U.S. FOOD & DRUG ADMINISTRATION

PUBLIC MEETING ON CENTER FOR DRUG EVALUATION AND RESEARCH STANDARD CORE SETS: CLINICAL OUTCOME ASSESSMENTS AND ENDPOINTS PILOT GRANT PROGRAM

AUGUST 28, 2020

8:31 A.M. - 12:15 P.M.

HELD VIRTUALLY

MODERATED BY: ROBYN BENT, FDA

ATTENDEES:

ELEKTRA PAPADOPLOUS, Division of Clinical Assessment and the Office of New Drugs

KANECIA ZIMMERMAN, Associate Professor of Pediatrics at Duke University

DAVID CELLA, Professor and Chair of Medical Social Sciences at Northwestern University

R.J. WIRTH, Chief Executive Officer at Vector Psychometric Group

MICHELLE CAMPBELL, Office of Neuroscience in

SHARON BROWN, COA-APTIC External Technical Advisory Committee

KIMBERLY BENNETT-EADY, NUCOAT Stakeholder Engagement Group

SCOTT KOMO, Office of Biostatistics

MICHELLE TARVER, Director of Patient Science and Engagement in the Office of Strategic Partnerships and Technology Innovations at the Center for Devices and Radiologic Health

P R O C E E D I N G S

MS. BENT: (Inaudible) Program and the attending Program Officer for the Standard Core Clinical Outcome Assessments and the related Endpoints Pilot Grant Program. I want to start by saying how much we appreciate you being here today.

The goal of this meeting is to hear from stakeholders both during the question and answer period as well as in the public docket so that as these Standard Core Sets of Clinical Outcome Assessments are developed the identified concepts, COAs, and Endpoints reflect what is most important and relevant to patients and support regulatory and potentially other stakeholder decision-making.

Disclaimers as stating that the views expressed in the following presentation are those of the individual speakers and do not necessarily represent an official FDA position. (Inaudible) transcribed and this live video cast is being recorded. Transcript and a link to the recording will be available on the meeting website.

I'm now going to take a moment to review the agenda. We're going to start with a short presentation that will provide an update on the Pilot Grant Program before moving on to a panel discussion of the impact and shared lessons of COVID-19 in the context of the grant program.

This will then be followed by an opportunity for you to ask questions.

We'll then begin hearing from the grantees themselves about their individual grant. We'll start with Dr. Richard Lipton from Albert Einstein College of Medicine who will talk about the Migraine Clinical Outcome Assessment, MiCOAS grant. There will be a question and answer period following Dr. Lipton's talk.

We'll then take a 15-minute break from 10:30 to 10:45 Eastern Time. When we return at 10:45, we'll hear from Dr. David Fellow at Northwestern University. Dr. Fellow will discuss the work being done as part of the Northwestern University Clinical Outcome Assessment Team, or NUCOAT, and then he and his team will answer your question.

We'll then move on to Dr. Bryce Reeve who will talk about the Clinical Outcome Assessments for Acute Pain Therapeutics in Infants and Young Children or COA-APTIC Grant.

After Dr. Reeve and his team have answered any question, we'll move on to the final panel of the day. This panel will provide you with some information about the latest funding opportunity announcement that FDA has released for the grant program. The panelists will talk a little bit about the priority areas mentioned in the grant and the funding opportunity in general, and they'll answer

any questions that come through the webchat feature of the webinar and we'll finish out our day with some very brief closing remarks.

This is my appeal to you, please ask questions. This meeting format where each panel or presentation is followed by a 10 to 20-minute question and answer session only works if you ask questions. If you click on the dialogue button the bottom right of your screen, you'll be able to submit your questions electronically. Please do.

There may be a little bit of a lag time as the questions move from one system to the other, so I would encourage you to ask the questions as they come to you. My colleague, Lena, who has been instrumental in the planning of this meeting today will be handling the questions and comments. If we're not able to get to your comment, please submit it to the docket, and that's a great segue.

With our final housekeeping item before we move on to our opening presentation, I'd like to again remind you to submit comments to our public docket. A link to our docket can be found on our FDA meeting site. We will view every comment and will share them with the grantees. Your feedback is valuable to us.

(Inaudible) gotten all the logistics out of the way, I'm excited to provide you with some updates on the grant program. As you likely recall, this program only

started last fall, so we're still relatively early in the process. This meeting is going to focus both on what we've done and on what we are planning. We'll be holding meetings twice a year to get feedback on grant milestones and on our program as a whole.

To start out, I'm happy to tell you that each of our grantees have developed a website to which they are posting their work and we have links to that on the FDA meeting page. We hope that you'll take a look at the pages and at any available milestone documents and provide your feedback either here at the meeting or to the docket that I just talked about.

So during our last meeting, I provided you with a little history of the grant program, how it really started in 2013 with the FDA holding disease-specific public meeting to strengthen our understanding of disease and this treatment burden and how we realize that these meetings provided an important opportunity to hear directly from patients, patient advocates and caregivers and how those meetings really reinforced that patients and their caregivers are the experts on what it's like to live with their condition.

The grant program has really grown out of these patient-focused development meetings and the realization that what's important to patients isn't always being

measured drug development.

In addition, as patient-focused drug developments have begun maturing, FDA has noticed that there isn't always a lot of coordination in the efforts to development the Clinical Outcome Assessments including within a given disease area, but there is a decent amount of duplication of efforts and diversity of measures.

Proprietary tools have been developed at great cost, but then are limited in their affordability and sustainability. And FDA reviewers may currently receive multiple independent Clinical Outcome Assessments for review, each of which takes time to understand and evaluate.

We also can see a variable quality of the tools and resulting data that may limit the tools utility for regulatory decision-making. And so we're hoping that the FDA grant program will enable the development of the Standard Core Sets of measurements and disease burden and treatment burden for a given disease area that would be made publicly available.

A Standard Core set can include different types of Clinical Outcome Assessments and their related Endpoints that assess, at a minimum, a list of impacts that matter most to patients are likely to demonstrate change including differences in trial arms related to disease burden, treatment burden and, if applicable, physical function and

should be recorded in a clinical trial.

