines in other areas, medical areas. If you want to get beyond walking in a straight line, then your option might be the Timed Up and Go which requires you to stand up from a chair, walk three meters around a cone, come back, and sit back down.

I would be a big fan to push whatever is -- whatever you decide, I would be a big fan to push this out into the activity performance level. And so, there are multiple variables now that are captured from wearable sensors that have very good data both in normative populations, and in patients with upper limb disability related to how that limb is being used in everyday life.

I'm happy to -- that's not the talk that I'm giving today, but I'm happy to talk to somebody offline about that.

If we're talking about walking performance in terms of direct measures, again, we can measure your steps per day either through an ankle device or through a wrist, wrist device, and calculate a bunch of variables that also have quite good psychometric properties.

Wheelchair mobility is probably the category that's the least underdeveloped in these methods. There's not been a lot of time or attention put into this, and we can hypothesize about why that is unfortunately, but there is a Wheelchair Skills Test which is similar to the idea

of a Timed Up and Go. And then it has a bunch of different wheelchair skills somebody has to be able to do, and they can navigate through those things. There's Wheelchair Propulsion Tests. There's actually a six-minute wheelchair test, if you want to look at wheelchair endurance. And then you can, you could also have an instrumented chair, of course, that could measure how far someone travels, how long they're using the chair, and the distance traveled.

And then relate to all of these there are a bunch of motor-related self-report outcome measures. I'm a huge fan of the generic CAT options, the Computer-Adaptive Tests, like PROMIS and Neuro-QoL. There are sub-scales for upper limb performance and physical function. I think those are a good place to start. They're not perfect, but they're a really good starting place for you.

And then of course there's disease-specific measures such as the Stroke Impact Scale, the Spinal Cord Injury--Functional Indices, and then WST-Q which is a questionnaire version of the Wheelchair Skills Test.

So just to wrap up. When you're thinking about motor function I would encourage you to describe what level of motor function you're trying to measure. Are you trying to measure motor function at the body function and structural level, which we call an impairment? Are you trying to measure it at the activity level? And if so, are you trying to measure someone's capacity for the activity, or you're trying to measure their activity performing that activity in daily life?

And then I would encourage you all to start with the measures for motor function that already exist. Motor is probably the easier one of these three options to measure compared to what my colleagues are going to present in a minute.

So I'm going to stop there.

(Applause.)

DR. FREY: Thank you, Catherine.

Good morning everybody. My name is Kim Frey. And as they said, I am the Director of the Speech Language Pathology Department at Craig Hospital in Denver, Colorado. We are a freestanding 90-bed hospital that specializes in rehabilitation of persons with brain and spinal cord injuries. So at any given day, we have about 45 people in our hospital, who have brain injuries, and 45 people in our hospital, who have spinal cord injuries. We are also TBI and SCI model systems funded by NIDILRR.

So in my job on, any given day, I also get to do kind of all four things that you might do in the academic setting, if you will. So I do get to do clinical work. I also get to do programmatic development. I get to do teaching, and kind of administration, and I also get to do research. But I want to be very clear, that I do not do implanted brain-computer interface research. My specialty is really kind of language and aphasia, and traumatic brain injury. I also do not receive any funding. So that's my pretty quick disclosure.

But I will say that at Craig, our department does provide assessment and treatment including use of augmentative and alternative communication assistive devices, as well as, access and gaming for people who have severe communication disorders related to brain and spinal cord injuries.

About three or four years ago, I was also the co-chair of the working group that Catherine just mentioned for NINDS looking at corded elements for -- communication was our group in neurorehabilitation.

So I'm going to begin by just kind of saying that in our field communication is really kind of the most guiding North Star for what we do with our patients and our families. That said,

best practices and recommendations for clinical outcome assessment measures have been a bit of a challenge, and I do think this is because communication is really present in and across everything that we do. It is considered so ubiquitous it can be affected by any -- a number of diseases and disorders. And then also, communication, as just itself can impact abilities with activities and participation.

So how do you measure something that is really across everything we do? It's kind of like breathing.

So we're going to begin with the definition. Communication is the active process of exchanging information and ideas. It involves both understanding and expression, and a variety of different modalities including very relevantly this day digital technology. It also includes language skills like naming, grammar, phonemes. And then communication participation refers to an exchange between at least two communicative partners in the context of a life situation in which they're exchanging knowledge, information, ideas, or feelings.

And so many others report that our ability to communication is really what makes us human. It is the essence of who we are. And so, our ability to communicate really includes things like being able to express your ideas, your emotions, your opinions on things of which I know that we have a lot of things in the current state of the election right now, as well as your appreciation for somebody else.

So there are some more specific things that we -- reasons that we do communicate. We communicate to express basic wants and needs. So expressing that you want juice or coffee with breakfast. Being able to express that you need help with pain. This morning, even for example, you probably had so many communication opportunities. You made the decision to wear this pair of shoes versus this pair of shoes. And if you put yourself in the, in the position

of people who cannot move, and who might be extremely dependent on a communication partner or a caregiver, the opportunity to make the decision or indicate that you, that you want to wear the Denver Nuggets t-shirt versus your Boston Celtics t-shirt -- why would you have both? That's another topic. Anyway, but, you would like to wear your Denver Nuggets t-shirt, is a seemingly very simple construct, but such a powerful communication opportunity.

So, second way we communicate for information transfer. Being able to share personal information about your medical history, being able to direct your caregivers on how to help you. We communicate for social closeness. So discussions with or about family, friends, current events. We communicate to tell stories whether that be stories from what you did last weekend or from many, many years ago. And this really again allows us to express or share the essence of who we are, and build connections.

And then, lastly, we communicate for social etiquette. These are the niceties that we all experience every day; your pleases, your thank yous, your asking questions, your showing appreciation for somebody, all of which helps build relationships with families and friends and caregivers.

I'm kind of stating the obvious, but for the purposes of a brain-computer interface conference these are some of the disorders that may cause or may impact one's ability to communicate. I think importantly to consider is that all of these really impact the sensory motor cognitive and behavioral systems of our brain and body.

So the communication system as a construct is usually described in two simple manners. It is expression of either verbally or non-verbally, and comprehension of what you hear, and what you see. And then, again, related specifically to our topic today we're talking about an exchange of information and ideas between two or more communicative partners in the

context of a life situation.

And so each one of these occurs due to the complex interaction of, again, motor sensory cognitive behavioral body structures a functions of the brain and the body at the level of the central nervous system this is really the control center for our ability to communicate. If there's damage to the pons or damage to the brain stem, it can affect your -- it can make communication difficult if not actually just impossible. It makes it impossible to be able to speak, as well as, be able to access a communication device, if you will, as if like locked-in syndrome or C1, C2 spinal cord injuries. At the level of the body structure and function, these all allow us to execute the motor or the movement parts of our ability to express ourselves, as well as, receive sensory input for understanding and comprehension.

Moving to the, more of the cortical level, are cognitive abilities, each of which can either directly as with language disturbance and aphasia or indirectly like inattention or learning and memory problems can impact our ability to communicate.

And then lastly, but definitely not leastly, maybe more specific to the population we're talking about today, are concomitant factors; things like fatigue, frustration, your effort level. These can all impact device use as well as device satisfaction. And even more importantly than that are some environmental pieces, such as, this is a huge piece, the impact of your communication partner or your caregiver.

So from an ICF model communication really bridges every single level of the model or every single domain of the model. So communication effects bodies function and structure, impairment, and activity, and participation.

A disease disorder like ALS impacts the body's structure or functions required or necessary in order to speak which then can result in a motor speech impairment called

dysarthria which then can make communication or participation in communication less efficient, less effective, or perhaps less successful. And then, again, there are personal factors that may impact the experience of communication; your fatigue level, your satisfaction with a device, your frustration level, the effort that it takes. And, again, mostly importantly how well is the, the caregiver or the communication partner able to help support you in these communication opportunities?

There are many different authors who have provided so many recommendations for clinical outcome assessment measures in the realm of communication. I'm not going to review each one of these. But the point being that, there are communication outcome assessment measures that have been recommended at the disease or disorder level. So for specifically, cerebral palsy or specifically, ALS there are COAs or instruments or tools that can be used to measure body structure and body function. So oral strength or respiratory coordination. There are so many instruments and assessments that have been recommended for impairment level things. So assessments for something like aphasia. And then a lot of personal factors.

But if communication is ever present and crosses everything that we do, and can be impacted by every single level of the ICF model, when the question is posed what are clinical outcome assessment tools for communication, the answer is going to be it depends. It depends on what you're trying to measure.

And so with getting more specifically into brain-computer interface, we need to consider every level of the international classification of functioning. But there is an additional level that we need to take into consideration that really comes with the complexities that occur when you're having to learn these very complicated new systems.

And so, what we need to be considering are the abilities relative to the sensory, the

motor, the cognitive, the behavioral, and the environmental capacity for the user to be able to learn how to use the device, to be able to execute use of the device. Their device satisfaction. The level of effort that it takes to be able to use the device. And then the same also holds true for the communication partner or the caregiver. How capable are they or what is their capacity for being able to learn how to program these complex devices? Their ability to create communication opportunities for these folks. Their ability to engage or interact with the user of the device.

So, again, there are a lot of communication outcome assessment measures that have been recommended for every level of the ICIF model. I'm not going to review those today, but I'd like to get a little bit more specifically into brain-computer interface. Anderson in 2016 did a review of 15 core outcome assessment measures for assisted technology, and provided some suggestions. She broke down the domains, and the construct of each one, and mapped it onto the ICIF model. I'm not going to go into this one either because we actually have the expert in the room. So this is the -- Dr. Melanie Fried-Oken has created the RSVP Keyboard Screener which is probably one of the most commonly used tools in brain-computer interface. The nice thing is it covers all, all the necessary thing, sensory, motor, and cognitive aspects. And I'll refer you to her for more information on that.

To wrap things up, I do want to -- I also speak to another more specific BCI screener created by Dr. Kevin Pitt at the University of Nebraska, Lincoln. He has spent the past several years trying to refine this in a population of persons with no neuromotor disorders. He has also paired it with the Neuro-QoL. So another great tool to use. He has compared it to the RSVP Keyboard Screener, the ALS Cognitive Behavioral Screen, as well as the ALS Functional Rating Scale.

The BCI screener covers every modality that I mentioned; sensory, cognitive, motor imagery importantly, as well as getting the experience of the brain-computer interface user. What is their motivation? How fatigued are they? Are they in pain? What is their comfort level with computers?

And so this is what it looks like. Again, it covers introductory information, your handedness, some cognitive aspects, motor imagery. So it's a pretty comprehensive tool as well as containing a patient feedback questionnaire that gathers information on again the motivation for the use, their fatigue level, and the effort level that it takes to control the device. And it is available on the University of Nebraska website free of charge.

Final thoughts. When we are considering the clinical outcome assessment measures for communication because it is again, such a broad construct we must begin by defining and determining what aspect of communication are we wanting to assess. Perhaps, as related to the ICF model. Are we looking at body structure and function? Are we looking at impairment, activity, and participation? We need to understand the why that we're using this measure. Are we looking at the presence of a communication impairment, the severity, the change, or maybe perhaps the progression of the communication impairment, either the progression of the illness or the disease to inform perhaps the timing of introducing brain-computer interface systems or augmentative communication systems? Or change may be improvement in their ability to use those things. We need to take into consideration the user learning abilities, and their experience, and very importantly the communication partner or the caregiver capacity for using, learning these complicated devices.

We need to understand how we're going to assess it. Is it a standardized measure? Is it a performance measure? A questionnaire, like it rating clinician rating? Who is going to be

giving us that feedback, the clinical, the user, the caregiver? And then lastly more specifically for brain-computer interface. So many of these other considerations we need to think about especially in this population who is using a complicated device, and is often completely reliant on other persons for communicative abilities.

Those are my references, and thank you very much.

(Applause.)

DR. BAUM: Hello. My name is Carolyn Baum, and I'm a newly retired emeritus professor at Occupational Therapies, Neurology, and Social Work at Washington University, Saint Louis, the School of Medicine.

Given the challenge of activities of daily life, I know you all experience them yourself every day. You had them this morning. Your basic self-care of bathing, grooming, toileting, resting, eating, dressing, using personal tools. And then we all have lives to live, and that daily life goes into the instrumental activities of daily living with not only care for yourself, which is the way that I was the co-chair of the NINDS and MCMRR Committee that put together the common data elements. We made self-care as care for self, and defined it, and instrumental as care for others, and also the daily life activities for maintaining daily life. So that's work, and finance, and shopping, and many of these other things.

But the reason daily living is so complicated is it crosses so many biological domains, cognition, physiology, endurance, sensory, motor. And then we have the psychological issues of depression, motivation, and self-efficacy, all which are studied individually, and have their own languages.

The environmental domains are critical to our daily life activities to each of us. We have our emotional support, and our informational support, and our instrumental support, maybe

tools, might be your classes or you drive a car, or you've got many, any tools in your life. And then the social capital resources who can help you do things, and do you have access to care and payment for care, and then the physical environment and tools.

So these are the things that relate to people having a life, and participating in a life, and doing for themselves, and doing for others.

So with our common data elements we only found three instruments that met the criteria for activities of daily living measurements to put into the common data elements. And you've already -- the -- some of the insurers mentioned these, but the functional independence measure which measures basic self-care, and gives a level of assistance needed to an individual. The Barthel which is not as specific as the independence measure, but is one. And when the pain group was looking for their common data elements, they wrote this statement. The physical function quality of life, the difficulties associated with carrying out activities of actions, but they are really measuring difficulty, the difficulty doing. And that's true also of the one ADL instrument that was approved by our committee. The Assessment of Daily Life Habits. And it's a self-administered questionnaire to capture social participation, and again relies on difficulty.

But I want to point out to you, that the amount of difficulty does not measure what it doesn't measure. It doesn't measure what people do, what they want to do, how their impairment or chronic condition affects their engagement in daily activities. It doesn't measure the impact of intervention. It doesn't observe, doesn't measure what the family observes. And it doesn't produce quantitative data to show actual performance of tasks.

And what I'm going to do today is give you some insight to the measures that answer these questions, and by doing so I'm going to pose some questions that you might want to think about.

But before I do that, just like Kim told you, the complexity of communication, the complexity of doing, but it involves the brain processes to achieve performance with the sensor input and the motor output, but the cognitive processing has to be in the middle.

And I just want to -- I'm working with engineers right now, and we had to define a task that they were going to videotape, and use machine learning for. And I guess, I've always been as an OT, I've always done task analysis. But we had to go more specific than what I would say was the task analysis. And just making oatmeal involved 30 steps. Some of them are sensory. Some of them are cognitive, and some of them are motor.

So I just want to call that to your attention, as you're starting to look at people doing tasks, that they are very complex. And so I'm going to point out, why cognition is needed and going to give you a recommendation.

In order to do a complex or novel task the person has to be able to maintain attention, hold information, and mentally manipulate it, suppress irrelevant information, phone might ring, think and plan strategically, sequence the task, monitor the success of the strategy, and correct errors, and make safe judgments.

So there's a lot going on in the brain as they are doing or trying to do. So this is a study that Allen Heinemann and David Tulsky, and a number of people that you might know were doing a project to look at, at establishing validity of cognitive measures. And we also looked at people's daily life performance because these were people living in the community; 200 with spinal cord injury, 200 with stroke, and 200 with brain injury. And we looked -- we were able to use our testing to do a neural network to look at what level of cognition was involved in the tasks, as they were performing them in community.

And we found that it requires fluid cognition, crystallized cognition, and functional

cognition. And so you can see here on this diagram, well, it's the actual data that came out of this, that inhibitory control, and processing speed was pretty much the most important thing of fluid. The verbal knowledge and receptive vocabulary were important in the crystallized. And the organization and sequencing was the most important in the functional cognition.

So how did we measure this? We used the National Institute of Health's toolbox cognitive measure which gave us the cognitive flexibility, inhibitory control, working memory, the reading and vocabulary, and then the Executive Function Performance Test for initiation, organization, and sequencing and judgment. And I've made a handout for you all with, with the actual addresses of the electronic versions of all these tools I'm talking about today because I can't discuss the at a level in 15 minutes.

But so, the reason I spent so much time, sort of, introducing the idea of cognition, I want you to think about a question. Does cognitive status impact test performance as the person employs effort using brain-computer interface? And what having a baseline knowledge of their cognition will do will determine what factors contribute to success, and what, what ones are causing difficulty. Because I've had a lot of experience working with people with Alzheimer's disease and stroke, and there are always people that are really successful, and there are always people that don't do so well. And if you haven't got a way to classify those in terms of their cognitive capabilities that are processing between the sensory and motor, you may not be as specific with your understanding of what the person -- what really the success of the technology is.

