ME/CFS. Finally, it assesses harms and benefits of diagnosis and treatments. Next slide.

[Slide shows image of people working on a puzzle and lists stakeholder talking points in bullet form] So we recognize that stakeholder engagement in the early part of the systematic review was critical. So, we involved stakeholders as key informants in developing key questions to guide review. These stakeholders included ME/CFS clinical and research experts, individuals representing patient's perspectives, and individuals with family members with ME/CFS. Next slide.

[Slide shows key questions in bullet form] The key questions that the informant developed were as follows. In patients undergoing evaluation for possible ME/CFS, what is the frequency of non-ME/CFS conditions, also referred to as comorbidities? What are the benefits and the harms to the patient of diagnosing ME/CFS versus non diagnosis? What are the benefits and harms of therapeutic interventions for patients with ME/CFS, and how do they vary by patient subgroups? And subgroups were defined by many things, so defined by age, sex, race and ethnicity, presence of bio markers, ME/CFS severity or duration, type of onset, the criteria used to diagnose ME/CFS, and associated comorbidities. These therapeutic interventions targeted symptoms prominently present in people with ME/CFS, such as coarsely, orthostatic intolerance, pain, fatigue, cognitive problems, depression, multiple chemical sensitivity, gastrointestinal symptoms and urinary symptoms. Next slide.

[Slide shows status information in bullet form] The current systematic review completed by OHSU's searched publications through January 2019. Data sources included Ovid MEDLINE, The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, [Inaudible]. The draft report has been cleared by CDC. And to collect comments, we plan to use a federal registry notice, which is going through a separate clearance process. The final report will incorporate the comments from the public through the federal registry notice, and from a peer review conducted by OHSU. And new studies that are identified from an updated search in 2020 will be incorporated in the final report. Next slide.

[Slide shows bottom line findings in bullet form] The bottom line of the current systematic review was that since the last review there have been essentially no therapeutic advances in ME/CFS, as there was very little information on the treatment and management. The new information was limited to the following two major conclusions. There was such limited evidence on medications that the reviewers could not draw conclusions. And there was limited evidence on exercise versus other active therapies. The studies did indicate that exercise probably has a positive effect on the fatigue in adults compared to usual care of passive therapies. However, no evidence to support the applicability of this finding to patients diagnosed with case definitions other than thoughts or [inaudible] criteria was identified in the literature review. The final take home message is that more clinical trials are needed to provide an evidence based for treatment of ME/CFS. Next slide.

[Slide shows next steps in bullet form] As far as next steps go, our team will initiate public comment phase through the federal register notice, as mentioned before. And after finalizing the report, and posting it, along with its comments on our website, we will revisit plans for the treatment guideline development. The CFS Advisory Committee, or CFSAC, was considered a federal advisory committee, or FACA option for this treatment guideline development. But in September 2018, CFSAC was dissolved, and after that we were unable to identify another FACA option. But we did consult with many experts in the agency, and we learned that a non FACA route was the most viable option. We have considered organizing a guideline working group, which would comprise federal experts from multiple disciplines involved in the development of clinical guidelines, from patient representatives to clinicians, methodologists, to name a few.

It's important to note that using these options means the guideline working group has to be made of only federal employees who could elicit outside opinions not only through an FRN but also through an open workshop forum. After the working group develops this guideline draft, another federal notice, register notice could be posted to solicit comments. But given the current situation and the conclusions from the most recent systematic review, perhaps it's not quite the right time to start developing federal clinical

guidelines for ME/CFS. In our consultations with experts, other alternatives, like compiling expert opinion, have been discussed. Next slide.

[Slide lists guidelines in bullet point form] And on that note, it's worth pausing to consider that the landscape has changed since we started this process. There have been a number of clinical guidelines and recommendations put together by experts since this systematic review's process was started. And it's important note that in the absence of systematically collected evidence, these guidelines and recommendations are based solely on expert opinion. These include a primer published in Frontiers in Pediatrics on ME/CFS diagnosis and management, a handout for clinicians on the basics of diagnosis and treatment put together by the U.S. ME/CFS Clinician Coalition, and updated guidelines from the U.K.'s National Institute on Health and Care Excellence, expected to be available this April. Next slide.

So, thank you for your attention, and we look forward to the discussion. Thanks.

Dr. Elizabeth Unger: Thank you. And so, we, we felt like this was really impetus to talk about the situation with clinical trials and discussing the situation with Vicky. She thought it was timely to discuss the, her thoughts, and NIH's thoughts on clinical trial design and workshops. So, Vicky.

Dr. Vicky Whittemore: Yeah. Thank you. If you can take the slide down, I don't have slides. So more than a year ago, the trans NIH ME/CFS working group discussed organizing a workshop to bring together people to talk about the barriers and challenges to doing clinical trials on ME/CFS, and what could be done to change that landscape. Then COVID hit. And so, our attention was diverted to lots of other things, especially long, or COVID and now long COVID. Excuse me. But the workshop is back on the table, and I think very timely. In terms of thinking about how do we go about putting clinical trials for ME/CFS in place?

And back a year ago, we had a call, we are meaning a few of us from the working group, had a call with representatives from the FDA who were going to be very involved in the workshop, and we would make sure that they were involved again. Because several of the things they pointed out was, number 1, we don't have a bio marker that

can clearly identify and diagnose individuals with ME/CFS. Secondly, we don't have objective measures to look at progress of disease and response to treatment. So as many of you know, Ampligen, there was significant improvement on the clinical outcome that they utilized for that clinical trial, but the FDA felt that it was not clinically significant to the patients. And that the Ampligen, at that time, was not approved by the FDA, as a treatment for ME/CFS. So, our FDA colleagues pointed out that we really have to have objective clinical measures going into clinical trials and know what those are going to be. Along with then, the last part of this, well identified cohorts and the ability to characterize and phenotype the cohorts that are going into these clinical trials such that we have individuals with clear diagnosis. We don't have a mixed bag of individuals who may or may not have ME/CFS. So again, clear clinical, a clear way to diagnose.