FDA expects our grantees to conduct well-managed, transparent, and methodologically sound process that provides for our consistent application of appropriate methods, consideration and use of vetted publicly available measures, milestone workshops engaging key stakeholders, and milestone work products that are made publicly available.

We see these core sets that are being developed my multi-disciplinary teams with significant input from patients, patient advocates and caregivers as a way of ensuring the sustained incorporation of the patient's experience in drug development and decision-making. We also expect that these core sets will be made publicly available for a free or nominal cost. (Inaudible) and grants that have been funded thus far and that you'll hear about in our upcoming presentations.

It's really been a pleasure to work with these teams over the past year. They've put together some really impressive teams with expertise in clinical areas, Clinical Outcome Assessment methodologies, and have a strong commitment to including the patient community as they develop these core sets.

(Inaudible) a bit on the administrative portion of the grant. These grants are funded under a cooperative agreement that has the FDA and the grantee team guided by

the grant PI, or principal investigator who is ultimately responsible, working together towards a common goal.

These grants are funded using a two-phased approach. The first phase is the UG3 phase, which is a one to two-year phase focusing on planning activities, and the second phase is the UH3 phase, which is the implementation phase where the Clinical Outcome Assessment sets will be developed and validated.

An administrative review will take place between the first and second phase to ensure that the projects are moving in the right direction. And today as we go through the presentations, you'll notice that the different teams are in slightly different places in their grants and this really is to be expected because of the flexibility that we built into the timeline.

(Indiscernible) this is a cooperative agreement and as such FDA and the grantees work together towards a common goal. And this is a pilot program, so we're really figuring out how to make this work best especially given the ambitious timelines that the grantees have set for themselves.

So right now what's working for us is monthly meetings between the grantee teams and FDA reviewers where we discuss work product, next steps, and how to move the project forward. And I think we're learning a lot from

these collaborations and I hope that our grantees are as well.

Within the FDA, we have multiple internal stakeholders involved. The stakeholders, many of whom you'll hear from today, include our Clinical Review Division, our Clinical Outcome Assessment staff, biostatisticians, and really anyone else who will have -- who has a vested interest in the success of the project.

(Inaudible) and into the grant, multiple opportunities for stakeholder input. As I mentioned, we're holding these twice yearly public meetings. Each grantee has put together an external Technical Advisory Committee made up of disease experts, Clinical Outcome Assessment experts, biostatisticians, patient experts and other technical experts as appropriate to oversee and monitor the specific projects.

The committee members come from industry, academia, clinical and regulatory, and I've had the opportunity to attend the E-TAC meetings for three of these grants and I have to say that the teams that they put together are really world class. And when I say "world class," I mean both in caliber and in the fact that there's a degree of international representation on some of these committees.

And finally, because we realize that many of the

trials are multi-regional or are used by multiple health authorities to make decisions, we've convened a Scientific Policy Board to bring a global perspective to the Standard Core, COA, development process. The Board is currently made up of representatives from the FDA, the National Institutes of Health, AHRQ, CMF, the Veterans Administration, MHLWPMDA in Japan and EMA in Europe, and we anticipate that as the program expands this will likely expand as well.

In the end, we really hope that this grant program will bring us closer to making our vision for patient-focused drug development a reality. We want to ensure confidence in the reliability and accuracy of patient-experienced data for regulatory decision-making.

We want to reduce regulatory uncertainty for the sponsors by consistently applying standards in order to promote rapid and consistent adoption of new guidance processes and resources through good communication both internal and external the FDA. And finally, we really do just hope to see sustained incorporation of patient experience in drug development and decision-making making it a standard of practice.

And so as you read this slide that outlines our vision for patient-focused drug development, I want to talk to you a little bit about the feedback that we received in the last docket.

We heard from grantees that -- we heard that grantees and FDA should conduct a comprehensive evaluation of existing instruments and/or tools for potential inclusion in a minimum core set of COA and Endpoints for each program. This should include performance of a gap analysis and literature review as well as application of other existing methodologies and approaches.

And I think today you'll hear about some very comprehensive literature reviews that are in (indiscernible). We heard that you want to hear more about the reasoning behind the selection of disease areas on which we're focusing. During our final panel today, we'll talk about this.

We heard from multiple organizations on the importance of engaging with patients early and throughout the development to obtain their perspective on disease and treatment burden, and I think that you'll see from our upcoming presentations that the grantees are really doing just that. And they're doing that during a public health emergency which brings its own set of challenges.

(Inaudible) of the public health emergency, we're now going to move to our panel discussion of the Impacts and Shared Lessons of COVID-19. At this time, I would like to invite our panelists for the session to turn on their video and audio to join the panel discussion on Impacts and Shared

Lessons of COVID-19.

We are fortunate today to be joined by several members of the FDA staff, a representative from each of our grantee teams and two patient representatives. I'm going to provide a brief introduction of our panelists and then each will speak for about five minutes. Please note that at the end of the panel discussion we've reserved approximately 20 minutes for questions from the audience.

And our panelists are Elektra Papadopoulos from the Division of Clinical Outcome Assessment and the Office of New Drugs at CDER FDA. Dr. Kanecia Zimmerman, Associate Professor of Pediatrics at Duke University. David Cella, Professor and Chair of Medical Social Sciences at Northwestern University. R.J. Wirth, Chief Executive Officer at Vector Psychometric Group.

Michelle Campbell from our Office of Neuroscience in CDER FDA. Sharon Brown, Patient Representative and a COA-APTIC External Technical Advisory Committee member. Kimberly Bennett-Eady, a Patient Representative and a NUCOAT Stakeholder Engagement Group member. Scott Komo from the Office of Biostatistics in CDER FDA, and Michelle Tarver, Director of Patient Science and Engagement in the Office of Strategic Partnerships and Technology Innovations at the Center for Devices and Radiologic Health, also here at the FDA.

(Inaudible) start with Elektra. Elektra, I know that your role in the Division of Clinical Outcome Assessments that you've been thinking a lot about the implications of COVID on clinical trials and that you've been involved in the drafting of the FDA guidance on conduct of clinical trials of medical products during COVID-19 public health emergency, particularly in the drafting of Question No. 13 in the questions and answers section of the guidance.

Question 13 talks about remote Clinical Outcome Assessments. Can you tell us a little bit about that?