Question two. What activities does the person already do, or what have they done in the past, or what do they know how to do, what are they motivated to do, and do their activities change as they make progress with BDI? It's a really important question. And what

I'm going to introduce to you we've had the Activity Card Sort, and it's validated and used in countries all over the world with different ones for different cultures. But we had an NIH SBIR, and have been able to put together an Activity Card Sort tree that's electronic where the person tells you that they've never done it, they're doing it now, they're doing it less, they've given it up, or they would like to do, which gives you a profile of what they were doing before their accident or before they got their disease so you know what they might already know, and be able to think through the processes of doing. They won't have to learn a new task. They would be doing something that was favorable to them.

And the interesting thing that we've been able to do, because we use it so much, it's used in neurological problems like MS, and stroke, and spinal cord injury, and head injury. But what, what we've been able to do is it goes into REDCap. The data downloads into REDCap, and also can go into an EMA and the medical record.

But what you'll find out about the person is, is what they're doing now, what they're doing less, what they've given up, and what they'd like to start. So you have a profile of a hundred activities that have come from -- the people in the pictures that they're looking at are using mobility devices. They're different races. They're different cultures. They're different ages. So they can kind of see themselves in it.

So this gives a real sense of what activity means to them, and what they like to do. And it gives you data on an individual level, but also tells you how much of their activities have been retained by what they have -- what their situation is now. And this is on a strip population, and you can notice in the, in the age groups of the 40s, 50s, 60s and 70s people haven't retained even like 70 percent of their activities. But there are a lot of things they do do, and they want to do, and they are motivated to do, and you need to figure that out.

The other thing is that when you're talking about, like, I was interested when you were talking about things have to be specific to a diagnosis. Activities really don't have to be specific to a diagnosis. They have to be specific to the person because everybody does things more for themselves not because there's something they're supposed to do.

So in our use of the Activity Card Sort with stroke, we see that people who have an NIH stroke scale of even zero that have cognitive problems that are not -- some are retaining 100 percent of their activities, and some are only doing 20 percent of their activities.

And so you can see that there's not a relationship here between how many activities they've retained, but what this tells us is that there's a lot going on in their social life, and with their friends, and their family, and the people that are helping them to do things. And so it's not just activities that it's just an individual process either.

The other thing this particular tool tells you is what, what do they think is limiting their ability. They feel tired. They don't have anyone to do with it. They're not -- they're having trouble paying attention.

So it's a good way to, sort of, find out who the person is that you're trying to help, and what their meaningfulness is, and what, what's meaningful to them.

Question three I want to pose. Does the family see a difference in the abilities of the person to do things when they've had BCI? What behaviors can be observed by another? Well, we know that problem solving task performance and social interaction can be perceived by family or by a clinician, and that the functional behavior profile is a way to record their observations. So, how are they doing socially interacting, solving problems, and performance? Now, this is data from a declining population with -- situation. But you could also track their improvements in social interactions, their engagement with solving problems, and performing

tasks by the observation of the family member. And the task performance. Do they finish the task? Is it timely in doing tasks? Do they have an attention span? Are they maintaining those kinds of things? Can be observed by the, by the family report.

Question four. What can they do? And this is what most ADL has been at this difficulty level. IADL has not really been well-developed in measurement until really trying to come forward with the Activity Card Sort which has been used mostly for clinical purposes, and by specific researchers. But there are new approaches to record actual performance of tasks. And I think, this is where you might find some interesting work to be done with yours.

First, the Ecological Momentary Assessment with accelerometry. So when you take a dynamic approach to characterizing and assessing activities you can capture it in real time data in the natural environment of individuals. So you can find out what they are doing at points in time, and over time. And we were worried a little bit about whether stroke, people with stroke could accept accelerometry and the Ecological Momentary Assessment, and we had 93.6 percent EMA survey completion rate, and 99 percent on the accelerometer. And they didn't -- they felt it was integrated into their lives. It wasn't something that was foreign. They were happy to have measurement collected. And I want to show you what kind of results you can get. EMA identifies what the individuals or groups of people actually do. So you can actually find out with five pings a day what are they working on, what are they doing. And most people are pretty sedentary. But they're working -- the top two are -- some of them are working, but the second one is watching TV, or eating, or drinking at home, or resting. And nothing is here, down here, this green one, down a little way. But what -- this can categorize the activities they're doing by ADL or IADL, and whether or not they're low demand leisure or high demand leisure. So, you can see somewhat about sedentary in this. But the accelerometer also tells

you the energy expenditure of their activities, and you can see that you can classify the work, the work as ADL, IADL, low leisure, high demand leisure, and social. So those are ways that you can get with wearing the recorder. And certainly Catherine was saying that a lot can be collected by an accelerometer that's being worn. Ours were worn on the leg.

Then we're just into some new work that I think also has some real options for you all, and that's with engineering, and using a machine learning approach with AI driven measurement in daily lives. So that it's an unobtrusive data collection using camera and sensors, and it's an automatic performance measure because you're, you're -- the data driven is coming from the actual video capture of the task as they do it. And then you can see if there's a performance breakdown. And so we're doing something called SmartKitchen, which detects errors in cooking, and the camera captures these live videos, and detects the organization errors with object detection, and detects sequencing and safety errors with action recognition. And the reason we're doing this is because we'd like to get to a point where we might be able to deliver cues through some type of smart technology to -- mild cues, like, not direct cues, but is there something you need to do to keep people on track for the, for the task?

So I've got -- I have a handout at the front, and I've given you the names of people that are doing the AI stuff, and the technology, all these technology assessments. Because they -- I couldn't explain them to you technically, but they, they are being done. And I just wanted to review that I've given you questions that could be answered to document your CBI outcomes if they exhibit cognitive problems, if they do so, do they respond to CBI differently than those who don't? That's the toolbox in the EFPT. What activities have the participants done, and will not need to learn steps and new tasks to direct their effort and skills? What would they like to do for motivation? Would be ACS. Does the intervention make it possible for them to be more

active in their home and community lives? That's the ACS. Are they having less difficulty with their basic ADL activities, the FIM or the Barthel? Is the -- family see them more engaged in doing tasks, making decisions, and engaging socially? That's the FBP. Is the participant moving from sedentary to more demanding activities? That's the EMA and accelerometer. And are they experiencing fewer errors, as they learn and gain skills to do activities to optimize their health and well-being? And that's machine learning.

So there are contemporary valid methods that measures are available. The actual doing of tasks is very complex, and requires the integration of many things. So the model must be multimodal. It will be important to recognize the issues like cognitive impairment, depression, self-efficacy, and motivation because they could influence the person's performance. And it will be important to have longitudinal data on these factors to understand the success.

And I just want to say that measuring daily life is more important than just measuring and effort or an effect. It is central to optimizing health, and preventing or reducing illness for all people because as their ability to do what they need and want to do is essential for their health, their wellness, and their social engagement. And I think the work that you're doing to come up with new technology to help people do is such an important new aspect to being able to put brain behavior performance and participation together. Because you have to get to participation to have this daily life.

Thank you.

(Applause.)

DR. WU: Thank you, Dr. Baum, Dr. Frey, and Dr. Lang.

And coming up next is our last session this morning which is a Systematic Review of Clinical Outcome Assessments for Communication BCI in ALS. It's a grant update from

Dr. Nivas Asok Kumar.

DR. KUMAR: Hey everybody. So I got here kind of early today; one of the first people to be here. So I had a chance to see all the badges on the table, and it immediately took me back to my PhD days. It wasn't too long ago. And especially the lab meetings where I had to present papers from a lot of the names on the badges I saw. And there's always that one guy in the lab who would ask some obscure question from the method section about, how is this done? I don't know, man. Just e-mail them, and figure it out. So -- and realized I would do the same for them too. So in all seriousness this -- I've learned so much from the papers that I've read from all of you. And it's an honor to be here to speak in front of all of you.

My name is Nivas, and I work as an applied neuroscientist with Blackrock Neurotech. So in the next 15 minutes or so, I'll be talking about our project which is a collaboration between Blackrock Neurotech and the FDA, titled Clinical Outcome Assessments for Communication Brain-Computer Interfaces in ALS.

I also have a project disclaimer just like everyone else. The project is supported by the Office of Orphaned Product Development at the FDA. However, the views expressed here today do not represent Blackrock Neurotech's business, marketing, research, or development strategy.

The purpose of this project is purely scientific to better understand how we can assess the efficacy of communication BCIs or cBCIs in ALS patients using clinical outcome assessments or COAs. Our primary goal is to explore how BCIs can potentially improve communication abilities for those affected by ALS. The study consists of how cBCIs can potentially improve communication abilities for those affected by ALS.

It consists of three efforts, as you can see on the screen. First, is a systematic literature

review to identify relevant COAs. The second, is interviews with key opinion leaders to gather expert insights. And third, which is about to begin, is ALS patient interviews and caregiver focus groups to further refine our understanding of cBCI usage in real-world settings.

So ALS is a highly complex degenerative disease characterized by progressive motor function loss though the pattern of degeneration varies widely between individuals as most of you here know.

As you can see on the diagram on this slide, in some patients, the disease may begin with weakness in the arms or legs, while in others early symptoms may involve speech difficulties known as, bulbar onset. Regardless, of where the disease begins most ALS patients will ultimately experience the complete loss of communication ability. This loss is primarily driven by progressive motor decline that leaves patients unable to speak, write, or type. This creates a unique challenge for ALS patients compared to other conditions like stroke where communication deficits are often due to neurological impairments such as aphasia rather than motor dysfunction.

To address communication deficits brought on by ALS and similar conditions many individuals use augmentative and alternative communication, or AAC devices. These can range from gaze tracking systems, wearable technologies, to tablets that assist people in communicating without speech. Communication BCIs, or cBCIs, are a subtype of BCIs designed for this specific purpose. They allow for communication without any movement whatsoever. This could be especially appealing for ALS patients as their motor function declines making traditional devices like tablets harder or even impossible to use.

Now, cBCIs come in many forms. They can be noninvasive like EG-based systems, or highly invasive such as fully implantable devices that directly record brain activity. Also, the

output of these devices varies too. Some generate verbal speech while others produce digital outputs such as text on a screen. Additionally, cBCIs differ significantly in their hardware and electro designs, and in how they decode neural signals to translate them into communication. This wide variability poses a major challenge when developing standardized methods to evaluate their efficacy. However, creating clinical outcome assessments is crucial, and these assessments will enable us to measure the effectiveness of not only current cBCIs, but also future innovations in this space. I'll spare you with the FDA definition of COAs. They're up there. There are four different types, and we've been through this in previous presentations.

So at present, there are no COAs specifically validated for evaluating cBCIs in ALS patients. To address this gap, we conducted a broad literature review screening nearly 14,000 papers that discussed neurological conditions, communication technologies, and other related assistive devices used in clinical settings. Through this process we identified 21 clinical outcome assessments that could potentially be adapted or serve as starting points for evaluating cBCI efficacy in ALS patients. These COAs originated from analogous conditions and technologies, and they represent an important first step in developing a robust assessment strategy.

So we categorized the 21 COAs we identified using the FDA's classifications while also examining what each assessment was designed to measure.

I apologize for the scale of the, of the bar graph there. I'm not sure what happened.

Of these, eight were patient-reported outcomes; six were observer-reported; six were performance, performance metrics; and one was clinical-reported.

It's important to note that the total shown on the screen, if you can see what's on the screen, adds up to more than 21 because some COAs belong to multiple categories. While most of the COAs focused on communication efficacy, we also identified some that measured

quality of life, caregiver burden, cognitive load, and patient satisfaction with assistive technologies. Additionally, six of the COAs included performance metrics which could serve as objective, quantifiable measures of communication speed or efficacy.

However, these performance measures need to be used in combination with other assessments such as quality of life and satisfaction metrics in order to gain a comprehensive view of a cBCIs clinical impact.

Although we identified several COAs with useful components, we found that no single existing measure could fully capture the complexity of cBCI efficacy in ALS patients. Surprise, surprise. Most of the measures had useful subsections which could be combined into a novel COA or used as part of a broader battery of assessments. During our key opinion leader interviews some additional COAs were mentioned, but none that hadn't already been identified as part of the literature review applicable for evaluating cBCIs in ALS.

The key takeaway here is that the complex nature of ALS, coupled with the multifaceted applications of cBCIs, demands more nuanced and multidimensional assessment approaches.

To deepen our understanding, we conducted interviews with 15 key opinion leaders, or KOLs, who have demonstrated expertise in fields such as, ALS research, physical and occupational therapy, speech language pathology, assistive technologies, BCI systems, and communication in patients with severe language deficits. These semi-structured interviews allowed the experts to share their insights on a wide range of topics including daily living activities, assistive technologies, caregiver burden, cognitive assessments, and quality of life. This qualitative feedback has been invaluable in shaping our approach to developing clinically meaningful measures for cBCI evaluation.

After conducting -- well, I am not sure what happened to the slides. After conducting a

thematic analysis of key opinion leader interview data, we identified several key themes that are crucial for evaluating cBCIs. The experts agreed that any comprehensive assessment must incorporate, one, device performance; two, cognitive and neurological assessments. This may include tests for assessing cognitive burden, but also includes prescreening tools to ensure patients have sufficient cognitive ability to use the device. Three, patient quality of life, patient satisfaction, and caregiver perspectives.

These insights emphasize the need for a holistic evaluation that covers both the technical and functional performance of the device such as communication accuracy and speed, and the subjective experiences of the patient and caregiver. This combined approach is vital to fully understanding the impact of cBCIs on the quality of life for ALS patients as it ensures both the practical and personal dimensions of using these technologies are considered.

As many of you know, ALS is a disease that progresses differently for each patient. Therefore, any clinical outcome assessment must be able to account for these unique variations in disease progression. The KOLs highlighted the need for evaluations to reflect real-world communication scenarios rather than simply testing in a clinical environment. This is especially important because the needs and abilities of ALS patients vary drastically depending on the stage of the disease. Early-stage patients might still have significant communication abilities while later-stage patients may struggle with even basic communication tasks.

Therefore, the performance and subjective outcomes need to be measured against cognitive and disease-specific factors reflecting what is meaningful to the patient and caregiver at each stage of the disease.

In the second year of this project, we will be partnering with Johns Hopkins University, Rancho Los Amigos, and University of Utah, to conduct interviews with ALS patients and focus

groups with caregivers. Our goal is to gather stakeholder feedback to gain a deeper understanding of how cBCIs fit into the daily lives of ALS patients. This will help us provide the FDA with a comprehensive landscape of how COAs can be developed to effectively assess cBCIs in ALS.

Before I conclude, I'd like to extend my heartfelt thanks to everyone involved in this project. Special thanks to our PI, Dr. Spencer Kellis, and co-PI, Dr. Shana Melby at Blackrock Neurotech, as well as the FDA for their support. I'd also like to thank our clinical partners at Johns Hopkins, Rancho Los Amigos, and University of Utah, for their ongoing collaboration and contribution to this important work.

Thank you all for your attention today.

(Applause.)

DR. KESZLER: Thank you, Dr. Kumar for that update. And thank you for all of our, to all of our speakers this morning. Thank you to Guangying for MC'ing as well for NIH.

Before we break for lunch we have some updates. My understanding is that this is the first public workshop, or one of the first public workshops, our center has hosted since COVID. So I appreciate all of your patience as we work through some hiccups. For those who are U.S. citizens, who do not have a visitor badge, please find myself and Dr. Julia Slocomb at the registration desk so we can make sure you get a visitor badge. And then we'll all, we'll pick up lunch from the cafeteria on the way back here. Otherwise, you can purchase lunch at the same kiosk where you got coffee this morning. And we'll meet back here at 12:30 for the afternoon.

I believe those are all the announcements. So thank you.

(Off the record for lunch break at 11:36 a.m.)

(On the record at 12:36 p.m.)

DR. WU: Attention please.

DR. KESZLER: We'll have more opportunity to chat a bit later this afternoon. So, hopefully, you all are energized and ready for this afternoon's session. For those who I haven't met beyond being a professional herder it seems, I'm Molly Keszler. I'm medical officer here at FDA. And so for -- we're going to start the afternoon session with this prerecorded panel from People of Lived Experience. This was coordinated by Rebekah Corlew and Eric Atkinson from NIH.