And so, we had, at the time, also had, a year ago, several conversations with the people in, Professor Fluge and his colleagues in Norway who have conducted clinical trials for ME/CFS, to learn from them. And they essentially told us exactly the same thing, that they would not go into another clinical trial without having clear bio markers, without having clear objective measurements of response to treatment. So, our, what we feel is needed is to bring people together at this point and say, if these are the things that are needed in order to go into clinical trials, how do we get there, first of all. And once we have those things, how do we identify, as Nancy was suggesting, a clinical trial network who would carry out these clinical trials?

And then I guess, the last piece of it, that I think is maybe more challenging, but I think equally as important, is to understand how we pull industry and pharma into this, as well, so that they're a partner at the table, and thinking this through with us, and trying to understand what are the clinical trials that we could move forward. We, as some of you may know, NINDS supports some clinical trial networks. But for most of those, right, I shouldn't say all, there's one called NeuroNEXT that will do clinical trials on neurological diseases. There's Strokenet, which is specific to stroke. But in all of those situations where there are clinical trial networks, there's a clear pipeline of pre-clinical to translational to clinical research that's feeding into those clinical trial networks. And so it, as the trans NIH working group has discussed it, it's premature to set up a clinical trial

network without having a pipeline of trials coming in, otherwise you're just wasting funding on infrastructure waiting for a clinical trial to come along.

But these are all of the kinds of issues that we really agree need to be addressed. We absolutely agree there needs to be clinical trials done in ME/CFS. But again, it's going to take us coming together and really addressing head on what these issues are and how we can overcome them, whether it's research to develop objective measures. There's a lot of research going on in the funded collaborative centers trying to understand the path of physiology that could lead to those bio markers, as well as in other funded research from the NIH, from OMF, from research that's going on in Europe.

So, bringing all that together to try to understand what it is we need to put in place so that we can go forward with clinical trials. Because clinical trials are incredibly expensive. And to move into clinical trials with just some hope that something is going to work is not going to happen. NIH tends, and looking at Dr. Koroshetz, I may or should not say this, but I think going into clinical trials we're risk adverse. We really want to see that there's strong evidence that this clinical trial is going to be successful, because you're investing a lot of time, a lot of money, a lot of resources into large studies.

So, stay tuned. I'm sure I'll be in touch with many of you about thinking through how to pull this workshop together, because it was timely a year ago, it's even more timely now. And again, there may be aspects of this that we can piggyback on clinical trials that will be coming through for the long COVID. But I think that it's something that we absolutely need to move on, and there's significant interest in doing so. And I would love to hear thoughts from anyone else about this. But I'm just wanting to put out, sort of, our position at NIH. And the recognition that we know this needs to move forward, and we just need to do it in the right way that we can really move into clinical trials in a smart and efficient way that will benefit the community. I see Oved has his hand up.

Dr. Elizabeth Unger: Yes, yeah, go for it.

Oved Amitay: Thank you, Vicky, this was incredibly encouraging. And we would wholeheartedly support this effort. I can only say from my own experience of 25 years of

developing therapies, mostly in the rare genetic disease space, is that this, you know, this challenge is one of that we face very often with fully understood diseases. I would say one thing, which may surprise you, but industries actually even more risk adverse than NIH. So, this is, you know, this is a familiar situation.

The only way to address it would be for, ultimately for the FDA to issue what they often do, which is a white paper guidance to the industry, in which they describe what is acceptable, what is not acceptable, and what is negotiable. And that gives the industry a sense of what's on the table. In other words, what are the end points would appear, patient report outcome, a measurement of quality of life for instance, is that something that would be acceptable. I think it would have to apply, the FDA would need to apply the risk management calculation that they do for rare diseases, [inaudible] diseases. Although epidemiologically, ME/CFS is not one, I think it really deserves to be treated as such.

And so, if there's anything that we can do to support this kind of a workshop from the patient community, we're in. And I think you're right. This is something that needs to happen, and which is why we definitely need to have the FDA be part of this discussion.

Dr. Vicky Whittemore: Absolutely. The FDA did issue a white paper. I'm not remembering when. Beth may remember when, but many years ago. But absolutely. We do need to engage them in this discussion, right? Absolutely.

Dr. Elizabeth Unger: Yeah. They have an initiative to qualify markers for end points in clinical trials. And the PROMIS instrument is PROMIS fatigue, is being advanced as one. It's almost, we've been collaborating with a group that's trying to get it fully qualified as an endpoint. And you know, the work is slow, and but it's progressing. So, but I, so I think it's timely to totally revisit this. It has been a number of years. So, Dr. Argue, do you have a comment?

Dr. Kathryn Argue: Yes. I just wanted to mention a few of the ways that CDMRP can kind of help with this de-risking clinical trials. We do kind of have some ways in which we can be helped with this. One is that we do offer an award mechanism that does not really require preliminary data. It's a discovery award. This is also something that can be

Christine Pearson: Excellent. I should have thought to ask that earlier. Appreciate it.

Monica Payne: No problem.

Dr. Elizabeth Unger: Okay. Well, thank you, everybody. I think it's been a great day, or I mean a great afternoon. Just and we will begin again tomorrow afternoon. Thank you.

Dr. Inger Damon: Thanks.

Dr. Vicky Whittemore: Thank you everyone.

Dr. Inger Damon: Thanks Beth and Vicky, on your work on getting this agenda together.

Dr. Vicky Whittemore: Thank you. Goodnight.