MS. PAPADOPOULOS: Thank you. So I'll just maybe start off by providing a bit of an overview. So we all know that COVID-19 has had a profound influence on biomedical research and that is including some of the research done under this pilot grant program. And so I wanted to highlight some of the things that we were talking about in the setting of clinical trials with regard to assessment of clinical outcomes.

One of the questions that we were getting frequently was how do we continue to preserve patient safety while also collecting reliable and robust Clinical Outcome Assessment data. And so as you mentioned, Question 13 to the guidance for industry addressing managing clinical trial conduct during the pandemic really dealt with the assessment

of clinical outcomes and factors that sponsors had to consider when switching from in-person assessment to the potential for remote assessment.

And so this question is really just one part of the overall guidance and I won't be able to talk about everything this morning, but just wanted to highlight some of the things that we considered that also are linked to some of the challenges that were encountered with the pilot grant program research.

I will say that Question 13 originally stemmed from inquiries that the Agency was receiving regarding the conduct of interview-based clinician reported outcome assessments and these were coming in primarily in clinical trials in psychiatry. And one of the first things that the sponsor needed to consider was whether and how assessments of patients impacted by pandemic-related restrictions including the stay-at-home orders could still support robust study conclusions.

And in many of these assessments, there was a need to assess psychosocial aspects of a condition including social functioning, for example, and so to some extent this could be impacted by the pandemic-related restrictions and stay-at-home orders and so sponsors needed to consider whether those things could still be assessed and whether and to what extent the pandemic could attenuate results from

those assessments. And so I think there is similar considerations with qualitative research conducted in some of the grant, pilot grant, programs.

Another key consideration is whether the trial's Clinical Outcome Assessment could be conducted remotely, and we know that certain outcome assessments just aren't feasible remotely such as some physical exam assessments. And again here, similar issues were encountered in screening assessments for patients and participants for the sarcopenia research done as part of this pilot grant program.

In addition to that, we needed to advise sponsors about potential for variability of assessment when switching from in-person to remote assessment, and to this and the guidance really emphasized strongly the need for training for both investigators, other trial personnel and trial participants.

And another challenge was, with remote assessment always, is technology, and so the guidance recommends provision of any necessary technology and tech support as well as training to avoid missing assessments, but also to encourage participation of diverse populations in research and populations who may not otherwise have access to technology, to cell phones and internet, et cetera.

So this is really an important consideration for all types of research and including interviews and other

research as part of this pilot grant program because we really want to ensure representative patient populations in our research.

In addition to the safety of trial participants and resources to adequately complete the assessment, we also needed to consider whether there was a private and quiet setting to conduct many of these assessments including the patient interviews. And again, so that we could ensure that we could trust the data coming out of this research while also protecting patient's privacy.

So I would say another key issue that we faced in many clinical trials was that patients reporting PRO assessments very often would conduct these assessments in the clinic setting and so, obviously, this was impacted by the stay-at-home restrictions and so sponsors had to consider whether and how to go to remote assessment of PRO which is really not a trivial matter.

And so there's discussion in the guidance about -- well, the potential for paper-based assessment, but really that could lead to poor compliance and missing data, and so the guidance goes into some other options including the possibility of switching to electronic assessment, perhaps interview-based assessment and others. And here, again, patient privacy comes into play to minimize any sort of interruptions or bias.

And so I'll just kind of sum up by saying that I think, you know, this guidance really emphasizes, in my view, the degree to which the Agency is flexible and willing to work with sponsors to preserve patient safety and privacy first and foremost while also aiming to reduce missing data and maximize reliability of data collection.

And I think another thing I've learned in this is that just how much the pandemic has encouraged us to really embrace new ways of doing things including remote assessment, and I think this is here to stay. And so that -- with that, I'll turn it back to you, Robyn.

MS. BENT: Great. Thanks so much, Elektra for sharing that information and really kind of sharing the thinking that went on behind some of it. I hope that others found it as helpful as I did.

We're now going to move on to Kanecia Zimmerman, one of the principal investigators of the COA-APTIC grant. So Kanecia, I know that we talked about it during some of our monthly meetings, but can you share with us some of the challenges that the public health emergency has introduced to the already very challenging process of developing a core set of measures to assess pain in infants and young children, and maybe share how you've worked to overcome some of those challenges?

MS. ZIMMERMAN: Absolutely. Thank you, Robyn. So

as Robyn mentioned, we certainly have a challenge on our hands. COVID-19 has made that a little bit more difficult. We have been fortunate to be able to leverage the Pediatric Trials Network which is a multi-national network that is sponsored by NICHD under BBC legislation in order to improve labeling of drugs in children.

There's substantial infrastructure with the Pediatric Trials Network across the country where sites are already set-up really to do clinical trials and where clinical trials are ongoing particularly around pharmacology and around safety of drugs. So we had, I think, a pretty decent idea to try to leverage that infrastructure that currently exists.

And one of the major things and important things about our project is that we -- it's really necessary to recruit from inpatient settings, not only caregivers and as well as patients in order -- and clinicians to get an idea of what's really happening and to really make sure that we're addressing the place of most need which is like after surgeries, for example, where kids are going to be hospitalized.

As you all know, there's been a number of things that have happened with the pandemic that have -- make that a little bit more difficult. One, it's been interesting to see kind of changes across the country or the different

restrictions across the country that have impacted our sites where in some places where COVID-19 was of higher incidence, certainly the restrictions were greater. In other places, the restrictions maybe weren't so great and so you couldn't necessarily have a uniform approach across the entire country.

That being said, I think everywhere, non-emergent surgeries, elective surgeries, non-emergent procedures, and kids coming into the clinics, et cetera, have certainly gone down, which decreased our pool for the people that we are able to recruit.

The second thing is that physicians are -- you know, you guys have heard the calls for physicians to go to different places in order to make sure that we're taking care of the public health emergency and that's been no different in pediatrics.

Despite the fact that kids have had lower numbers of COVID-19, we certainly have seen physicians going to help out and being redeployed to different places, even within their hospitals, which is meant, in many case, that they're necessarily available for not only our questions as we're doing the interviews, but also for recruiting patients for us.