(Video recording being played.)

DR. WU: Again thank you to all the speakers in our patient panel, and also thanks to our Dr. Rebekah Corlew and Dr. Eric Atkinson from NINDS for organizing this amazing panel.

And then coming next, Molly and I will start our task setting. So basically, now, all the audience here will have a job to do. So basically, we will separate our staff into different breakout rooms, and discuss the following questions, and it's an open question, and open discussion, and hopefully we'll collect more thoughts from our community. And to -- leading up to our tomorrow is another round of breakout room discussion.

So in speaking of the questions to be discussed for each breakout room.

So the first one is, what are the challenges in evaluating effectiveness of devices for this purpose; communication, activities of daily living or mobility. What are the gaps in current available clinical outcome assessments? Can any of them be updated to meet the needs of this technology? Are there additional clinical outcomes that arose during this workshop that should be considered? How should performance outcome measures be used to evaluate individual device effectiveness for consumers, device user, to compare devices?

DR. KESZLER: So to continue on. Other things to consider. What other factors should

be considered when selecting or designing COAs to evaluate if the device is reasonable and necessary? What is needed to align clinical and technical performance such that technical performance could be used as a performance outcome in the future? And, finally, should there be a universally applicable assessment or a toolbox of various COAs? So what would need to be included in core common outcome in a core common outcome data set? And who should be involved in developing such a toolbox?

So now, we're going to go into our breakout rooms, and all of you have on the back of your badge it will say the topic of discussion, mobility, ADLs or communication, and a room number. And so the majority of people are going to be in Building 32, and you'll be escorted by FDA staff to those rooms, and they'll be participating in the breakout room as well, and we'll have -- we have spots for everyone to meet up outside.

There's a moderator assigned to each of the breakout rooms, and they'll come back, and present, like, a five-minute summary of what your discussion was, and that will be available on the web cast. So I recommend using the last bit of the breakout room time to consolidate your thoughts. And there's one -- we have two groups that are going to be staying in building -- in this building, in the great room, and another room down the hall, and I'll make that update at the end of this. And then we're going to be using the same groups tomorrow.

So with all of the excitement this morning we have some updates to the rooms. So let's see. Have my FDA colleagues show off their folders and wave.

So we have Kristen who is going to be escorting the people. You may have to walk up here. So Kristen has the white folder, and she's going to be escorting people to Room 1215 to discuss ADLs. So everyone, this is Kristen. So and there's a sign for everyone to meet up there.

Ambarish , you have a red folder. You're also going to be discussing ADLs, and you --

those are the people who are going to be in Room 1227.

Meijun has -- where is -- there she is. You've got a turquoise folder. She's going to Room 1309 to discuss ADLs.

Zach, where is Zach? Has a yellow folder, and he's going to Room 1321 to -- for communication.

Gabriella, there we go, has a dark blue folder. She's going to 1325, also discuss communication.

And then Phoebe has a purple folder, and that's to discuss mobility in Room 1333.

And so the numbers kind of go up as you go around. There are people who are in a new breakout room with Heather. That is 1408, that's here. That is Abby, David, Hugo, Samuel, Natalie, Amelia, Anapama (ph.), and Adam. And then Jamie and Tom are staying here in the great room to discuss communication with Julia.

(Off the record at 1:27 p.m. for breakout rooms.)

(On the record at 3:30 p.m.)

DR. SLOCOMB: Okay. If you guys will take your seats, we'll get started so we can hopefully get you out of here a little bit early. And after we go through our moderator presentations, we'll talk about what that might entail.

All right. So in the interest of getting going we're just going to start, and then people who are still trickling in can filter in, but we're going to ask that we start in this conversation now so that you guys can hear.

Thank you all for participating in our breakout rooms. We had a lot of fascinating discussion in our group. Hopefully, you guys found the same. From what I hear, that's the case.

So we're going to get started with presentations from each of the moderators of our

working groups, our breakout groups. I will call you guys up one-by-one. You're going to have about five minutes roughly, each to review what your group talked about. It looks like Molly set a timer on the podium on the right so you can see and keep track. But I'll start flagging you down if we go over time, all right?

So we are going to get started with the ADL-based groups, and we'll start with Edward Keefer, who was just up front, but I've lost -- there you are. Come on up. Yeah. Mic's yours.

DR. KEEFER: So what are the challenges in evaluating effectiveness of devices for activities of daily living? There was absolutely on consensus, but the topic, the topics that were discussed were -- seemed to focus on the activities of daily living tasks not being specific for function. Should the activities of daily living versus improvements in mobility be weighted more or less heavily? Should we consider restoring a skill versus replacing a skill as something that would be to be evaluated? What is the reliability and reproducibility of the available outcome measures? Can those things be improved? Should they be reevaluated as far as like the -- should it be in the 80 percent versus the 90 percent, that type of thing? A different threshold. And above all it seemed like the group, the room was -- did reach a little bit of consensus on that the most important thing is what is the most important thing to patients is -- should be the way that this question should be evaluated.

Let's see here. Number two, what are the gaps in currently available clinical outcome measures? The main thing that came to mind, I think, was just the lack of precedence in this particular domain. What is the regulatory and reimbursement overlook, outlook, look for the future as far as the, the brain-computer interface device development?

Let's see here. One of the, the sub-questions there was can any of them be updated to meet the needs of this technology? Really didn't have a great many ideas about that, but are

there additional clinical outcomes? And so then we started to focus on the possibility of including or exploring or developing, expanding possible digital outcome measures. Is moving a computer cursor X, Y coordinates, the ability to type X number of letters per minute, those type of things. And there are some assessment tools available, but it didn't seem like they -- at least in our group's expertise, were particularly, maybe particularly well-focused for the, for the use case that we're looking at.

Maybe, possibility of having a different model, a patient-centered model versus a medical-centered model. I guess, that gets back again, to, like, what is most important again, you know, maybe the activities of daily living versus the mobility versus are we treating a specific condition, does the patient feels good about it, or is it actually altering the progress of the disease or improving their ability to cope with the disease?

And then how much, and how far can you take the incorporation of wearable devices? For instance, one example that was mentioned was, like, if you had on a smartwatch, and you leverage the GPS function to show that the person was actually engaging in more activity, they were outside the home more than they were previously before using the device.

Let's see, number three, how should performance outcome measures be used? And there wasn't a great deal of discussion, to be honest with you, about that. What is -- other than what -- how, how can you evaluate that on an individual versus population level of -- for importance? And that comes down to the context of the use, and what is it? Is it most important for this individual particular patient or is there a way to expand that to a thousand patients with similar or closely-related symptoms?

Let's see. Number four, what other factors should be considered when selecting or assigning COAs to evaluate the device as reasonable and necessary? That, I guess, the main

points that we considered there was, what is the actual burden on the patient as, as primarily important. And from an insurance CMS, Workers' Comp, the payer perspective, are you able to show that you are saving them money? And then if possible is there any data to possibly indicate that you're maybe able to alter the disease trajectory, and slow the progress from needing more medication, or able to change the dosage of the medication that they're currently on.

Let's see. Number five. What is needed to align clinical and technical performance such that technical performance should be used performance -- could be used as performance outcome in the future? And so we considered things like for BCI, and it was mentioned that there is in most of the, or many of the publications, things such as byte transfer rate, information transfer rate, or technical performance that has been widely published, and seems to be accepted in the, in the clinical community.

That it? All right, sorry.

DR. SLOCOMB: No, no, no. You did great. Thank you.

(Applause.)

So now we're going to move to -- thank you. To Gianna Perez. Next breakout group for ADLs.

MS. PEREZ: All right. Hello everyone. So much spirited discussion in our group, but I will hit all the main points within our time.

So, first, for challenges in evaluating the effectiveness. There were a few main themes that were raised for us. One was heterogeneity, both in the kinds of issues that people experienced with needing their ADLs improved, and also with just the level on the pyramid, and also the level of benefit that people would want to see. So that's one issue.

The other is this idea of granularity. So how specific should something be defined? Whereas like the example we saw in the presentation from Dr. Baum, do we care if someone can actually make the entire thing of oatmeal, or do we care if someone can pick up the spoon and stir maybe, right? So that's another issue. As far as figuring out where along that scale we have the most value.

Another issue is avoiding confounds. Other challenges would be things like standardization. And, lastly, the tradeoff between meaningful outcomes for patients, but balanced with risk. So those are just some of the main challenges that we identified.

As far as, gaps in currently available COAs, one thing that our industry partners lamented were the clunkiness of some of the available questionnaires, right? So going through hundreds of questions with patients isn't necessarily optimal for the -- either the experimenters nor the patients. So they're not necessarily, they're not necessarily usefully effective in that sense. The other issue is that they're not always capturing exactly what people might need, right? And so, as far as, updates for the needs of this technology, perhaps there are certain measures that can be abridged. But, as far as, additional clinical outcomes that people were made aware of as a result of this workshop, things like incorporating technology, incorporating the ideas of caregivers, although primarily putting at the front the kind of outcomes that patients and people with the lived experiences with these devices care about was really a big one that emerged for everyone.

As far as, performance outcome measures being used to evaluate an individual device's effectiveness or to compare for consumers, right. The main thing that we talked about were participants wanting to actually use their device, right? So in performing well enough, and having good enough outcomes that people are excited and motivated to continue using the

device. People brought up maybe that could be measured through how much the device is being used, how much like what it's like for someone to engage with it. But that was, that was where we landed for outcome measures, again, centering the patient perspective.

As far as, other factors to be considered when selecting or designing. So, again, patient benefit came up as a main one for us. Patients being excited, again, and willing to use these devices. Another big factor though, was the idea of the placebo effect when we're designing our outcomes, making sure we can effectively distinguish that as well as other confounds especially with activities of daily living related to people's social situations.

And then lastly, the other factor is, again, the risks that are present, and what promises are made given the current state of the technology as was echoed in the patient panel.

So then, as far as needing, what is needed to align clinical and technical performance such that technical performance can be used as an outcome measure in the future, we talked a bit about the idea of maybe biomarkers one day eventually, right, but that would require a lot of data, a lot of standardization, a lot of going back and forth between different parties. But that was something that we would -- that we think things would eventually progress to, to be effective there.

And then, as far as that, there should be a universally applicable assessment or toolbox. As far as, universal assessment there was almost a resounding no with some caveats. People were much more amenable to the idea of a toolbox, mainly just given the diversity that patients are experiencing, and really the amount of problems that people are trying to solve right now with BCIs.

And so, as far as the toolbox though, that might be something that could be more effective. As far as who should be involved in that, right? The parties that we are -- that we all

have here today. So researchers, payers, regulatory agencies, patients, device makers, occupational therapists, physical therapists, really learning about kind of not, like, another theme, not reinventing the wheel, but what we can incorporate together. And basically, from there figuring out the kind of standards, and things that we would need.

But, yeah, overall we addressed a lot of the complexities, and a big theme for us was the idea of making sure that people are no longer speaking different languages where you don't have the payers wanting one thing, regulatory people wanting one thing, researchers trying to do one thing, patients wanting one thing. Basically a lot of our discussion centered around moving past that, and coming together to reach a consensus.

(Applause.)

DR. SLOCOMB: Thank you, Gianna.

All right. Next, we have Leigh. I don't think any of you have heard of him before. He's a new researcher that we invited today, up and coming. Also on ADL.

DR. HOCHBERG: Thank you Julia.

Our outstanding group did not feel constrained by the instructions we received, but hopefully we're -- I think we, we got too many of these really important questions. So, I'll try to do this chronologically because I think the evolution of our discussion is informative. So we began with really, just a straw person example of is the box and block task useful if we're thinking about a BCI? And initially it was mentioned, came up in discussions earlier in the morning, that that task is a rehabilitation measure, and not a restoration measure. And by some, by some estimates as a result it's off context for BCI the way we ordinarily think about them and, therefore, it was dismissed for awhile in our group as a task that might be useful later on. But it's going to come back in a little bit.

We then thought, because we were asked to think particularly about upper extremity function, whether ADLs were something that BCIs would be able to achieve. ADLs generally require use of the upper extremity. They're also a really big ask for today's state of brain-computer interface.

On the other hand, the instrumental ADLs many of which also require the upper extremity are quite applicable to what BCIs in the near term could potentially achieve. And so there was some interest in focusing on, on how those instrumental ADLs might be used as to at least inform clinical trial end points and outcomes assessments.

There was an observation that while lots of the clinical outcomes assessments successfully evaluate functionality many don't adequately indicate the value of that function, and certainly don't indicate the value of the person who either did or didn't achieve that particular function.

Third challenges that were identified were the question of whether we're adequately evaluating the device itself, as opposed to, the device and the effector, or the effector, or the combination of all of those which we just need to think about when we're designing clinical trials.

The importance of the context of use was -- came up many times. If a BCI can enable a function to occur both inside the home and outside the home, and the device that it's being compared to only works inside the home, if we didn't ever test it outside the home, we wouldn't know that, and there might be considered to be equivalents between something that's not a BCI and something that is a BCI when in fact that BCI adds enormous value, but we have to make sure we're testing it in the right context to know that.

That was really the inflection point of our discussion which was the development of the

PVR task which is the pickles, violin, refrigerator task. That -- where's Nick? Thank you, Nick Langhals for the PVR task. This was really when we began to discuss what is it that the future users of a BCI really want to be able to do? They want to be able to open, perhaps, a jar of pickles. They want to be able to play a violin again. They want to be able to open the refrigerator. And this was really kind of the, the moniker that we used to think about patient-oriented, patient-selected, user-selected end points or outcomes for clinical trials that we just heard about, the importance of them. If we can ask our future clinical trial participants, what do they want to achieve with these devices, then we might have a Boolean output. You decide in advance what you want it to do, and you ask the BCI to help you do it, and it's either a success or a failure. And having that kind of output is quite useful for clinical trial design. Could also apply in visual analog scale if being able to do something or not do something isn't, isn't quite right.

But by developing that suite or toolbox, was the phrase used earlier, before predetermined, or before that trial starts for that individual might allow us to have a very clear answer as to whether that participant is a success or failure or the device is a success or failure for that participant in the trial.

With that, we also discussed thinking about value again for each of these individual functions; the concept of being reasonable and necessary. If voice control alone allows one to achieve a particular task, and the BCI can also achieve that task, but if you have to use one's voice it's not a private event, and if you can use the BCI it is a private event. For example, managing one's finances, which is number two or three on the IADL list, how do we make sure that we capture the value of the BCI in allowing somebody to manage their finances, again, in a private manner as opposed to anyone that might reveal to the person next to them what

they're doing?

Another challenge that was indicated, one that we'd like to see captured, is that speed is not often captured in an ADL list. How long does it take for one to manage one's finances? And it also, as mentioned before, doesn't capture the environment or the context in which that ability is, is captured which is -- may be very important for payers. Again, as we think about finances, can you manage your finances? Can you not? If an available technology allows you to manage your finances in a public environment, maybe the BCI no longer qualifies as having added any additional value, and we want to make sure that that value is captured and recognized.

And at the end of our discussion where -- which was really about developing a suite, developing a toolbox that -- and emphasize what that particular person wants to achieve with the BCI. It was hoped that either prior surveys or upcoming about to be started surveys might be able to develop a list of all of the reasonable near-term outcomes that a BCI could provide. And then for some of them to be able to identify the available objective outcomes measure that provides a little bit more insight into what opening a jar of pickles actually requires, or being able to play the violin actually requires, so that maybe for that individual future clinical trial participant we would both know did they achieve what they wanted to thanks to the BCI, and when needed what would the additional already validated objective outcome measure provide to provide a little bit more insight.

And with that, that's the summary of our group.

(Applause.)

DR. SLOCOMB: I told you that kid's going places.

So next up, we have David Putrino also talking on ADLs, and then we'll be switching to

mobility after that.

David, are you -- yeah, there.

DR. PUTRINO: All right. Thank you very much for having me to talk about this. Our group was the group of foreigners that no one wanted, but didn't know what to do with. So we got put into a room. And I think a lot of the conversation around the gaps and things like that have been done quite well, and also just like Leigh's group, we weren't really constrained by the questions.