And then the third is that institutions have really placed some limitations on research, particularly

that they see as non-emergent or at least not directly related to COVID-19.

I think that we've been able to overcome a number of these things by being a little bit creative and trying to talk with people within our sphere about what their plans were so that we can at least have a plan for moving forward, making sure that we are able to do things remotely as Elektra mentioned and some other recruitment in working with the sites in order to try to do some of that recruitment more remotely than not.

And then I think some of this has required a little bit of patience and altering our timelines a bit with regard to doing our massive literature review and perhaps focusing on clinicians instead of patients initially, but I'm confident that we will make it to the end of this and have been very excited to continue to work with people across the country to make sure we have a very diverse population.

MS. BENT: Thanks so much, Kanecia. It sounds like you've been really busy. And so now I'd like to ask the same question to Dave Cella, the principal investigator of the NUCOAT grant. Dave, can you talk to us a little bit about how COVID-19 is impacting NUCOAT?

DR. CELLA: Sure. Thank you, Robyn. Good morning. Let me just put this in context first for people

unfamiliar with what we're doing. So we're based in Chicago at Northwestern University and our activity is all happening in that particular geographic area. That's the context that's relevant for this planning phase of the program.

Also want to mention that we're studying sarcopenia, which is muscle loss, and its effects on physical function across various conditions as well as physical functioning in rare diseases or rare disorders, so that's the context of our work.

We would sort of categorize four different areas where we're having challenges based upon COVID-19. Fortunately, those challenges are relaxing a little bit, but as we all know, not as rapidly or as much as we might have liked. Those four areas are the Institutional Review Board which is the ethics board that reviews our work and approves our work, screening of patients, recruiting patients, and actual data collection.

So talking first about the Institutional Review Board, we've had to prepare numerous IRB modifications to account for the evolving recruitment strategies and screen strategies and interview procedures that we've had to change to a more remote mode, and we've had to track not just state regulations, but city regulations, which sometimes differ from the state, and university regulations, which sometimes differ from the city and the state.

So we have to track university, city and state guidelines regarding COVID-19 and all of them change sometimes not in -- to the same degree of requirement and then filter that through to the IRB for review and approval of modifications. This, as you can imagine, is true for the IRB load for all kinds of other research going on on the University, so they have been very backed up and so they have not been as responsive or as fast as usual, so that's one source of delay that we have incurred.

The next one is patient screening and the challenge there is that for some period of time from March through May we have not been allowed -- research was shut down. In-clinic research was just simply shut down in the University and health system so we couldn't do the screening that required in-person performance assessments of grip strength and gait speed.

As you can imagine with sarcopenia, you need to be able to identify indicators that signal that the patient has experienced significant muscle loss. And so we use grip strength and gait speed for that, and that we couldn't do at all during the March to May period, and then we were allowed to start considering doing that with appropriate precautions in June through August.

However, the clinics control that decision and still have not wanted us to introduce new devices into the

clinic setting that have to be wiped down after each use and introduce increased risk. So that has delayed recruitment and interview completion on the sarcopenia side in particular.

In terms of more about patient recruitment, as I mentioned, we had all research stopped from March through May and then gradually reintroduced in June through the current time. But we have not been able yet to recruit patients in the clinic due to the COVID-19 restrictions that the clinics have imposed and it's complicated by the fact that many of the clinics have gone to telemedicine for a large portion of their patients.

Some up to 70 percent of their patients are now being seen remotely for clinical purposes, so they're not even coming in either by the patient's choice, or by the clinician's choice, or a shared decision. So that's also delayed recruitment. Nevertheless, we have been able to get about halfway toward our goal of recruiting for, mostly for rare diseases with the help of the National Organization for Rare Disorders and recruitment through their channels for remote interviewing, and we're now moving forward more favorably on the sarcopenia side which is half of the study.

And that gets me to that fourth challenge, which is the data collection. So as I mentioned, our original plan was and probably will return someday to being looking

at grip strength and gait speed, but we worked with the FDA to modify that procedure to use a self-report measure of high probability of sarcopenia and that has now been approved for use.

So now we can actually, through remote self-report, assess whether patients have a high probability of having this muscle loss that's the critical issue in this particular population with a screening tool called the SARC-F and that led us to have to rechange our procedures, again get IRB approval, and now we're approved with that modification and we're ready to go. But as you can see from really early March through 'til now we've had these significant slowdowns and just pushing our way through nevertheless.

Hope that addresses your question, Robyn. I'll say one other thing that's really not about the project itself, but about our people. Some of you, looking at the age bracket of many of the participants on the screen, I imagine some of you have young children. I feel for us. I don't. My children are older. Our staff that have young children at home who haven't been in school, who haven't been able to go to camp, they have to both work full time and take care of their children full time and that's put a great strain on many of our staff, which is another source of delay that, as I say, isn't directly related to the

project, but is certainly related to COVID. Thanks.

MS. BENT: Thanks so much, Dave. I think that last point was -- is something that we all do kind of need to remember as we move through. But I just also wanted to touch on something that Dave mentioned about working with the FDA to adapt to some of these challenges. Elektra, do you want to say anything about that from the FDA perspective before we move on and hear from R.J.?

MS. PAPADOPOULOS: You know, I think this really highlights flexibility by the Agency and on all sides. It reflects, you know, the strong desire and need to move forward with the research. It's really, I think, a balance and also I will say that the instrument that Dave referred to, the self-report measure, we thought in this particular setting was fit for purpose.

In other words, it served the needs of this particular research question at the stage of development of the research and so, which was more of the scoping stage of development, and really served to, as Dave mentioned, identify patients you had a very high probability of having sarcopenia.

So, you know, the hope is, obviously, that the next stage of research will be able to use these other tests that are more traditionally used such as the grip strength and gait speed metrics to identify patients because these

are really the types of tests that we anticipate will be used in future clinical trials in sarcopenia.

So, but I will say that, you know, we did talk about this quite a bit and in the end decided that, you know, this flexible approach was really fit for the intended purpose and the question you were asking.

MS. BENT: Thank you.

DR. CELLA: Robyn, let me ask. I just -- I'm noticing that there are some questions that are coming through the chat. Should we --

MS. BENT: Yes.

DR. CELLA: -- should we address those or are we waiting on those?

MS. BENT: So we'll talk about -- we're going to get to kind of each one us talking a little bit about our experiences and then we'll move on to the questions at the end, but I do thank everybody who is submitting questions because we do want to get to those.

So now we're going to move onto Dr. R.J. Wirth, one of the principal investigators of the MiCOAS grant and R.J., can you talk to us about some of the challenges that COVID has brought to this grant?

MR. WIRTH: Sure, and thank you for the -- on behalf of Dr. Lipton and the rest of our team. Thank you for having us and giving us this opportunity. I think we

were -- we've been very fortunate, you know, given all that's going on and just how well I think we were positioned for a pandemic not seeing it coming.

And I'll sort of -- I thought sort of the best way to go and describe this is just, sort of, walk through what our last six months, believe it or not, has been. But I think probably the biggest impact and the part, sort of, that struck us the most and put us down the most is building on what Dave said just a few minutes ago, that sort of initial shutdown.

You know, when the U.S. started shutting down and the, you know, horrible toilet paper crisis of 2020 was raging, we, sort of, stopped working for a little while and I think everybody did, right? So we, sort of, sat and said, "How does this impact our family? How do we stay safe?" You know, "What does our work look like?"

And being in a business as opposed to a university, it's not always given that we'll, you know, be here in 50 years, so it's -- it was taking a couple weeks or a few weeks of sit down, come and go, "Okay. What does this mean for all that we're working on no just this grant?" And, you know, that, of course, slowed us down, but was needed time.

You know, fortunately, you know, after a little bit I was, sort of, readjusting to what the world is. We

felt like we were in a good position in, you know, maybe a month or so into this and decided that we really need to hit the ground running again.

So we turned our attention back and said, “All right. You know, we’re losing time here. Let’s get this going,” but at the time, we were in the middle of finalizing and writing up our first round of qualitative work. We were writing up the protocol and interview guide. So we’re like, “Let’s get back. Let’s finish this up. Let’s get it through IRB. Let’s get it to FDA. Let’s get their input so we can get out there and start talking to patients in one way or another.”

We were very fortunate that from the beginning we planned on this to be remote. So we -- before the pandemic hit, we were planning on doing remote screening, doing e-consents, having, you know, any information gathered and even all the interviews with people living with migraines. That was all planned to be over the phone for the first round here, so there was no shifting that we needed to worried about there.

FDA, for those of you who don’t have a lot of experience with FDA, their (indiscernible) timing is wonderful. So as we were finishing the protocol and the interview guide and, you know, it was submitted, they -- you know, they reached out and said, “Well, you know, we are in

the middle of a pandemic so is this really the best time to start asking people to volunteer? So let's just, you know, sort of, pause for a minute and work through," and very rightly so.

Let's sit down and think about and make sure that, you know, reaching out during this time is really the best use of -- you know, patient's time is really -- are they going to be able to focus on what we need to continue or are people sort of too distracted with the world?

So we took a quite a bit of time, had a number of interviews -- well, excuse me, a number of conversations internally as well as with FDA and after some time we decide that, you know, this isn't something that's just going to be here and gone in a week much like they alluded to. Unfortunately, it's going to stick around for a while, so let's see how we can update what we have. Think about how can we learn more about how COVID is impacting those people living with migraines and take advantage of a bad situation. Let's see how we can understand this better.

So we spent probably another month or so rewriting our interview guides, having multiple conversations with FDA internally to come up with a strategy that we thought not just would it give us some understanding of what's most important to the patient in terms of, you know, living with a migraine and any treatment that would be developed or

migraines, but also how has COVID impacted their life with regard to the migraine and can people, sort of, differentiate, you know, living in now world as opposed to living the world now.

So we spent a lot of time and again, I think at the end of the day, we ended up with a better interview guide not just in terms of COVID, but I think it required us to go back and think a little bit more thoughtfully about how, sort of, external stressors can impact migraine, how they may serve as a trigger and how, when there are major social changes, how that can impact sometimes in a positive way, how a person can, sort of, manage living with migraine.

So again, so, you know, this is -- what started off in March or so when the world started to shutdown, really led to maybe a three, four-month process of just reevaluating where we are, whether it is right to continue, and then given it was right to continue, how do we take advantage of this to make sure that we understand how COVID is impacting people.

And I'm happy to say with the help of CHAMP and other, you know, patient advocates that we were able to get through this and we've sent out our recruitment. At this point, we've had over -- you know, we've had a few hundred people volunteer for a initial qualitative study. We've done screening, gotten a few people in. Would have had a

chance to look at their transcripts and meet again with the FDA. We've sort of taken a pause on that.

I'm not going to get into too much of that because that's all for a topic we can talk about later, but I think what we're seeing here is that, you know, obviously, COVID had a huge impact on people, but people are able to differentiate that and think about the world pre-COVID and think about the world now and, hopefully, together, you know, taking all that together, that while it's put us behind schedule and obviously slowed things down, that we can actually learn more than we expected to walking into all of this. Thank you.

MS. BENT: Thanks so much, R.J. And I think this is really a great time to build on your experience by bringing in Michelle Campbell from the Office of Neuroscience to share what FDA was thinking when we initially started talking about the pandemic and its potential impact on the qualitative work being done by MiCOA. Michelle, would you mind speaking a little it to that?

MS. CAMPBELL: Well, thank you Robyn, and thank you R.J. and good morning to everyone. So as R.J. said, while they -- while his team was having to make determinations of the impact of the pandemic, not only on their own individual lives, but how to continue this

research, we were also considering should we pause this research or continue, knowing that the impact of COVID on patients with migraines and their lived experience may be different. And we wanted to make sure that if we did continue, would we still be getting the same information collected pre-COVID as during this current pandemic.

And so as R.J. stated, they were submitting their qualitative protocols to us during this time and we had a lot of thoughtful internal conversations amongst our teams and also with the MiCOAS team about what we should do. And they were very thoughtful conversations and everyone was very open and listened to each other's concerns and what could possibly solutions be.

And some of our concerns were would patients reporting of their symptoms and experience be different or enhanced because of COVID and their current lived experience with migraines. What would be, you know, any recall -- thinking back pre-COVID, what was that experience going to be like knowing that this was a chronic condition and that we are building something to be able to use in future clinical trials, we wanted to make sure we were going to be collecting the correct data during this time.