So I think we, we really came down to a few bullet points that I think are important. The first is that one of the things that we decided upon with regard to ADLs and the ability of BCIs to restore the ability to do ADLs is that if you're dealing with a BCI that controls and end effector that will restore or replace a limb, that would then influence things in the physical world, outcomes that already exist should be self-evident for these devices. So, Catherine Lang did a really good job of talking about all of the ways that we evaluate how someone can walk, how someone can reach, how someone can grasp, how someone can go out there and do things in the world. And so when those BCIs are out in the wild being used independently in home environments, those are going to be great outcome measures. How quickly can you walk 10 meters? Can you stand up from a chair, walk, turn around, walk back to the chair, turn around, sit down? How good is your balance? These are things that will be very useful for CMS, very useful for the FDA. And these are good outcomes to power clinical trials, et cetera.

The IBCIs that exist out in the wild right now are really -- they're a different problem, and they're a different animal. And they are IBCIs that control digital devices.

Now, what we drilled down to as a group was, okay, well, what is the difference between an IBCI that controls a digital device and any other non-implanted device that allows a

patient to control a digital device? And the answer which came from us, but also from patients that we've spoken to, is continuity. When you have a switch, or when you have an eye tracker, or when you have something that is not implanted that thing can fall or become uncalibrated or move away from your hand. And, therefore, you, you need somebody to come and bring that thing back to you, recalibrate it, et cetera. Ideally, an IBCI that controls a digital device can always be on, can be very easy to calibrate, and not need to be calibrated every few seconds, can be used without a caregiver, allowing privacy, allowing agency, allowing dignity for digital device users without a caregiver looking over their shoulder. So that is the difference. That's the thing that gives us something different to an eye tracker or a switch or a button. This is also an analogy that we've used here is glasses allow someone to see, but you can lose your glasses or forget your glasses. Lasik eye surgery allows you to see without having to forget something or lose something. And at some point, CMS said, yeah, well, that's worth reimbursing for, the ability to have this independently without asking anyone for permission. So that's a nice analogy to think about.

So then we proposed to measure your ability to independently do stuff digitally. We proposed that we should create an instrument. We said an instrument because it could be clinician, patient or caregiver-reported, or it could be all of those things. So we could get into it. That measures digital ADLs. So your ability to engage in -- and, again, the digital ADLs of importance should be determined by patients and caregivers, but things such as how -- do you engage in online shopping, communication tasks, alerting caregivers of a safety issue, finance management, environmental control, all sorts of things that these days, we can do through a digital device. And we would evaluate, not just your ability to perform these tasks, but also your ability to perform them continuously. Can you perform it none of the time, some of the

time, all of the time? And relative success or failure on that would be an outcome measure by which we could measure the suitability and effectiveness of an IBCI that controls a digital device.

And then we wanted to end in a call to action, and there is a wonderful program that is called the Medical Device Development Tools from the FDA, MDDT, which really is a set of tools that can be used to guide outcome measures for people who -- device manufacturers when they're saying, hey, I have an IBCI that can control a digital device, the FDA would say, hey, here's our MDDT for that. So our call to action would be that we should create and validate a DADL that could be added to an existing, well, added to an existing MDDT for IBCIs that would then streamline the path for anyone who is creating a BCI to control a digital device, and make it very easy for us to show efficacy for CMS and FDA. And that's where we ended.

(Applause.)

DR. SLOCOMB: All right. Next we are going to switch to mobility. Jose already knows he's --

DR. CONTRERAS-VIDAL: Thank you.

DR. SLOCOMB: -- save him any trouble.

DR. CONTRERAS-VIDAL: Yeah. We have really, really interesting session, and it always catching.

So challenges. Well, I think the, the first thing we need to -- we discussed was what kind of mobility, right? Transfer mobility, sit to stand, stand to walk -- type of mobility, maybe even virtual mobility. And the other question is, we're really talking about a complex system or systems here. And the implantable BCIs for mobility are probably the ones that have been less developed, right? And so we, we can think about BCI to FES, BCI to X, or BCI to all of that. And

so how that changes the scope of this, right?

The other thing I want to note that we haven't talked about pediatrics, right? I mean, when are we going to start talking about that, right? I think it's time to acknowledge that, you know, that's going to bring out some additional challenges because of the development process, right?

Again, this allow how communications and ADS upper -- but the emergence for mobility of this system is no -- to appear.

Now, we spend some time discussing Frederico's Christmas tree problem, right? So when you have many, many sensors, right, that you attach to your experiment, to your study, to your clinical trial, and then what do you do with that? That can actually kill your, your clinical trial, right, having so many, so many sensors. Too many options. Too many things to describe, characterize, and measure may lead to systems failure.

Now, I think that the PROs are very important, but probably you don't want to use them as the primary variable here, right? Why they important, right, you know, they are important why? They're important to understand, maybe, to ensure the adoption of the technology by the participants. So we need to have them. They -- that -- that is changing over time. So they are difficult to use as a primary outcome.

The other is the context, right, context of use. We had some discussion about, you know, the indoors, outdoors, what are the changes in global of state that affect the activity that, that you are recording for the BCI.

So the outcome here, the -- one of the main points is that the indications of use needs to drive the end point here.

Now, in terms of gaps for covering glass, I think it was mentioned before, we need to

contact in the real-world data that we are getting from these sensors, many sensors, accelerometers, and other things with the COAs, right? And if you are thinking about outdoors, BCI -- impact from BCI from mobility outdoor, you can think context will be very important, and you're going to have a lot of sensors. I want to think about this -- how we distribute the log between the machine and the human here, and how do we capture that into cause.

Also, you know, we will need to adopt some existing COAs. For example, for wheelchair mobility. I think this -- the power wheelchair, but we need to do that for the, for the IBCI as well. And what if you are using the IBCI as assistive device or as a device that for rehabilitation? So that's also very important, what's the use of the technology.

Now, I think we have very interesting about how do we go about identify and selecting these COAs, right? So we thought maybe, early, the early clinical trials we use the -- we use all the sensors. And some common COAS, right, 10 meters walk test, right? So that then we can start figuring these as, as we make progress, and go to clinical trial, right?

So I think that was a really nice concept that we can, we can gain information about the device from all the sensors, gain information from the patient. We need to get information from the context surrounding this, this device, and based on that make some, some decisions. So we think that these, these COAs, you know, you have a common subset that's going to be filtered, and by the end you're going to have your primary one, but you have learned the process for using all these sensors that you have.

So ideally, by the end of this, you want to perhaps assess if the participants are able to work in the community, right? And so as you can see you can gradually refine these COAs as you go from the early to the pivotal trials.

So I think that going back to the question, what's needed to align the clinical and the

performance, the technical performance, we believe that it's a question of aligning. Again, aligning the real-world data you're getting from all these sensors, right, and with these COAs that you have been identifying or adopting.

We also believe that we need in the future to have a toolkit with measures for different settings in the lab, in the clinic, at home, on the street, and that we can use to, to guide our, our work.

So I think that that covers what -- our discussion. I'm done.

(Applause.)

DR. SLOCOMB: All right. So next up we're going to switch to communication, and we have Matt first.

DR. FIFER: All right everybody. So, yeah, I was in the room focused on communication. We largely had a discussion centered around the context of ALS and speech BCI. Although, as time expired, we started to open up the aperture to other conditions like subcortical stroke, cortical stroke. Started to get into the differences between congenital versus acquired challenges. But we didn't really have time to really delve into that. I'm a little jealous of the PVR task. I don't think we came up with anything as revolutionary as that. But we did talk about some of the challenges, particularly some of the individual variability, and some of the technologies that you might be comparing against some individuals. For example, late-stage ALS cannot move their eyes. And so are you bench -- what are you benchmarking against? You might not be able to benchmark against an eye tracker. Again, just a large degree of heterogeneity which is then compounded by very small numbers of participants, particularly in the early stages of some of these BCIs technologies, and then compounded by the rapid progression of illness which kind of further sub-categorizes the patient population; makes trying

to make grand statements, and aggregate performance measures challenging.

We had the benefit in our room of Sergey being there. So he gave us a little bit of a, an update on his research, and talked about just how empowering some of the speech decoding capabilities could be. Talked about the fact that his participant is using their system for about 12 hours a day, but then talked about all the -- you might consider direct measures of that use case. So impacts on the family life. But then, so that then kind of spun out of conversation about, how do we measure the impacts on the caretaker. Talked about improvements to the -- to social life so friends coming back, increased participation kind of in the community. Later in the conversation we had a -- our rep from the ALS Association was talking about participation in events like this, in different regulatory proceedings, as a measure of engagement has been noted to provide a lot of quality of life to individuals in the community.

So, again, both the importance, but then later on some of the challenges of trying to quantify what is a very large set of activities that might have meaning, and could be valuable to individuals.

Let's see. So then we talked a little bit about, what is the difference between some of the raw technical metrics that we think about, speed, accuracy, things like word error rate. Some things that maybe, that doesn't encompass that, we talked about kind of lack of metrics around false positives, and what happens when you're not actively studying the device. Are we capturing things that might inhibit utility? And we talked about usage time as an important metric to kind of gauge the on-balance pluses and minuses of using a technology. And then also, setup and maintenance both initially, and then day-to-day as things that kind of need to be incorporated in some way with the error metric. So maybe, if you have a very performant device, but you can't use it until 4 p.m., because you're calibrating, what's the, what's the

impact of that?

And then we got a little bit into trying to speculate about what kinds of regulatory and reimbursement stakeholders might be looking for. And so, started talking about more quality of life metrics as ways to kind of capture, again, some of the more broad base of effects that some of these technologies might be able to have. Our FDA representative said that they're having some initial discussions with CMS to kind of back propagate. So what are exemplar technologies that have received reimbursement in the past? What was the evidence that was compelling to them then? And then how do we create COAs and other metrics that will be applicable for motivating BDI reimbursement and regulation now?

Then that brought back the small end challenge of, if we do have to invent new metrics that can kind of add this double challenge of first, you need the population to validate the metric in before, then you are doing the study with the validated metric. We talked about whether there are valid simulated populations that we could work with. Either folks using other technologies. Maybe, otherwise, healthy individuals that we are asking to use, kind of, similar technologies or similar settings to try to see if that can give us appropriate metrics to validate.

And then, yeah, I kind of mentioned the quality of life metrics not just for the participant them self, but also for the caregiver. And, yeah, I think that's when the bell rang. So that's as far as we got. So thank you all.

(Applause.)

DR. SLOCOMB: Thank you.

So now, we're going to move on to Allanah Beazley, arguably the most exciting room today. Also the room I was in.

She's coming from the back. So she's giving me another 10 seconds of material here. Yeah, a few fights broke out, but she's going to tell you more about it.

MS. BEAZLEY: Okay. As mentioned, wildly exciting group. Oh, my goodness. We, similarly to other groups, did not necessarily want to stay on task, but that's okay. We covered a lot of ground. So trying to condense what we talked about.

Right off the bat how does one define communication really? That was pretty difficult especially, looking at traditional clinical outcomes for us whether that was speech, motor function; where we start we can't always align necessarily with the outcomes that BCI has to offer.

And we had, yeah, there were some, some people were like you know what we need broad definitions of communication because we need to be able to meet a wide range of patient needs, and the abilities that BCIs can offer. But then on the other hand, there were expressions that we needed very specific heartstring tugging cases to justify coverage decisions.

But then there were some concerns that a narrow definition could also not appropriately capture the unique ways that BCIs restore communication.

So in that, we identified a key challenge in ensuring that communication BCIs are evaluated using outcome measures that are flexible enough to accommodate any sort of novel, non-verbal, and adaptive methods of communication that may emerge or demand flexibility over time, while also noting that we, ourselves, may lack a shared definition across our respective disciplines for the terms that COAs may measure.

So then, in looking at the gaps that currently exist, challenges in COAs, well, maybe they focus a little too heavily on technical metrics, speed, accuracy, and they don't adequately represent patient-centered outcomes like independence and autonomy or patient preferences.

And a key issue raised during the discussion is that patient preferences, including the desire for independence of communication or private communication, it's kind of hard to quantify. And then it's hard to actually integrate that into our clinical outcomes, and that may include how well a patient can communicate or how intuitive that device is to use. And that is intuitivity included in communication. It's difficult.

From there, we touched on the importance of considering existing assistive technologies and access methods, and considering perhaps going down an access method route, and that included how BCIs compare to or complement other communication technologies which include assistive technologies like eye gaze systems or speech-generating devices.

Moving towards a modular approach to COAs was a proposed solution. Very similarly, to other groups having a bit of a toolbox. And we actually did kind of okay, I think, in outlining a few things that were important like message generation speed, the intelligibility, and comprehensibility, independence in communication, what sort of patient-reported outcomes such as how empowered the user might feel when using the BCI. Of course safety, efficacy, speed, accuracy, communication participation item bank is a place we could perhaps look. Communicative Effectiveness Index is another space. We also considered activities of daily living, and within that specifically, functional abilities and goals as a pre-req to communication.

Let's see. Notes, notes, notes. Ultimately, there was some pretty large discussion around balancing technical performance and patient-centered outcomes because we need to not just focus on the efficacy of communication, but on the functional independence where the patient can communicate autonomously and without assistance, which would mean that we need to integrate quantitative measures such as speed and technical accuracy with the qualitative measures including independence and patient satisfaction.

At the very end, in the last 30 seconds, someone mentioned fatigue as perhaps an underlying thread to all of this that was a COAs that could be easily transferable from motor to communication.

And universally applicable, not necessarily, not when it comes to COAs. We need to develop a robust toolbox. And that's where people like the IBICC come in. We've got to work on that because collaboration is important, and these COAs are important.

And that's where I'm --

(Applause.)

DR. SLOCOMB: She skipped over the fights, but there were a lot of them. So last up, but not least, we have Katya Hill. And I haven't said anybody's last name, but I'm -- before you speak I'm just going to say last name of the speakers for the transcript. For anybody else, first up we had Edward Keefer, then Gianna Perez. I'm going to apologize in advance for pronunciation errors. Leigh Hockberg or Hochberg, David Putrino, Jose Contreras-Vidal, Matt Fifer, Allanah Beazley, and now Katya Hill.

DR. HILL: I love your humor. Because this was fun, but yet it wasn't fun. We had a very talkative group. A lot of contributions. And we took this meandering path down these questions that it was very difficult to take notes because we'd go one question, and then I'd realize that several questions down that that would have fit much better.

But I'm going to cut to the chase, and say what I think is the most profound thing we have to think about, and Kim contributed this more than once, is to remember that communication is a basic human right. And for those people that need a BCI of an IBCI it's the right to be able to communicate. And I think, if we keep that in mind that takes away some of the regulatory issues or policies in funding to get away from just thinking that the technology

meets medical necessity, that we have functional communication goals that are very important to our patients that we work with.

So that gets to what are the challenges in evaluating the effectiveness and the purpose. Well, that led to a discussion about the different types of IBCIs have different expectations, and are different risk benefits to invasive and maybe minimally invasive BCIs that result in different COAs.

So that means, we need to look at what terminology we're using, and what the definition is for those -- the terms that we're using so we are all talking about the same thing. It's a matter of semantics, but if we are using different terms to say the same thing, we're never going to get far. We have different professions, and that is a challenge. We have clinicians that are speech language pathologists, occupational therapists, physical therapists. We work with social workers, dietitians involved with our patients. Naturally, the neurologists. We have biomedical engineers, engineers in general. So we're coming from what would be the goals and objectives of BCIs from different clinical or educational or academic experiences when we're talking to each other.

The modality of communication impacts. It's not just voice output or speech or communication. There are many modalities involved. So communication is multimodal.

What are the gaps of the currently available COAs? Again, a lack of standardization in our definition or standardization in measures. Identifying the COAs that may or may not be available, dependent on the type of IBCI. COAs may not be the same across different clinical populations. Certainly, different assistive technologies are not the same with different clinical populations. So defining and identifying the end point is another gap. And what metrics are being used to determine whether an individual could benefit from an IBCI, and an eligibility

criteria.

We jumped back and forth on, how should performance outcome measures be used. Well, to capture communication throughout the day. I thought this was an interesting question, discussion was brought up. What is the relative gain with a BCI over a current speech-generating device with eye gaze to be able to justify if you're very efficient with that? And of course that then gets into eligibility, and what are seeing in deterioration of skills of somebody that can no longer use their speech-generating device? And difference performance outcomes may be suited for different purposes.

As I was listening to the discussion, trying to fill in what other factors should be considered in selecting and designing COAs, I have a lot of one-word responses because I was listening to the way a person was discussing this. So independence. We came -- went back and forth with independence, and defining it in the level, and that got to the privacy and autonomy, being able to call for help, availability of the system, reliability, used ability, productivity. We discussed being able to map onto the ICF framework, and that needs to become more commonly shared among those of us that are working in this area. The heterogeneity of the populations that could benefit. Caregiver burden, and the burden of care is another important topic. And improvement over our previous ability.

When we got down to discussing -- or actually we didn't get down to it. We jumped down to it right away, and then we went back to questions back and forth. But should there be a universally applicable measurement or a toolbox? And at first we started to discuss universally acceptable assessment, creating one, but then there's a multiplicity of outcomes. So how about a composite outcome measurement. The importance of starting with a baseline score. Mentioning being able to measure was important based on our CPT codes for clinicians

that currently would not allow for measuring what we want to measure because there aren't billable codes for measuring these tools or using them.

But I think in the end we pretty much agreed that we would need a toolbox of COAs, especially, as we move into different clinical populations. We're thinking of adults now, but we're starting to move down into peds, and that will certainly look different in clinical practice when we get there.

And again, I want to end with communication is a basic human right. So that should be something we all are promoting.

Thank you.

(Applause.)

DR. SLOCOMB: So I made a lot of jokes earlier, but I just want to take a moment to thank all of our speakers from today for taking the time to come down here, and put together such thoughtful presentations. And for those of you who are coming here from outside of your field for kind of, being the sacrificial lamb of the day, speaking for your whole field or speaking on behalf, maybe, of an entire government agency to a room full of people that really want your feedback, we really appreciate your thoughtful input, and the effort and time that you put into your presentations, and all of the feedback you gave today. So thank you.

And to everyone attending today, thank you for being such active participants. That's really what made this such a fun day, and so interesting.

And I know we didn't make a clinical outcome measure yet for any of these -- for mobility, ADLs, or communication, but we still have a whole morning tomorrow. So it's still possible. But we really appreciate the focus today, and how much conversation was circulating around patient preference, and focusing on really the patient perspective, the focus on the

intellectual burden, and the weight of using a BCI, and the focus on caregiver burden as well, and really thinking about people as whole people, and not just a single person, but part of the family, as well. And I think that's an important perspective that it's easy to lose sight of when you're just talking about regulation or about device development, right? So having these kind of interdisciplinary meetings is a really great way for us to reset the conversation, and reevaluate how we've been approaching things.

So thank you all for participating in that.

I have a couple announcements. First, those of you who had to get visitor badges, you will have to get them tomorrow, especially those of you who are not citizens. We will make sure tomorrow that we have FDA representatives at the security station to escort you in; make sure we don't have any delay or backup there tomorrow.

The second, and most important announcement we have an unofficial, entirely non FDA-funded, or backed, or recognized happy hour. If you were to show up, we might also be there at Silver Branch Brewing Company Lager House and Beer Garden. It's very hard for me say that without an accent like I'm German, but beer garten (verbatim). So please, come and join us. We're going to start at 5:30. So you don't have to be there at 5:30, but there's no end time. So have -- yes, it's in downtown Silver Spring. If you can find somebody who has a car to drive you over there, all the better.

And I think that was it as far as announcements.

David did say he would pay for all the beers tonight. So send him your bills. No.

But thank you all, and we will see you bright and early tomorrow morning.

(Whereupon, at 4:31 p.m., on September 19, 2024, the Workshop was adjourned, to reconvene on September 20, 2024.)

SEPTEMBER 20, 2024

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M E E T I N G

(8:34 a.m.)

DR. DEAN: So let's go ahead and get going for this second day of the Workshop. I'm excited to see all the connections being made. This is really fantastic. So my name is Heather Dean. I am the Assistant Director in charge of the Acute Injury Devices Team here in CDRH, and that is the Team that covers assistive devices, and it includes brain-computer interface devices for mobility and communication.

So I'm supposed to introduce our second day. So I'm going to start by kind of summing up yesterday. So yesterday we talked about the types of clinical outcome assessments that FDA often sees, and our current guidance on those. We heard about COAs that are currently used for mobility and communication. We heard from payers about what they look for in studies to determine reimbursement for medical devices. We also heard from those with lived experience about their needs and expectations for the BCIs. We discussed in smaller groups what clinical outcome assessments could potentially be used for BCI devices.

I don't know about you, but what I really got out of that is that this is a hard problem. There is such heterogeneity in the population that could benefit from BCI devices, and there's an ever-increasing potential number of uses for these devices as well.

So today, we're going to hear more about how NIH and FDA will work with this community to support the development of clinical outcome assessments and BCI development more generally, and we'll continue to discuss potential outcomes, and the need for finding those that can move the field forward.

Yesterday, I hear the beginnings of calls to action, and today I hope that there will be many more plans for next steps. I look forward to seeing what comes out of today's discussions.

So with that I would like to introduce Dr. Walter Koroshetz. He's the Director NINDS, the National Institute of Neurological Disorders and Stroke, and I think that's -- he's been leading that for going on a decade now, and as such has, has had a leadership role in programs such as NIH Brain Initiative. And as David mentioned yesterday that that is funding that has clearly helped move this field forward to the wonderful stage that we see it at now. As I look forward to hearing a little bit more about what Dr. Koroshetz has to say about NIH's next steps here.

(Applause.)

DR. KOROSHETZ: Okay. It's a pleasure to be here. Sorry I couldn't make it yesterday, and I'm sure -- I apologize for any redundancies. I'm going to basically talk a little bit about a couple of things that might be of interest to folks, some of the things that NINDS is doing, and then kind of just throw out a couple of kind of crazy ideas at the end that might be worth considering or not.

So first of all, just to mention that the field is exploding, and you probably heard that yesterday. And this just shows the funding going up over the last four years. And you can see the breakdown from the different institutes, NIBIB, bioengineering, bioimaging, NIDCD Communications, and NINDS are probably the big ones.

Our folks looked through our portfolio, and this is just kind of a breakdown. Most of the grants, as is true for most of our grants, are in the RO1 space. So these are investigator-initiated grants. And we have a smattering in the, in the F's which are the, the training

grants, and a couple of big projects which are what's called the U's which are cooperative agreements. And a DP2 which is kind of a transformational out-of-the-box thinking type of grant.

We funded a number, we funded a number of biotechs in this space. As well, we have a really robust translational program where we work with folks to bring devices to the point where they can get a -- have the package to come to the FDA for an IDE. And hopefully in those cases they can then go on to get funding from other sources to do the more expensive clinical trials, but sometimes they can't, and certainly we are interested in making a difference so people have the kind of conditions you talked about yesterday. So we tend to bend over backwards to kind of move that forward. We have really good staff in this space. They're very knowledgeable to devices, and they're also pretty knowledgeable about the diseases that people are looking for in these devices.

As John probably mentioned yesterday, the real impetus for moving this field forward is really coming out of the Brain Initiative work. The Brain Initiative, as people know, is a project set up to develop the tools to map, monitor, and modulate circuits. And, of course for brain-computer interfaces, you're basically monitoring circuits for different purposes. And so, it falls right out of a lot of the Brain Initiative work, and a lot of the work that's actually devices in people is through the Brain Initiative. So I think that's one of the early wins for the Brain Initiative is the advances that have occurred in this field.

And this is just the beginning. So the technologies that the Brain Initiative has come up with are, are just increasingly sophisticated particularly in the monitoring and capturing electrical activity to run brain-computer interfaces. But there's probably going to be a lot more stuff coming particularly in how we can better modulate circuits. We're currently

using electricity which is pretty crude, but sometimes it works which is great. The key now is to tie it into signals that are in the brain when something happens. So you're depressed, you feel depressed, device goes on, stimulates, depression goes away. Same thing with pain, obsessive-compulsive thoughts. So these are interestingly brain-computer interfaces that are within the head as opposed to sending the output to a prosthetic device or a computer. But they're not that dissimilar in certain -- in trying to think these things through in terms of what, what's going to be, what do you need to prove things, and how do you know if things are working.

And so, as everybody here in the room knows, and I think it was brought out yesterday, both the FDA and the NINDS are really very much in the weeds with the people who have these conditions. It's pretty clear that when you're trying to help people you've got to find out what is it that they want, and I think that's going to come up today. And I have a couple of ideas at the end I'll throw out.

But we have, we have set up most recently kind of a more of a continuous stream of input from people with lived experience, and to each our actions in, in the institute.

I think in terms of the, you know, the ultimate goal is always to improve quality of life. Not so easy to measure, but I think that's going to come up, and it should be something that is measured as we look at these devices. That is the purpose to improve quality of life. I mean you can have drugs that are really good for seizures, but they ruin your quality of life because you sleep all the time, and you can't think. And so that's, that's not going to cut it. So I think that same, same kind of thinking has to come in this space if the ultimate goal is to get a quality of life.

Now, it's not, it's not as discrete a measurement. So it may not be your primary, but

I think it really needs to be in there because I think also when, when something is approved, and you want to tell patients about it, and they have to make decisions about whether to undergo this surgery, have it put in, they're going to want to know about what, what was the effect on quality of life.

So we have tools that we worked on. I think when I first came we started -- or maybe it's even before that -- developing a particular quality of life measure for neurologic conditions. This was part of the NIH toolbox, but it was a separate piece that was -- we built at NINDS with help from other institutes on neurological disorders.

So just a couple of examples, and maybe people talked about it. Nod you head if this already came up yesterday. The national report on ALS. Okay, if not, I would -- if people are interested, I would urge people to look at the video recordings of this national report where they had video recordings of the, of the working groups and the meetings. Because you really understand what somebody with ALS is going through, and you really understand that in our current environment their resources are really not anything one would be proud of. And that's part of it is due to the fact the disease is terrible. We don't have good scientific products to help them, but it's not just that. It's also that the whole system is, is kind of set up, the healthcare system, and the long-care system is set up to really defeat these kind of efforts as best they can to save money. And the really nice take home point was the VA is what -- the VA system does it really well. And so it was interesting that most people don't get what they need, but if you're in the VA system you do get what you need. Which means it's possible. It's just our system is broken.

But they do, they did kind of bring out that they wanted supports to help with large -- speech and language, and this is certainly where the BCIs have really shown tremendous

benefit so far. In the academic space in terms of publications how that gets into commercialization and scale up is still to be seen. But offers a lot of hope I think.

Functionality in the home is something that is really important to folks who have these impairments in motor function and to communicate, also to -- even just basically perform activities of daily living. And until you live with someone who has this condition it's not that intuitive to us people who are not impaired. So that's why you really have to kind of get -- put yourself in the shoes of somebody who has these conditions to really understand what they're -- what they, what they're going through.

Just a kind of aside. I remember when I was a student, and there was a classmate who suffered a spinal cord injury in Alaska working on the pipeline. Then he went to become a PhD neuroscientist. And he had this device which would allow him to go from a wheelchair to a standing position, and he was really excited about it, and I, when I first heard about it I was like I'm not -- I don't quite understand what's, what's the big deal. Maybe if you're sitting you can do everything when you're sitting. But as a scientist the lab benches are higher than a wheelchair would get you, and even if you could elevate the wheelchair the lab benches oftentimes don't have space underneath them. They have closets and things. So you couldn't get the wheelchair in. So you'd be have to work like this, and even, even if it's elevated. But with this little device that he built he could go from the wheelchair to a standing position, and he could work at a lab bench which is really what he wanted to do. So it's kind of getting into that mindset is, is what I think you have to do to understand the usefulness of some of these devices.

So there have been a lot of surveys about -- to people about, what would they want, what kind of things are important to them. And this is really important to understand as

you go in. So things like turning on a light switch, being able to move, control a television, control the room temperature, reclining, working with a computer, having bed control, control over your bed. So these are the kind of things that come up which are not necessarily intuitive to us, but that's where you find out what are important to people.

The other thing I'd say, just from my experience in previous areas somewhat similar, when you do surveys you get certain set of answers, and then when you actually test things you get a slightly different set. So you can't expect that the surveys that occur pre-development and implementation that the answers are going to line up exactly with those in the post-implantation part.

So there's another study with people looking at EG BCI for patients, and you can see that there's, you know, there's definitely some benefit, some changes over time. But improvements in this space at least out of this study where EG has its limitations would certainly increase the utility of the device.

This is another survey priority setting from UK, and people with spinal cord injury. So the things in yellow here. Bladder management is a really, really, really important in folks reducing the number of urinary tract infections and secondary complications. So these are discrete things that you could measure if you are looking at a device which has this functionality in it. Improving bowel function again, as you can see, comes up really big. And so that may or may not be intuitive to folks that -- but bladder and bowel function is really one of the most important things in folks with spinal cord injury.

Another one, a spinal cord injury from Sweden. So managing pain is a big one. Gastrointestinal problems. And preventing and remedying breathing problems, pneumonias in people with spinal cord injury come up high.

Another one in people who are quadriplegic on the top and paraplegic on the bottom. Can see in the quadriplegic's arm and hand function is way at the top. Sexual function is second. And people with paraplegic sexual function was at the top, and bowel and bladder was second. Trunk stability was third. So even in people with spinal cord injury depending on where the lesion is the needs are going to be slightly different. And so again things to consider.

Not sure that's too helpful, but and this is another one, a study of 57 veterans with spinal cord injury, and again you can see the differences between the tetraplegic and the paraplegics. And, but the, the main categories are similar across them, and they're also similar across the multiple studies, but there's a little bit different depending on the level of your injury.

And then there are issues with regard to the kind of pain in the neck parts of having devices in. So having periodic battery replacements, having going back to clinic. Turns out -- I know there's another study. I forget exactly where the disease was, but the major outcome that was important to patients is that they didn't have to go back to see the doctor so much. So again something you wouldn't have imagined right off the bat, but doctors are just not that popular. But also it's a pain in the neck if you're -- if you have one of these disabilities to travel to go see a doctor, or if you have a kid who's got a severe neurological problem to travel the kid to come in and see the doctor.

So again, these things are I think important to kind of talk in the industry people to understand what these issues are, and try to mitigate them. Certainly important to consider.

And just to end up with the promise looking forward. I think people probably have

seen this video before and the, and the paper, but it's really quite remarkable how now using these devices to capture the single-cell activity raster plots are firing, flowing through a neural network. You get some kind of phonemes out of that with the, with the electrodes implanted along Broca's and motor cortex. And then the interesting thing was moving that data was into a large language model to basically predict the next phoneme after the previous one, and the next word after the previous word. So a lot like a ChatGPT might do to really speed up moving from collecting the data to predicting what the patient, person really wants to say. But you can imagine that's not just for producing words. You could use that for controlling an arm or fingers or a bladder control device.

So I think that's the other thing that's happening, and probably was mentioned yesterday, that the use of AI on these data is going to make these correlations occur so much more quickly, and it's the correlation that -- between what's coming out of the brain and what the patient wants to do that is really what controls the interfaces.

So in this case the -- I thought there were a couple of things here that were interesting, and about the word error rate, looking at trying to reduce the error rate, and the utility in terms of how this was used over time by the person who was implanted. And it was pretty clear what the utility was.

So did you guys see this yesterday?

(Video playing.)

DR. KOROSHETZ: Okay. So, yeah, I think this is just the beginning. So this guy was able to put words up on a screen at a pretty amazing rate. Then there were corrections that were made. I'm not sure how the corrections were done. Maybe Leigh knows. But then when it, when it looked like it was all fine you have a sentence, maybe two or three

sentences on the screen, he put a red button if, if there was a -- if it was not what he wanted to say, or a green button if he said if it was what he wanted to say. And then the voice that came out of the computer that was his voice, right, from before. Yeah.

So, oh, everybody's here who has done this. All right, good. All right. So little advertisement. Stand up and take a bow.

(Applause.)

DR. KOROSHETZ: Thank you. All right. So what's next is the question. But anyway, all right. So just a couple of thoughts, and these are -- everybody I think probably, it's probably redundant and not that helpful, but certainly the first thing you're going to have to deal with is safety issues. So it's the usual stuff about device is interacting with the tissue. So you have the questions of the material interaction with neural tissue, what happens over time. Do you start to get gliosis? And I think if you ever got something that could spread from one part of the brain to the other, you'd have a problem, certainly like a prion type of thing. But I think mostly the devices you've seen we don't see major injury to the brain unless you hit a blood vessel when you go in, or if you get infections. So infections are unfortunately always something that can happen any time you instrument the brain. And they're really bad. They're really hard to get rid of.

So that, if anything, you want to look at a device, and minimize any chance of infection, any chance of untoward reaction between the materials and the tissue.

I guess, the other thing that we might think about, and I'm not -- it may just be hypothetical, but since you're basically recording from neural circuits I guess it would have to always be concern that the device doesn't somehow affect neural circuits. So, but that would be, I imagine that the electricity would have to go the other way, as well as, as well

as out.