And so during those thoughtful conversations that we had both with the FDA team and some of those members are also on the screen today, as well as the MiCOAS team, we

learned that patients may most likely be able to really reflect on their lived experience with migraines pre-COVID and be able to complete an answer in a way that shouldn't impact the results because of the current pandemic.

And so with some of that back and forth and as R.J. said there was a couple rounds of editing, we met maybe a little bit more frequently, more conversations and emails during this time to really keep the project going, but ultimately we made a collective decision to continue and not hit the pause button on data collection, but to build in maybe some steps to just confirm what some of our assumptions were.

And I think Dr. Lipton will be sharing those results of some of those decision we made such as let's do a few interviews, see what the patients say; do we need to make any modifications to our interview guide; and what are the lessons we learned from that. And you'll get to hear more about that shortly and they were actually very positive and it was really great to hear that we made the correct choice to move forward at that time.

The MiCOAS team built in a protocol or interview guide to make sure we were able to tease out maybe some COVID-related concepts, or symptoms, or things like that knowing that it may come up sporadically when we talk with our participants and our patients and so how to handle that.

So there was really great building into an interview guide ways to really capture what is needed, but not minimize the current lived experience of the patient because this was important information to collect.

So I really thought that from our side it was a really thoughtful process and collaboration where everyone was listening, and what we've come up with so far seems to have -- seems to be working and I know that we'll be looking forward to reviewing more of the data as it becomes available.

MS. BENT: Well, I think this really is a great example of how we're working together to create a really sound core outcome set. So we all sat around the virtual table and kind of problem solved together. So now I'd like to turn to our patient representatives who are joining us today, and I'm going to ask you both the same question and that is how has the public health emergency impacted you and your health care or your child's health care, and how has it impacted how you participate in research or even your willingness to participate in research. So I'd like to maybe start off with Sharon.

MS. BROWN: (Inaudible) everyone.

MS. BENT: Good morning.

MS. BROWN: Very thought provoking question. At the time when the world started turning upside down, my

family and I were actually living in Durham at the Ronald McDonald House and we had been living there for almost two years. So when the pandemic came, it affected us because we wanted to be closer to our medical facility, but we also wanted to go home so we can be stationed at home and at least try to figure out how to live at home. So we went home.

So how has the COVID affected us? Well, a lot of his appointments were changed to telemedicine. Some things were changed to where we would have to come in once every two weeks, and we had lots of screening, only one visitor. So one parent will go with him. And they were being very cautious and careful. I know at some appointments before we would make the three-and-a-half-hour journey, we would have to send in our body temperatures prior to leaving the house and then, hopefully, we're still at the same temperature once we get there.

So it has definitely affected the way he was being provided health care, but in respect to participating in different types of research programs and what have you, despite the fact that we were -- the country was turned upside down in some respects.

Participating, to me, in research programs still because of the benefit and the particular one that I was -- I am involved in, which is the COA-APTIC, it was very

important to me because the nature of what they were asking me and my input was vitally important. So no matter pandemic or not, I thought it was very valuable to be able to participate and they made it easy to participate because we could do things in a virtual manner and still give our thoughts and concerns, and they listen. So it makes a big difference.

So my willingness is still there. I think it's still very, very important to have stakeholders not just from a medical perspective, but also to have stakeholders from a patient perspective or a caregiver perspective, because we're in the trenches along with the patient. So I think that's important.

So COVID-19 has impacted the way we move around. However, we've learned to stay safe. We've learned to stay home. We've learned to use alternative methods of telemedicine or picking up groceries from the parking lot because you've already called your order in, so what we're learning to deal. Thank you.

MS. BENT: Great. Thanks so much. I know that I've always been really impressed with your dedication to this project and very much really impressed when we met during the external Technical Advisory Committee meeting right before -- right before everything started. I don't think either one of us knew kind of the journey that we

would be taking from there, right?

And so now Kimberly, how about you? How would you share that -- could you share how the public health emergency has impacted you and your health care, and how it might have impacted how you participate in research or your willingness to participate in research?

MS. BENNETT-EADY: Sure thing. Good morning, Robyn. Good morning everyone.

MS. BENT: Good morning.

MS. BENNETT-EADY: I'm really, really happy to be here with you today representing a SEG. Like, it's an honor for me to be here. I'm a little nervous, so please forgive me, but I had to basically just think really hard about this question and -- I'm so sorry. During these extremely difficult times navigating the world in this global pandemic that is COVID-19, there are a few things that are shared by us all and the first is uncertainty.

We're all scared, unsure of where things are going. We've seen so much in the loss of life, loss of jobs, housing, really loss of hope because all together these losses have most of us feeling helpless, depleted, cheated, and we don't have any control regarding our external factors. Many of us have been quarantined alone for over five months and it's been isolating. It's the new normal and the adjustment/learning curve is really steep.

Well, I'd just like to let you in on a little not-so-subtle secret. The aforementioned feelings regarding living within the COVID-19 era aren't foreign people like myself living with rare diseases and disorders. You may have just realized the commonalities of our shared emotions of uncertainty, helplessness, and loss of control. Our respective conditions are unpredictable.

I have Scleroderma and pulmonary fibrosis, and with a few other comorbidities to include the battle of my confidence physiology. Many of us don't know how it will feel from one day to the next so I could feel fabulous one day, meaning like my pain level is only a 7 and then bed-ridden the next with unbearable pain feeling like a level 20 and beyond.

The loss of control over my life without my consent. No recognition is like horrific. I did not envision this as part of my future. No one does, but here I am nearly 20 years later and I'm still not adjusted to my newish normal. I have been isolating in quarantine long before the world changed in March 2020.

When I first learned about the stay-at-home orders, it was like, "Okay. I could do this." Like I do it all the time anyway, but the component of unpredictability affects how we show up in the world. Often we're too sick to even actively participate in the narrative of our own

lives and you're forced to become highly skilled in constantly pivoting and changing courses.

And due to my illnesses, often times, of course, cancelled (indiscernible) and appointments on short notice or I have to opt out on family functions based on, you know, geography, far distances. It's really taxing on my body and the inability to, like, carry all of my medical equipment that's literally life sustaining.