And the other safety issue is going to be privacy issues with regard to taking neural data out of someone's head. I think the devices that we saw allow people to speak, but there's a lot of other information that's coming out of those devices all the time, some of which people want to make private. And so ensuring that privacy is certainly going to be important, and something in the consent process. Because people will be looking at -- if people are going to be looking at the data, they're going to be -- they can make associations that the person never really wanted them to make.

In terms of performance I think there's going to be issues like we mentioned about battery placements. Durability of the device I think should be taken into consideration. And I think that's also relative. If someone has ALS, and they have limited time on earth, then what we think is a short durability issue may not be so short to them, and so I think that's got to be kind of depending on the context of use.

Then I would think that you would think about as kind of with this device that we just saw in terms of the errors. So the performance of the device, I think you could think of it in broad terms as there's errors of omission where you wanted something to happen and it didn't happen, device couldn't do it, and there's errors of commission where you want the device to do something, and it did something that you didn't want it to do. So there be controlling a car an error of commission, a real bad one would be the car hits something. But I would think in those two terms of error rates, omission, and commission.

And then you get to the question which is the biggest one is what's, what's useful to the patient? And that as we mentioned is, you know, when we talked about the quality of life issues is a little bit difficult. But that's what the FDA is going to have to do. They're

going to have to look at the utility of the device, and make a decision based on the risk, and the, and the utility of the device, and what it can do. And so, in trying to think about how to do that especially given the fact these devices could be doing a whole bunch of different things, I had the idea what's called the Utility Index. So the idea behind this is that if you, if you want to know how useful something is, and you implant it in somebody, one way of getting at it is, how frequently does the person use it? So if you put in a device to help the person communicate, and they never use it, that's not good.

So how would you measure that? Well, I mean, in the hypothetical space you would break down the activities that you want the device to aid the person to do, and then you would raise -- collect data that says of the X amount of times the person was planning to move their bowels they used the device X percent of time. If it's zero, it's not very useful. If it's 50 percent, and the -- I'm not sure if it's useful, but at least that would be an indicator of how good this thing is, and would help patients decide whether or not to have it implanted for that purpose. So some kind of ratio of the number of times the device is used for an activity over the number of times that activity occurs during the day.

And I think that that could be thought about -- I'm just throwing it out there as a general kind of rule for whatever you're trying to test whether it's bowel, bladder function or communication.

And then in a clinical trial, the Utility Index really tells you over time how useful it is to that patient. And then you -- certainly the more the errors are probably the less the person would use it. The harder it is to use the less they would use it. And so that would potentially give you some kind of measure that may not have a cutoff, but at least some kind of a standard for the industry moving forward as they try to get better and better

devices for people.

So how would you capture that? Well, I think the one thing about the brain-computer interface is that there's information going into computers. So on the one hand the number of times the device is used probably could be captured by the, by the computer interface itself. The hard part is -- harder part would be capturing the number of activities that occurred during the day. So how many bowel movements were there during the day? How many bladder emptyings were there during the day? And there you would need some kind of sensor, survey tool, a button press, or something like that to capture that kind of data. But given the fact that you have the computer interfaces the question is whether you could collect that kind of data in the same systems that you're using to, to use the brain activity to create actions.

Certainly, the digital biomarkers of people -- we actually have a NOFO coming out soon on studies of digital biomarkers; might interface with that kind of an idea where capturing these number of actions that the device is really supposed to help.

So, and then as it gets -- my sense is that these -- that the brain activity it's set up right now to do one thing at a time, but my guess is, and I'm -- ask you people in the audience who know better, that there's so much redundancy in that brain activity, there's lot of -- that you could, you could collect information from the motor cortex that would help you drive car as well as communicate on a, on a computer system.

So I think in the end you'd be -- we'll be looking for that for brain-computer interface to have multi, multiple functions.

And then how do you look at that, those? And that potentially having a matrix of these utility indices for the different functions would be one way of doing that.

So, anyway, those are just a couple of ideas. Clearly a lot of effort going in this space. The things we think about today people will laugh at us 10 years from now, but we've got to get there first, and then fine if they want to laugh, okay?

All right, thanks a lot. Happy to help.

(Applause.)

DR. DEAN: So I mentioned in the intro that I was looking for calls to action, and there you go. Utility Indices and across multiple functions. So I'm glad that people are thinking this way starting, starting the day thinking about next steps here.

So next, our next speaker is Dr. David McMullen. He is the Director of OHT5, that's Office of Health Technology 5, here in CDRH, and that's the Office of Neurological and Physical Medicine Devices.

David.

DR. MCMULLEN: Good morning everyone. I didn't think I was going to start today's talk off with a caveat, but please talk to us before you are going to have a participant drive a car. I'll just say we will get there as a field, but let's -- maybe not the first step.

But thank you Walter for your, your thoughts and contributions, and continuing on the ideation that everyone's been doing in these great breakout rooms. So today, I am going to talk about clinical outcome assessments to objective performance criteria, and how the clinical outcome assessments can inform the next generation of BCI clinical trial design.

But, before I start off, I just wanted to build on something that came up several times yesterday. And there was this idea of, well, can you give us an example or sort of what is the answer? And a lot of times FDA I wouldn't say we, we deflected, but we did try to highlight that there's a lot we can learn from the medical device ecosystem, and even

across the entire medical ecosystem in general. So there were examples that came up of gene therapies, and how those are evaluated. BCI is also a pretty paradigm shifting approach in medical interventions. And so we can look across the broad swath.

I would highlight, in particular though, these two workshops that were really informative for me as I started my journey here at FDA, and I hope that they would be informative to you as well. So both of these were co-led by our internal eye office I'll call them, and I'll show you where they reside on our org chart, our OHT1. And the first one was a workshop cosponsored with the University of Pittsburg where there's several very clinical researchers who have driven forward the field of retinal implants for vision restoration. And at that workshop a key theme that came up was this idea, this duality of the Visual Function Test versus the Function and Vision Test.

And so, on the first you're collecting some critical information. Can you see a white light on a computer screen? That's really important if you're trying to provide low-light vision restoration to patients. It's critical to know if they can do that. But real life is not sitting in front of a computer screen in the lab doing an assessment. It's going out there, and using your vision for functional benefit.

And so other types of assessments were also discussed there. Can you walk around a room that's dimly lit? Can you standardize that? How can you assess that?

So you can really assess for patients that, that you're giving them function and vision back? So that was one critical takeaway that I had there.

And recently another co-listed workshop with the National Eye Institute really focused on developing clinical outcome measures which when I was at NIH might not have been the focus of the research I helped fund and oversee there, but is really critical. And

NEI and Dr. Michael Chang was one of the initial speakers, and really laid out NEI strategic plan, and how quality of life, and measures for that developing COAs is part of NEI's mission.

So, again, I do recommend trying to look to that, and as we think about other examples, looking at sort of the lessons learned from retinal prosthetics especially, as they transition potentially to cortical visual prosthetics is really helpful.

So just a brief agenda of what I'll continue talking about today. So, of course, here we are -- I particularly like to show our org charts to really help you understand who we are. Now, there are several people in this audience that know very well everything I'm about to show, but for those in the audience who are online who may not have interacted with FDA previously I do want to go down the different steps to really highlight that there are human reviewers at the end, at the end. And part of these teams that are really working hard on every submission you submit. Every time there's a meeting they're working with you. But do want to provide some context for where we all reside.

I'm going to really get into the FDA regulatory approach. I heard after our BCI collaborative community meeting that the slides weren't exciting enough. So I added some, some U.S. Code, some laws, some federal regulations to really spice things up. But it is an early class on a Friday morning. So just, do just want to make sure everyone's paying attention.

But this is an open-book test. Our regulations, how we think about this are all out there publicly. It's in our regulations. It's in our guidance documents. So please read those. Again, some of you, many of you in the audience may read these be very well aware. But for those that are thinking of going towards market authorization or wonder what we

actually do look long-term at FDA even if you're working in the -- in human space, I'll take you on the journey there, and leave it to you whether or not you home and read some of these.

But I'll really highlight the uncertainty, and how that plays a role, and how we think about this. And then to get to the actual title of the talk. We'll talk about COAs to OPCs, and I'll provide a little bit of definitions there to help guide that. And we'll end on talking about some of FDA's efforts in this phase.

So who are we at FDA? It's three letters you all probably know very well. We help regulate and oversee a quarter of every dollar spent in the United States. It's absolutely massive. But we're located here in the Center for Devices and Radiological Health. You might be aware of drugs, biologics for vaccines we're overseeing. But we're here in what we, we call CDRH. Within CDRH, again in red, we're in the Office of Neurological and Physical Medicine Devices. I highlighted OHT1, or Office of Ophthalmic, Anesthesia, Respiratory, ENT and Dental. We basically take a review of systems approach for those of you with a medical background similar to NIH. You can always look at the acronyms. Our acronyms are a little bit more confusing I admit, but all these slides are online. And just so you understand there's always a place for any of the type of research or device you're trying to develop.

With the Office of Neurological and Physical Medicine there's a wide array of different types of devices. So just to highlight neurosurgical devices. What frame does someone use to do their surgery? Neurointerventional, stroke devices, is something we heard about recently. And then all the vision focused -- all the exciting work of neuromodulation, neurostimulation, DBS, spinal cord stimulation, vagal nerve stimulation.

And of course the team that Heather leads, and we have many members of her team here. Our Injury Devices Team where the -- for now all the implanted brain-computer interfaces reside, but you may also depending on the type of device, invasive, non-invasive, what indication you're looking at, you may interact with staff members from across the OAHT. So I just want you to be aware of that. And, again, even at the different office levels depending on the patient population you're looking at you may end up in different areas.

So many of you have probably learned about the Phase 1, 2 and 3 clinical trials. That's the language our drug colleagues use. Here in CDRH, we use a slightly different, but still three-part clinical, clinical trial terminology. BCI is traditionally or to date really resided in this Early Feasibility Study or first in human space, and these are a small number of subjects. It's critically important work. And I like to think about this as a funnel in this EFS, or Early Feasibility Study stage, it's the wider part. It's the most amount of flexibility. There's academic PIs. There are small companies. You're really trying to figure out what can these devices do? What are these benefits for patients? And so we understand, and there are many guidance documents on trying to help assist sponsors try to figure out about how to get to that first in human stage, and really get to the Early Feasibility Study to see what this can do in humans; move beyond the animal model, and see what this can really do for participants.

Traditional feasibility studies, when you're getting closer to that final Phase 3 pivotal study design, can really help you along the way. And that pivotal study which, it is great to be in a room where we're talking about pivotal studies for brain-computer interfaces. I don't know what timeline folks would have put 10, 20 years ago, but we are, we are truly here thinking about what are those final studies going to look like, and again, trying to think

about that device design being final, the study design, all trying to be on the same page.

Just a brief note on IDEs. Many of you are well-aware of these. You work very closely with many of the FDA team members in this room to think through your IDEs. I will just highlight that, again, thinking of that early feasibility study stage, first that pivotal study design stage; that the way the laws are written is that the IDE evaluation is very focused on safety. So if there are no safety concerns, pivotal trial IDEs may still be approved. However, I would really recommend you as a sponsor to really look at the study design considerations. And this is something we did at NIH to also ask for that letter, and ensure that the study design considerations are included because those same reviewers even though the IDE is approved may have some significant concerns that unfortunately that pivotal trial design will have high uncertainty of supporting a future marketing submission. And that's not something that anyone wants to waste patients time, the risks that they're taking, the money of your external funders, your taxpayer funders. And so, I would just really recommend taking a look and carefully considering to study design considerations.

So as I said, I'm going to put a few laws and regulations in this talk, and hopefully it will, it will make sense at the end.

But the FD&C Act, why we are here is FDA, CDRH really clearly lays out how a PMA is evaluated to assess the reasonable assurance of safety and effectiveness.

And I'm not going to read all of the words here, but it's really, it's, it's -- the safety and effectiveness in respect to the persons, the conditions, the labeling, and really weigh the probable benefit of the health against any of the probable risk of injury.

Our Code of Federal Regulations are how we, we interpret and put on page how we interpret those laws. And 21 C.F.R. 860.7, again it's not many words. It's short. You can go

online very quickly, and find it. But the reviewers here at FDA are looking for valid scientific evidence, and they are really looking for a reasonable assurance of the safety and effectiveness. And it goes on that they're looking that the, the probable benefits and significant portion of the target population, the use of the device, not other factors, the clinical trial design, not placebo response, but the use of the device itself will provide clinically significant results. And that is really it. That is how PMAs are evaluated. The rest is commentary. There's a lot of commentary. But this is really the core of it. And I think you, you might be surprised to say this is actually fairly understandable. That the regulations are straightforward, looking for clinically significant results.

Again, but the commentary is important, and there are many guidance documents that really elucidate how the reviewers -- when you submit that final PM are asked to review these. And we're -- the medical officers are really weighing those benefits against the risk. So it could be the type of benefit, how the patient feels, functions, and survives, the magnitude of the benefit, the probability they actually experience that, the duration. Everything that you may think the benefit that any intervention might provide to a patient. We're looking for all of it, but also weighing that against the risks, the severity types, number, duration, probability of that. This is really the underlying thought process.

But underlying all of this is uncertainty. Because we understand that we would love to see all the benefits give the best, the best interpretation, but also look at the risk. But it really is the uncertainty in being able to assess any of that in what are not 20,000-person large trials. So the uncertainty is always quite high.

Our Graphics Department helped put this together, but it really does help lay out. Again, this is not, this is not complicated. This is what is going through every reviewer's

head, and everyone externally who works with us really understands this is the core of what we do.

At the beginning of the trial these boxes are not filled. The priority -- we're naive. We know that there's some potential for benefits. There's some potential for risks. But before a study begins, we don't know. We all hope these trials work. We hope patients have access to safe and effective devices, but this is why you run the trials.

On the left, this is what we're all hoping to get to. We -- our medical officers, our reviewers, our teams, we want a clear win. You want a clear win. But to get there high certainty is really helpful. If you can fill up that green box, make it as large as possible, and de-risk it as much as possible, everyone wins, patients, device developers, regulators. It's clear. You've demonstrated a reasonable assurance of safety and effectiveness. You can get that FDA stamp, go market that, and hopefully improve patients' lives.

Unfortunately, clinical trials are often very messy. I will highlight that even if you have great potential to demonstrate that benefit, your box is large. If there is high uncertainty in the measures you're using, in the design, and how you've conducted the study, unfortunately it's a multiplier. You're taking the probability of that benefit multiplying by the uncertainty, and it's reduced. And in this space we are talking about implanted brain-computer interfaces. So the risks are quite certain. They may be clearly on the left outweighed by the benefits. We certainly hope so. But there will always be risks. And so, part of the mission of this, this week, the past few days, has really been to talk about the clinical outcome assessments because the better those tools are, the more certainty we can all have in evaluating these -- the benefit. And so we are all hoping to get to the, the left side of this equation.

Again, not to over trust it, but we are always concerned about the bias and variability in device performance. Again, for PMA the results need to be because of the device itself, not the, not the trial design, not any expectation. So we want to ensure -- and again the generalized ability I think is key here. Many of us in this room have run first in human trials in BCI. We understand the profound benefit in the experience that patients have. But it can almost feel like a job or a new group that these individuals work with. And you're all with them for hours a day for weeks on end. But that's unfortunately not likely going to be the long-term experience once these devices are out there on the market. The number of touch points will be much less frequent. They won't be trial participants. They will be patients who as Walter showed don't want to interact with you. They want to live their lives, and not interact with the healthcare system.

So, how can we design trials and develop measures that don't reflect the current state, and that high intensity type of clinical trial experience with the future state? So just want to highlight that.

We've had a lot of conversations on developing clinical outcome assessments. Last year we were out in Brussels. Great meeting at the BCI Society Meeting. And we had a workshop really focused on building consensus in this area.

Now, as you can probably tell we're here with a similarly-titled workshop. So I don't think we've gotten to full consensus, but we are hopefully continuing to drive for the work on this.

For those who weren't able to attend that, recently I had a manuscript accepted, and Nikole Chetty, and in the -- in JNE. So please do take a look at that. I'll pull a few of the figures that we talked about at that meeting just to, to provide some of the foundation,

make sure we're all on the same page.