And once I get invited to an event, instantly it's like mission impossible, plan-of-action moment. Like, I go from having the appropriate number of, “Okay. Let’s check in for battery chargers, car adapters, cording prongs." It's a lot. Eventually, like, I even have to consider, like, the architecture of the place. Like, whether or not there are a lot of stairs or anything because I have -- I can't walk far and I can't really climb stairs.

And since the pandemic hit, it's like I still can't do any of these things and the only place I venture out to is my lanai or the front porch. Like, I don't go anywhere. I'm super frightened to leave my house. Many of my medical appointments have been canceled by the provider or myself. I actually had to cancel some procedures that were scheduled, follow-up visits with my specialists.

I have had a nephrologist visit. One was by phone and the other by telemedicine, and basically people with

rare diseases and disorders, we're often told that, "You don't look sick," but we are and, I mean, now that my lungs decided to follow my other major organs, there's a beautiful canyon (phonetic) going on on my face. Like, you could tell that I have a situation going on over here and that's called progression.

And in all seriousness, like when the world came to a halt and while everybody was scrambling to continue forward, it's like the world is trying to find a new way to operate, connect, and interact with each other professionally and personally, and thankfully for the explosion of video conferencing has been extremely beneficial to people like myself because I'm currently both busy and I'm more connected than I've been in like a decade, and I could do it all from the safety and comfort of my home.

And all that time that we super exhausting spent getting ready for appointments or events, like thankfully that's a thing of the past and now all I have to do is concentrate on whether like my wi-fi connectivity is super strong, and that all my tech is charged, and I have extra cording and batteries ready to go for my O2 arsenal.

Like, thankfully for us on our side, like SEG has been able to conduct all of our interviews and research meetings virtually. So they take every precaution to

protect us at all levels and -- pardon me. Lung disease. As Sharon was saying, like, we get the chance to contribute and, like, make sure that we're speaking up for people. Like, COVID-19 has bring so much havoc in our world and within all of this, you know, I'm choosing to try to control the things that I can control. So I stay connected with my family, my close friends. I do only things that I love and that bring me joy because I can't control anything else. This I can, and it's super empowering. And I use my voice to amplify for the voice of the people like myself that were often ignored or, like, dismissed. I'm here. We're here. We all have value and I'm just, like, steadily praying for all of us, and that outside is open again next year safely and that we could just all continue forward. So I'm sending everybody good luck and thank you so much for this opportunity.

MS. BENT: Thanks so much, Kimberly and thank you for sharing your experience. I really appreciate your thoughts on how COVID has both impacted your life in negative ways, but also really on the positive impact that the move to a virtual environment has had on you. I think that's a really, really important point for us to remember kind of as we think about things moving forward.

Now, I'd like to turn to my colleague from the Center for Devices, Michelle Tarver. Michelle, you’re the

director of Patient Science and Engagement, so I'm sure you're very busy, but you likely have some experiences similar to what we've heard about from our other FDA colleagues today and our grantees. Can you tell us a little bit about what you're hearing over at CDRH?

MS. TARVER: Sure. I think one of the things that I'd like to, I mean, underscore that everybody has already mentioned is that our culture changed and that culture change led to more people having to manage their own medical conditions and that has led to work (indiscernible) and tools (indiscernible) provider and the patients to make important decisions as we move forward and (indiscernible) when they need to come in versus when they can manage at home.

So some of the things that we are seeing is increased use of patient-generated health data such as digital health technologies. COVID itself underscored the need for that. We're seeing a lot of remote oxygen monitors such as oxygen saturation measures, temperature, and other tools, but also that ask for patient-reported outcome measures. A number of providers want tools that will help them better understand how their patients are doing and track that.

And so I think this effort that you all are sponsoring has really led to -- highlights that importance

of having tools that people can use and integrate into their care paradigms. I also think it's important that we remember that in adversity innovation is born and I think every panelist mentioned that. And we are seeing more and more creative solutions, whether it be in (indiscernible) interviewing component of PRO development as we've seen in a number of our studies at the Center for Devices or looking at ways that they can bring novel technologies to integrate with global data sources, which is part of our review paradigms. So considerations of interoperability and diverse populations and ensuring their voices are reflected in the development process has been more and more sought after by moving our investigators.

So, you know, I mean, I'm encouraged to hear how adaptive the projects have been and we also seem to be very similar (indiscernible).

MS. BENT: Thanks so much, Michelle. I really -- we really appreciate that. And now I'm going to turn to Scott Komo from the Office of Biostatistics to kind of wrap up. Scott, you've also worked on the COVID trial guidance and have been listening to our other panelists speak. Is there anything that you have to add to what we've heard here today? Any point that you wanted to emphasize before we move on to questions from the audience?

MR. KOMO: Sure. Good morning. You know, I think

it's, as said, it's just critical that these modifications be made so these trials can continue or even be conducted. I think what -- as a -- from a statistician, what's important is we need to sort of -- these modifications should be documented so we can assess the impact of these modifications. In addition, what also would be important to document would be if assessments couldn't be done because of the of the public health emergency and restrictions, that should be documented too so when we review the results we can have a better understanding of what happened. Thank you.

MS. BENT: Thanks so much, Scott. And I think that this brings us to our question and answer session and interestingly, I think that this leads right into one of the first questions that you -- that we received which is you mentioned a variety of changes needed in different settings in a different time. How are you documenting as part of your research data how restrictions related to COVID-19 led to changes in the study, conduct, the duration of changes, which trial participants were or were not impacted and how those trial participants were impacted?

I think maybe we -- if one of our grantees would be interested in answering that. Maybe we can start with R.J.

MR. WIRTH: Yeah, and hi. Thanks, again. This

has been a really, a really interesting discussion and hearing everybody's take. I think, again, we're a little fortunate given that so much of our work was planned to be remote. You know, the biggest impact to date really for us has been the updates in transition and thinking around the qualitative work and the conversations we're going to have with people with migraine.