So, again, here at FDA we're -- for outcome measures we're really focused on fields functions and, and survives. So caveat we are not endorsing any one in particular of these measures. These are examples of measures that might fit under these, these various categories. Some of them may happen to be in bold. So you may possibly interpret that we are looking at functional metrics. Again, could that provide the highest level of certainty for us internally when we're trying to weigh the benefits against the risk.

So we're -- included in the paper is a very nice hierarchy of functional communication outcome measures. And I would say there's probably many an engineer who in the past few years have seen amazing speed and accuracy measures, and when they see the result a tear wells up in their eye that we've truly achieved something amazing. But as we saw in the video that Walter shared, and many of us have seen previously, and may have created tear in us, this is what, what leads a patient, a family member, and honestly everyone in the room to cry are results at a higher level in this hierarchy.

So trying to understand what sort of measures we can develop, how we can move on this hierarchy, balance both. These measures are critically important. These allow for comparisons of different BCI methods of rapid iteration. But how do we capture these measures so that folks outside of this room not online but in the wider community are able to also appreciate the profound impact BCIs can have on their lives?

This is also a nice rough schematic. We heard a lot about the gold medal, and we all want to get there as a field, and there's many dimensions to think about this in terms of developing clinical outcome measures. We'd love to see a completely well-validated used for 20 years metric that has so much validity that nobody even questions it. That is it so

clear that this will impact patients' lives. But we're also starting more in this quadrant.

So, how do we get there, and where might that initial bronze medal be? I would say, if you look at some of our uncertainty guidance, we do recognize the breakthrough nature of many of these devices, the dire patient needs that patients have, and there is some level of uncertainty that FDA is willing to, to use in the pre-market space. We can balance that with post-market think through. But when we think of where we want to apply that uncertainty, you can think through all the dimensions of an outcome assessment measure, and some may be more tolerant of uncertainty than others. Would we love to see a measure that's been used for several decades completely well-validated in the first PMA trials? Yes. That would help de-risk. But is that going to be the most likely? Maybe not. Maybe these are being developed in parallel by groups as yourselves, the BCI collaborative community. But we do want to see more certainty in understanding how this applies to patients, and leads to clinically significant results. And I do think that you all can help think through that. And for these various domains of function really think what can have some face validity, some, some initial sense that these work as they are being validated. We do want to get to this upper right-hand quadrant even if we don't, don't start there.

All right. So I have about one, two slides that are focused on the title of this talk. So from clinical outcome assessments to objective performance criteria. You can look in the design considerations for pivotal clinical investigations, if you want to get a little bit more into these definitions. They'll make general sense. But with new areas of medical devices BCIs are one of the newest, but there are many areas that, that are new, and have been developed. Again, we've heard a lot about thrombectomy recently. These fields often start with initial demonstration, and that could be a device for treatment as usual, versus sham,

an active control. Really depends on the patient population, the device itself. Please talk to us about that.

But often that initial demonstration it is some of the most robust data that is built upon as new -- as the label is expanding new populations are added. New technology is added. But that initial demonstration may have the high certainty in the data that, that FDA may have perceived, and then as new companies may come into the space oftentimes, but not always, non-inferiority trials can be run. You compare devices. Are you within the margins of what FDA has already determined to provide a reasonable assurance of safety and effectiveness?

Pretty clear result from current studies comparing controls.

Long-term as fields mature, strong heavy on here, as fields mature over time performance goal and objective performance criteria may be able to be utilized. And that's when instead of trying to compare to another device, another type of control arm, you can point to a specific measure, and say we're trying to beat that bar that has clearly demonstrated has enough data that it is clear that that is linked to that clinically significant result.

And so why would you do that? That can really help inform your clinical trial design so years on that can lead to label expansion, a quicker cycle for novel technology, innovative clinical trial design, and for modularity. Maybe something can point to, again, I hesitate to bring up any specific examples, but if someone could say a specific number of neuronal yield is a very clear surrogate biomarker for speech rate in this rate, and that leads to this specific outcome for patients, one day those, those performance goals and objective performance criteria might be able to help enable that.

So that's hopefully a part of motivation for this field that developing that clinical outcome assessment is critical for today. It's critical for the first devices that are going through pivotal trials to get the first PMAs for sure. But this is a field that will hopefully evolve over time, and adjust as more information is gathered as the certainty -- as our understanding of the risks and benefits become more certain over time.

And so I do just want to say that this is, this is something that can evolve over time. But let's acknowledge we're at the beginning today. Where do we want those initial demonstrations to be? But also how can we get to these future states to enable these helpful outcomes?

So I just want to wrap with some of the FDA's efforts to address these challenges. We are not the device developers. We are not out there treating the patients, but we are heavily invested. May of us come from, come from these areas, trained with you all. We also want to see these areas to succeed. So there's a lot of time, energy, investment from folks at FDA that you can tell that they're in the room, that they helped put on this great workshop. So workshops are one way we do this. We put out guidance documents to hopefully de-risk for you, and show you our thinking. We provide a small amount of funding. I will just reiterate this. I might have confused some folks. But we do provide some funding. It's just quite small.

We do outreach on our end as a sort of government-trusted partner. We can talk within the government, across governments, and there's a little bit of understanding of neutrality there.

We've had initial conversations with payers, patient groups, all of you as a network of experts. And of course we have some specific programs I'll briefly talk about such as our

Breakthrough Devices Program, and our TAP Program.

FDA has been very involved in this space for a very long time. NIH has as well. I'll just talk about the past decade or so. I think I saw Carlos Pena in the back. Please feel free to chat with folks. Let's get the, the entire history down, down at some point.

But about 10 years ago, I think in the same, same room, FDA put on a BCI workshop, and many of the -- you can look at the, the COA this year. Many of those folks are still represented in this room, and very involved in this space. But they really helped energize, energize the field.

Building on that the FDA put out guidance, and this was for implanted BCIs. This really helped a lot of the non-clinical testing and some of our initial considerations on the clinical side as well. And hopefully many of you in the room and online have used this. Or please be aware of this if you are interested in this space, and have not read this. This is the first stop you should take in terms of trying to understand FDA's thoughts in this space.

We've been involved in inter-government work, the Department of Commerce, and a variety of folks out there helped put together a great workshop to make sure we all understood where this technology is, and where it might apply to patients and other uses.

And again, to briefly mention some of the funding. Accel Access for Critical Therapies, that ALS Act, Act for ALS, provided some funding for, for -- that FDA was able to distribute. So we hard from, from Nivas yesterday on their findings for systematic review for COAs in communication BCIs, really highlighting the dire need. But just to highlight, again, the FDA should not be your primary source of funding. But we are co-hosting this Workshop, and we have leaders and staff across NINDA, NIDCD, Rehab Center, and across many others in the audience. And are freely available to go to online.

As Walter showed, the RO1 space is where a vast majority of this work is funded. It's investigator-initiated. So you all have to put that positive pressure that this is an area that should be funded; that it's important; that this is a hurdle that the field needs to overcome to really have transformational public health impact. So please work with everyone.

As I mentioned, we're also able to have outreach with, with government partners especially on the regulatory side across the world, and this is really to help make sure we're on the same page, de-risk it for everyone. But also to make sure we're thinking similar things when it comes to how we assess benefit numbers. We do speak in the regulatory world similar language. So we just want to make sure that we learn from each other. That sometimes we, we have ideas of ways we're approaching this, but we can certainly learn from, from international partners about their approach. But want to make sure everyone does have a baseline understanding of BCIs that not just the science fiction. It's not just the stories they read online. But to really make sure we truly understood -- understand the medical application.

Just too briefly note to the program. So Breakthrough Devices Program. Many people here online are part of that. Devices that can provide for more effective treatment or diagnosis of life-threatening irreversibly debilitating disease or conditions.

This is what we're, we've been talking about the past few days. How can you restore communication? Activities of daily living, mobility. Many of these, the devices, fall within this purview of this program, and that can really help have even more interaction with the great FDA staff here today.

TAP is a breakthrough on steroids. Not only do you have even more increased interactions with FDA staff, we really try to bring the stakeholders earlier into the process.

Because, yes, we understand that going through FDA can be confusing. It is a large hurdle in the device development ecosystem. But there are so many other stakeholders that, that should be considered as early as possible, so its not un-serial that this can happen in parallel. Again, FDA is able to make some of those connections. So whether it's an introduction to professional society because you as a device company don't have those connections to those clinicians, or patients, or payers, we can try to bring those conversations earlier so that when you then do get to that, hopefully one day getting that, that PMA approval, there's a quicker, a quick, quicker next-up to patient access. Because just getting FDA approval is not the end game here. It's really ensuring that patients have access to these new devices.

Yes. On Wednesday, the Implantable Brain-Computer Interface Collaborative Community had its first meeting, and it was great. FDA's an active participant, and really glad to help drive forward on many of these considerations. Clinical outcome assessments are one of the considerations. But, as you can see, in the list of working groups there are so many things that are necessary to happen before a paradigm shifting medical intervention is truly ready and accessible to patients. And so, really commend the work of that Collaborative Community of trying to think through those steps, and doing the hard work to ensure that there is -- the groundwork is laid for that.

So with that, I see the red light on. Just want to emphasize patients are at the heart of what we do. We're looking for clinically significant results to assess a reasonable assurance of safety and effectiveness. And look forward to continuing working with all of you today.

Thank you.

(Applause.)

DR. KESZLER: So next, we'll be going to our breakout rooms, but we have some updates.

First of all, we learned that there are more conference rooms available in this public space today. So that means fewer people, if any, will be going into the official FDA campus. So, yeah, less security. So I'll be updating you all with the room, your updated room numbers. So and we'll -- depending on the numbers today we'll see if we're consolidating groups so that way we don't just have a group of like three people.

And then we also have new prompts that are hot off the presses. So I encourage you to take photos when you see your group's intended use or indication for use, I should say, because there are -- the FDA folks have a handwritten copy of it, but it may or may not have been written by a physician. So I will offer translation services if needed. So apologies for that.

So your prompt for this morning is to design a clinical outcome assessment that you think would be appropriate to assess effectiveness of the described device for the proposed indication. This is purely a thought exercise. We aren't diving into the science of the feasibility of the proposed technology. Assume there's technical, technical success, and now we're looking at the clinical success of the device, and for the intended use.

So for those in the ADL groups your prompts are as follows. So think about an IBCI using a thin film array with 2,000 electrodes intended to control a robotic upper extremity prosthesis for adults with quadriparesis, as well as, an IBCI using a microarray with 2,000 electrodes intended to drive spinal cord stimulation to improve upper extremity function in adults with bilateral upper limb paresis.

Everyone got their photo? Okay.

For those in the mobility group, we're asking you to think about an IBCI with five electrocorticography electrodes intended to control an electric wheelchair for individuals with impaired mobility who are unable to ambulate, as well as an IBCI with microarray with 300 electrodes intended to control a lower limb prosthesis in adults with limb loss.

All good? Oh. Making sure -- okay.

Communication. The problems are as follows. An IBCI using a microarray with 100 electrodes intended to translate volitional speech in individuals who are 10 years of age and older with intact cognition, as well as an IBCI with 100 thin film electrodes intended to control computing devices for communication in adults with locked-in syndrome.

So those are your prompts for this morning. And then we'll come back around 10:45 to -- for the same, the same moderators to report back on the discussion that you all had.

So for rooms. For those who discussed ADLs with Kristen and Deborah, Kristen raise your hand, you guys are going to be in 1404 in this building.

For those who discussed ADLs with Ambarish, you'll be in this building in Room 1406.

Those -- and those who are with Heather in 1408 are still in 1408.

For now the group that was with Meijun the group that was with Mei in Room 1309 in Building 32, you're still going to be there, but we may consolidate you.

Julia's group who was here in the Great Room, you're still in the great room.

Gabriella and her communication group you're going to be going to 1504 in this building.

And Zack and Shelby's group that went to Building 32, Room 1321, the game plan is to be there for now, but we'll see. We may keep you in this building.

And then Phoebe and Chris' group that discussed mobility, you'll be in 1506.

So we have the meeting point signs out there so you can meet with your group. And then before the people go into Building 32, we'll assess the situation, see if you can stay, if they'll reconsolidate things to make it easier for you all.

See you back here at 10:45.

(Off the record at 9:43 a.m. for breakout sessions.)

DR. SLOCOMB: A little bit different activity. I'm interested to see what everybody thought about it afterwards, what complaints I get today. But I know our group was very spicy today, a lot more fighting, but all has gone well.

All right. We're still trickling in here. I'm going to give you guys another minute, settle in.

All right. So we have smaller number of groups. We left you a little more time in the breakout rooms to wrap things up, finish those final battles, whatever it was.

So I'm going to start off again with ADLs, and today we have Erin O'Brien who is moderator, and there she is. Oh, did you make a poster? Oh my goodness. You're setting that bar high. All right.

DR. O'BRIEN: That's the blanket. Okay.

DR. HOCHBERG: Got it. Oh, you think anyone can see this?

(Simultaneous comments.)

DR. HOCHBERG: Look at this.

DR. O'BRIEN: Teamwork makes the dream work guys.

So our group had ADLs, and this was our BCI product. And we spent a large proportion of the discussion trying to figure out which COA type we should select. There

are a lot of strong opinions about the different merits of different types of COAs. And we thought about how in an actual clinical study you wouldn't pick just one. A lot of these complement one another, and offset sources of error.

So we landed on picking PRO just to pick something to move forward with. Our construct of interest is activities of daily living related to upper limbs with a focus on being able to do these activities independently. Context of use is people who had quadraparalysis (verbatim), upper limb paralysis, normal cognitive function which is important, good vision. And this is for a single-arm study case control crossover design. Over the course of one year with 12 visits to the PROs administered every month. And then we administer it after they've received some training on how to use their device.

We talked a lot about activities, and how there's really a lot of different ways to measure the same thing with accelerometer data versus self-report data versus putting a video camera in someone's home, and have observer coded. There's just so many different ways to approach this. But landed on doing a PRO. We cam up with a list of activities, also acknowledging that there are a lot of existing measures that could potentially be adapted for this context, but and activities that we thought about are brushing your teeth, brushing your hair, drinking, feeding, dressing, being able to pet your dog or hold hands with a loved one, opening the door, using remote, laptop, phone calls, and taking medicine. So those are kind of the activities we thought about. Those kind of laddered up to some bigger picture concepts; hygiene, eating, social, environmental, electronic, and health. And then we kind of only came up with one example item, and that was if, basically if you have a toothbrush with toothpaste set in front of you, and it's within reach, how can you use it? And answers could be I can brush my teeth fully independently, I can brush my teeth with

assistance, or not at all. And this would be verbally administered.

Did I miss anything, Leigh?

Okay.

(Applause.)

DR. MCMULLEN: I would just highlight that is why you might want to get a psychometrician on your team or collaborating with you.

DR. SLOCOMB: All right. Thank you. And once again another shining moment from that new and upcoming researcher Leigh. Really holding that poster high and tall.

Next up we have Gianna Perez for ADLs. Oh, and another poster. We didn't have that in our room. So distinct advantage there.

MS. PEREZ: Okay. So definitely less specific than group one, but what we ended up doing was kind of adapting existing frameworks that we have, but to try to address some of the gaps that we discussed and learned about during yesterday's session.

So the first idea here would be to take a battery of tasks that already exist. So in this case maybe something like the upper limb extremities assessments from the Neuro-QoL data that we learned, and have sort of that as a baseline. On top of that, we would want participants to be able to choose a few tasks, maybe something like three that are important to them to be able to have improve in the course of their treatment, and this is to address the gap of patient inclusion in the design of COAs and the selection. But at the same time, borrow from other fields, things like people in the motor rehabilitation, the physical therapy field that have these tried and true kind of more basic tasks. Also incorporate of those in pre- and post-measures to start to get the data so we can have actually more specific thresholds for improvement which there's not really data to support

right now, and so that would be addressing that gap.

So then from there, we kind of go into -- where you go into from that menu there would be, of course, pre- and post-data. We also would want to think about things like the usability, and how that's going to the efficacy right for participants. So, maybe, using things like Patient Global Impression of Change, or Clinician Global Impression of Change Scale. Maybe looking at things like time, right, as far as, at the time that it takes for them to do something, a task before and after their treatment. So thinking about pre- and post-reaction times, again incorporating a lot of outcomes data. Then at the same time we want to consider usability. So objective measures of usability. Maybe, things like caregiver reporting, how often or how little they need to be helping or assisting the patient. And then, also, some subjective measures of the usability. Like, does the participant, are they satisfied with the device. Maybe, would they recommend this device? Kind of combining all those things together.

But also are there, under efficacy another gap that people have identified, and the thing that makes it difficult to communicate the current state to like the regulatory agencies for example is that quantification.

And so, one thing we thought about would be maybe also incorporating some sort of assessments that have Likert scales, right. So you could have a scale. You could have some sort of scale improvement that you could then bring and show as like okay we have X percent change in the scale, and really be able to have a much more definitive quantification of the benefits from the device.

And, yeah, and it's like we said as far as usability again one thing that's come up a lot is the patient, the patient input, the patient satisfaction. And so, having those sorts of

measures of like satisfaction, those sorts of measures of fatigue, those are all things that you would want to have in devices, especially when like we discussed yesterday one of the questions was, right, how would participants want to decide between devices or something like that some day.

So having all of this data in at this point would be important. And then also thinking about last point here we had the trajectories, and the durability of the use, right. So having some sort of incorporation, some checkpoints throughout the process. I mean they just did a one-month scale in the last one, right. But some sort of scale like that where we're seeing how long people are using it, how well the use is going on. But, again, just sort of bringing together all of these existing systems that we have in a, in a very comprehensive way so you have this kind of whole suite that becomes your COA.

Thank you.

(Applause.)

DR. SLOCOMB: All right. Thank you guys.

And next up, we have the last ADL group, last but not least, David Putrino, coming on up. Loving the shirt. Casual Fridays.

DR. PUTRINO: All right. It's good to be back. So our group, the foreign group, as you may have recalled from yesterday, we started off yesterday saying that if we're dealing with a BCI that is trying to touch the world physically from the outside in, we would want to rely on existing scales for COAs, and we thought that that would be useful. So we kind of went, continued in that vein, and we committed to that. What we did do, of course, is we broke things down into primary outcomes, secondary outcomes, a few considerations. And as we were determining the primary outcome measures, we split the two scenarios here into

robotic and reanimated, because we actually thought that with the robotic limb while a robot could resemble anything, right, it doesn't actually need to look like a limb. It could be all sorts of different things. And so, your primary outcome measure for that may be different from our primary outcome measure for reanimating a limb.

So, for the robotic limb we actually chose the Lawton Instrumental Activities of Daily Living Scale as this is something that will tell us what someone can do now with this robotic limb under control of 2,000 electrodes which I hope would be pretty, pretty good. What sort of instrumental activities of daily living, using a phone, engaging in banking, calling Ubers, controlling finances, et cetera, et cetera. With the possibility if it were to ever be developed of a digital IADL Scale also being thrown into the mix there as a primary outcome measure for the robotic control.

With regard to the reanimated limb, that was actually a fairly short conversation. We thought the ARAT would be appropriate which is the Action Research Arm Test, which is a very well-validated upper extremity metric consisting of evaluating your ability to perform 19 different tasks. And so, our thought process here was if you're reanimating these limbs with a very sophisticated BCI, high channel count BCI, you really just want to be able to see that this individual can now use their limbs in a way that is highly functional, and the ARAT is a good measure of that. It has good minimal detectable change, good minimal clinically important difference data. We did have some discussion around whether a BCI should be held to a higher standard on MCID than what we would expect in a rehab trial. And more on that a little bit later. But we thought that the ARAT would be actually a really good metric for this.

In terms of secondary outcomes, we really did like what Walter said about Utility

Index. Just understanding straight up is the person using this? Are they not using this? We wanted to build on that concept by having the NASA Task Load Index thrown in there. NASA Task Load Index is a metric that tells us how hard it is for someone to do a task. So how much cognitive effort are they using to actually operate this thing? Is it low, and remains low throughout which would be a huge win? Or is it high, and comes down over a six-month training period? That would also be good. Or is it high at the beginning, and then at three months it sort of plateaus and then you see the Utility Index start to drop because they're just like, okay, this is futile, and I don't want to do this.

Neuro-QoL, also a great secondary outcome measure. The patient reported telling us how much is their neurological disability affecting their quality of life, physical, social, and mental.

Then we also wanted to throw in some health economics data. Are the gains that you're getting worth it in terms of could you get similar gains with intensive rehab, or could you get similar gains with other opportunities that don't require an implant? Obviously, we wanted to throw in a caregiver burden questionnaire as well. Is caregiver burden going down or is it going up because they're helping you use this very complicated thing? We should try and understand that. We would measure time to independent use. So how long does it take you to become independent with the technology? And then we also threw in the system usability scale which is a nice measure of system usability to overall usability. We'd like the caregiver and the patient ideally to fill these out with the caveat that it shouldn't be -- that shouldn't be your usability study, but it's a nice validation of a separate usability study that should probably be done by whoever is making these wonderful devices.

And then just the final consideration, miscellaneous consideration, that we had was we do think that a clinical trial for the -- a BCI that reanimates a limb should go head-to-head with an arm that does rehab, intensive rehab to see if your outcomes from intensive rehab are approaching an IBCI implantation.

So we'll leave it there, but thank you everyone.

(Applause.)

DR. SLOCOMB: Thank you.

And so, I think that wraps up the ADLs. And then we have mobility. We've got Jose Contreras-Vidal, again, thank you.

DR. CONTRERAS-VIDAL: Yes. So to start we assume that the BCI is operational and reliable. That the ineffective, whichever the leveling procedure works, and that they can talk to each other, right, interpret probability. And so, for the first case the power wheelchair, we assume a Class III power wheelchair, and that, you know, Medicare prescribes these for neurological diagnosis, myopathy, or some skeletal deformity that the client might have. So we thought that the, the wheelchair test would be an ideal, ideal clinical outcome measure here to evaluate the skills, handling the wheelchair and safety. And it also has a questionnaire component which is a PRO, and we take 10 minutes. So I think that will complement that. As an aside, secondary measure, we thought the Utility Index would be great. It can be used to measure the, the adoption of the technology by the user. It probably will include the four factors, the ease of use, and other factors that were discussed before. So we like that. And it can be used probably also to compare with other devices. And have implication for determining which benefit at well. And so that was for the, for the wheelchair.

For the other case was IBCI microelectrode, right, 300 electrodes, lower limb prostheses for lower limb amputees. So we thought this could be used by a bilateral femoral amputee who is currently using -- who is currently ambulatory with a prosthesis. And so for this, we thought that the functional gait assessment will do the job, assess a specialist stability, doing walking and also assess the ability of the, of the user to perform multiple motor task during walking, like turning the head, and do some balancing, you know, stair climbing and others. We thought that, again, the Utility Index will be a good way to measure the level of adoption. It doesn't really make sense if this sophisticated device not being used, right. So this could be very, very useful as a secondary measure.

And so that, that's it.

(Applause.)

DR. SLOCOMB: And for the communication I'm not sure if Matthew Fifer or Katya Hill will be representing.

Katya, great.

DR. HILL: Let me get my page up. Well, we had a very interesting discussion because we're all coming from our personal points of view, and then as we were attempting to answer the first question we decided that we had to identify some of the assumptions around answering the question.

So first off, we are assuming that this was an acquired disability rather than a congenital disability because even the looking at the age going down to a pediatric population someone with a congenital disability you may not be aware of what their cognitive linguistic skills truly are if they've never spoken or used natural speech.

Then we started identifying some current outcome measurement tools, and what

outcomes might be in there, and it was brought up the Communication Participation Item Bank has a long list of potential outcomes related to medical necessity. And then others that are more patient preferences.

And then we discussed an assumption about the task versus the focus on the outcome. And Kim mentioned looking at the efficiency, effectiveness, and then the experience of how that might influence the outcome.

So as people were talking, I tried to fill in was it a patient-reported outcome, an observer-reported outcome, a clinician-reported outcome, or a measurement.

So I'm going to start with patient-reported outcomes although the discussion initiated with performance.

So just some outcomes identified. Conversation in a quiet room versus conversation with a physician on a phone versus the real-world phone conversation of ordering a pizza. Able to communicate in real-world situations related to this schema of wants and needs, information transfer, social closeness, and social etiquette. Digital access and control. So being able to control Google Home or Siri or Alexa. Also, an outcome on the restriction of use, and the effort of demand.

Observer outcomes might be the intelligibility of the speech as an outcome, that they're understanding what was spoken. Independence of the person so that there's a reduced burden on the caregiver. And then the frequency of needing to intervene on the system as the caregiver.

Clinician-reported outcomes could be being able to talk to the person face-to-face, being able to talk to the individual on the phone, and then being able to carry on a telehealth session with your patient.

Performance outcomes were related to words per minute measure, as compared to the baseline, an error rate. Metrics on a controlled task versus metrics on real-world tasks. Vocabulary size, and then a measure on intent. Was the intent of what was to be communicated matched with the actual outcome? And then usage.

Now, that discussion took a lot of time, and we really did not get to the second question. However, the assumption was is that we cannot assume that the language and cognition are intact in this individual given that they have a locked-in syndrome. So where was the neurological lesions for that individual? What was the cause of it? Would be different. But then many of the outcomes might be the same.

But I think an overriding theme of our discussion and how we ended is that issue of CMS requirement on medical necessity, and that being a barrier to the outcomes that the individual, and the family members, and/or the clinician want to be able to achieve, but that the decision for funding or purchasing the device, and then or clinical services are based right now totally on medical necessity. How do we work that in?

And so I like the approach that the group took on -- as communication as a basic human right, and that implants would be restoring autonomy, restoring independence, restoring privacy, restoring the right to self-protection, physical protection, and safety. So I really like how that was brought up as a basic human right.

So thank you.

(Applause.)

DR. SLOCOMB: And last but not least, we have Allanah Beazley for communication. There she is. And that was my group, the spicy group. Not in a bad way. In a good way.

MS. BEAZLEY: It was in a good way. I think we had a pretty productive conversation.

Even if it was a little bit spicy, we actually came to kind of, a democratic agreement I think here, which was impressive. So we went through a bunch of different methods, and ultimately, we centered around utility measurements. I would say almost as a three-pronged approach, but apparently the verbiage is equal to component measurement. So of accuracy that we feel could serve as actually clinically relevant that incorporate elements of function and feel when we think about the survive, feel, function sort of framework. So that's where we started.

And I don't have like a piece of paper so I'm just going to use my arms a lot. So the first thing was technical, and that's way up here. Now, yes, that's our highest order. We're like we can actually quantify whether or not the accuracy of what you intended to say was what was put out. We can see that. Did it decode the speech that was intended?

When it comes to function that's kind of the second lightly higher order mark that we wanted to measure. Did it -- were you able to communicate when you needed to in the means in which you meant to? Were you able to correct it? That was kind of a conversation point. And then, ultimately, hitting at that broadest sort of level just because it ends up being a little bit more quantitative -- sorry, qualitative at times is the, the function in field. Was the message that you intended to send communicated successfully in the way in which you wanted it to be received? Was it sent and received in the way you wanted it to be from one to another? It doesn't really matter if communication exists if you aren't able to communicate in the world in a meaningful way. So that absolutely needed to be included.

I think what was really important that came up for us was two things. The first is that volume we ruled out basically, completely as a measurement. Not to say that we don't

want people using it. Absolutely, we want people to use it. But it's not always the best indicator of whether or not someone is actually getting use out of the BCI especially when it comes to speech. You might not be so chatty. You might not want to say something. Why are you using it? We ended up looking a little bit more at need rather than want. So does it fulfill what you need it to fulfill, not necessarily what you might desire it to fulfill.

I hope that was the takeaway. I hope that was the takeaway. Maybe, not -- anyway, we also suggested going to the Bank of Terms. I think what was kind of interestingly proposed by our group was not necessarily going to preexisting Banks of Terms, but maybe having the patient themselves serve as their own baseline, and develop a bank themselves of what they would find meaningful to communicate, and being able to measure that as a -- were they able to do it or not?

Let's see. I'm like running through my notes. But the other thing that was probably important just to note is that we ultimately decided this was not a binary. It's not necessarily on a pass-fail grading. It's not was it accurate right off the bat. Like are you hitting 90 percent accuracy? That's not necessarily it. That we need to work on.

Thanks.

(Applause.)

DR. SLOCOMB: So I want to thank everyone for their input. This was really helpful. While I was watching I ended up taking a lot of notes, and I noticed a really common trend among all of these, and I think that there is a single outcome measure that we could all agree on. I call it the IDSTUEO. It's called the -- it depends, speak to us early and often.

I'm going to pass it over to Heather.

DR. DEAN: All right. So I really hope that you have found this as engaging and

exciting as I have. I've seen real energy and excitement from this broad community in BCI development and commitment to next steps.

So as I said earlier in the introduction, this is a hard problem. I don't know of anyone that noticed my necklace this morning. It says extraordinary claims require extraordinary evidence. We're making some big claims about what these devices can do. While the evidence might not need to be extraordinary, it definitely needs to be clear and valid. So I think that this hard problem requires community input and broad stakeholder engagement which is why all of you came to this these last couple days.

So I'm really, really heartened by the interest shown here in partnering across these stakeholder groups and technologies to tackle this really difficult problem. It's so exciting, but it was difficult to get you back into the room after each of the breaks and the breakout groups. Obviously, there are connections being made, and I know that there are plans for follow-up discussions and conversations. I think that's very important.

So I know that this community can and will make great strides in the very near future.

The collaborative community meeting on Wednesday, and this Workshop yesterday and today, have really continued and accelerated important conversations that I believe will bear fruit in the coming years.

I mentioned this morning that I wanted to hear more calls to action. I hope that you will leave this Workshop feeling excited, engaged, connected, and ready to engage this problem and talk to us.

So FDA, NIH, I hope it's clear that we want to be partners here. By tackling this problem, helping us figure out what the, the right clinical outcome assessments are you're

helping us to help you.

Please, please reach out. I hope you've also realized that we're, we're here, we're helpful, we're friendly. You have our contact information. It's gone up with the FDA slides. I think you know how to reach out to anyone of us. David has put his e-mail address up there. I think mine and Molly's are out there. Any one of us are very happy to engage, and work with you.

I just wanted to say that none of this would have been possible without the dedicated work of the organizers.

So I'd like to first thank Dr. Molly Keszler from FDA, and Guangying Wu from NIH.

Would you please stand up.

(Applause.)

DR. DEAN: They've taken the lead in putting this Workshop together, and it's been, I hope you'll agree, really amazing. And they have worked extremely hard on this.

I'd also like to thank the many people who have helped with the logistics of this week including those who printed materials, manned the check-in table, led everyone to lunch and breakouts, moderated discussions and more.

Let's thank all of the volunteers.

(Applause.)

DR. DEAN: Many thanks to the speakers these past couple days for setting the stage for these discussions. Thank you.

(Applause.)

DR. DEAN: And I can't thank all of you enough for being here, for participating and connecting. You've been thoughtful and clearly dedicated. You've come here from all over

the world to be part of this.

Also, I want to thank you, and wish you all well with the work ahead as we move BCI devices ever closer to accessibility for the patients who would benefit most from their use.

And I'll now hand it over to Nick Langhals to close this Workshop on behalf of NIH.

(Applause.)

DR. LANGHALS: Thanks Heather. And I don't have extensive prepared remarks. We did discuss potentially trying to put together a BCI-related theme song using one of the large language models, but ultimately decided not to go forward with that. But I just want to make sure and echo everything that Heather said. I also want to call out an additional thank you to Eric Atkinson and Rebeka Corlew for helping to arrange and get the patient feedback that led into our panel yesterday.

As all of us are probably aware, the only way that we're going to have an impact in this community is making sure that we're engaging the patients early and often because they're the ultimate ones who are going to benefit from all the technologies that we're developing here.

And beyond that, I also want to echo the thanks from both FDA and NIH leadership for being willing to support these activities to help bring us all together here. This is a partnership. And as Heather said, there are real people on the other side of these federal agencies that are here, and trying to do our best to help as well. So feel free to reach out to us early and often. There are many different funding opportunities on the NIH side of things. Like Walter mentioned this morning, we have a new opportunity coming out looking at using digital technology for biomarkers and outcome assessments. We have biomarker-related programs in our Translational Division. We have specialized programs with

additional resources like our Blueprint MedTech Program to help facilitate translation of novel technologies. And all of these programs here are there to help move these communities forward. So feel free to reach out, and we'll do what we can to help you through the process.

So beyond that I also finally want to thank all of you for coming, and we appreciate how everybody was engaged in the Workshop. And hope everybody has a good rest of your weekend.

(Applause.)

(Whereupon, at 11:45 a.m., on September 20, 2024, the Workshop was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

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were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health.

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TIMOTHY J. ATKINSON, JR.

Official Reporter