So to date, the documentation really is, sort of, Version 1 and Version 85 of our interview guide. I think sort of just seeing that transition is, sort of, outlined how our thinking has changed over time. But given the work that we're doing with the -- on the qualitative side now and trying to get a better understanding of how it impacts patients, I hope at some point we can actually -- wasn't part of the grant initially, obviously, but to take some time and look back and think about how this interview process was impacted and maybe do something a little more formally in the manuscript or something. But so that's how we're going right now.

Right now is largely just version control, but I hope to see that turn into something a bit more formal and informative that we could share to others as this process progresses.

MS. BENT: Okay. Do we have anybody else that -- any of the other grantees, would you like to speak to that

question?

DR. CELLA: Well, I -- this is Dave. So I would just add that I think it's better for this to have -- it's better for COVID to have hit us during the UG-3 phase then the UH-3 phase where we will be looking at the performance of the developed measures in -- you know, in longitudinal settings. So I am hopeful that by the time we get to UH-3, if that happens, that COVID will be enough in our rearview mirror that there is a, quote, “new normal” that allows us to perhaps not go back to life the way it was pre-COVID, but life that more normal than it feels right now.

I think in UG-3, because we're planning, we're scoping, we're not -- there's not any irreparable harm that's being done to what we're learning. I think we're still learning quite a lot and in some ways we're learning things that, as R.J. said, we didn't have opportunity to learn, so there's a bit of a silver lining there.

MS. BENT: Thank you. Thanks, Dave. I think that's really a good point. I think maybe if you guys are willing, I'd like -- Sharon or Kimberly, I know we haven't talked about these questions, but a question came in. Do you have advice looking forward to the next six weeks, six months or six years to give advice to FDA and these grants on what we need to keep in mind as we move forward with our research? And I think we're talking both within the COVID

setting and within even outside of the COVID setting just as we develop core sets of Clinical Outcome Assessments that really impact -- that really measure the -- what matters to patients. Do either one of you have thoughts?

MS. BENNETT-EADY: Well, I do have some thoughts. Imagine that. I think I have -- well, I know I've participated in different types of projects in my past and some projects I have decided to continue with and some projects I decided to discontinue with. And most of the time the projects or research things that I decide to discontinue with are those that don't value the whole opinion or the whole -- take in all the information, shall I say.

So with that, I would say going forward with any grants or any types of research programs that are funded by FDA or even these particular projects, to keep the focus of what is your outcome, what is your goal, and it's very important to be a stakeholder from the patient side because I felt like during the questions and things that they were asking of me they wanted to know, “How do you feel? What is your thoughts? When we ask you this question, how does it make you feel? Does it make any sense? Should we make any adjustments?”

So to me, I felt like I was a valuable player. So going forward whether, you know, pandemic, not pandemic,

whatever the case may be, just stay focused on your patients. Stay centered on what is the outcome not just what you want to say, “This is what we did,” but how did it -- was it really effective and was it a well-rounded outcome that was presented for us.

So going forward I would say continue to keep ones involved because if you're talking about patients or respect for patients, then ask them, “Well, how do you feel about this?”

MS. BENNETT-EADY: Yes, I agree a hundred percent with you, Sharon. In my own experience with SEG, it's been beautiful. Like, if I have a question, like, I’m able to contact them at any given time and I think going forward, the FDA and other grants, they need to start hooking us patient representatives in, or us patient stakeholders, in at the preliminary level because some of the way that the questions are worded, it's, like, is for, like, only seven days, or is that for two weeks, or is that for a month, because we have varying degrees of kind of experiences where you're down for, like, three weeks and then you have that one good week, but they contacted you during the bad week.

And so if we're in on the preliminary question side, we can help them, like, structure the questions in a way that we know firsthand how that may affect the patient's being screened.

MS. BENT: I thank you and I think that that is something that we've all -- we all spend a lot of time talking about here at FDA really, that patients need to be in at the beginning. We've been (indiscernible) involved throughout the drug development process not just at the end to hand over -- hand somebody a protocol and say, "What do you think about this," after it's gone through the IRB. It needs to be really factored in from the beginning kind of holistic, and I think that -- and I thank you for really bringing that point forward. I think that's a really, really important point.

I don't know if anybody else would like to respond to any of that or has any thoughts about what Sharon and Kimberly have just said. I'll pause here to see if we have anybody who would like to speak or else we'll move on to the (inaudible) question.

So moving on to our next question. This one is a question for the regulators. Does FDA foresee that these key learnings such as the learnings from Question 13 will be developed into a final guidance and how will these learnings be incorporated in the review process? And I'd like to start off with maybe Michelle Tarver.

MS. TARVER: Sure. So, you know, every time there's a guidance, we're looking at our draft guidance for any type of document. We're collecting information as part

of that process. So, you know, we're looking at it and things are -- as science evolves, things are adapting. we will potentially adapt, but we're -- but I don't think we can definitively say anything about a final guidance long term.

We're looking at the information that's collected, we're seeing the quality of the data and how it is informing our decision-making. So I would say, you know, I think Scott has laid out some really important principles about giving us context, documenting how things are being conducted, particularly this mid-trial or mid-study, so that we can understand that impact. But there's lessons learned as we're going along and I think we're all learning them together because none of us have been in a time such as this.

And so, you know, we hope that we can create efficiencies in trial conduct. I know that the Center for Devices is very committed to looking at real world data and how it can inform our decision-making and so I would say stay tuned. We're learning as we go and I think we're all learning as we go.

MS. BENT: Thanks. Thanks so much, Michelle. And I know that Michelle is always a hard act to follow as far as answering questions like this, but does any -- do any of the other regulators on the panel has something that they

would like to add to what Michelle has said?

MS. CAMPBELL: I can just say that you are right, following Michelle is always a hard act to follow, but I think it's both what Scott said with the statistical considerations for right now, how lecture laid out with the thought process and the questions that we have been receiving that are coming in from our industry sponsors and the considerations to take. I think what both Elektra and Scott have said is really the layout.

Things to think about now and those considerations and responses that we are providing, you know, we'll look at all of -- everything that comes in. We will learn from this experience and I think the opportunity through this grant experience and this cooperative environment also helps us learn a little bit as well outside of the drug development program learning from the grants. It's also been -- will be useful and maybe help inform us on the impact of COVID and some of these considerations that our grantees described that they went through today.

But I do echo what Michelle said about, you know, it's a little early to think about what it will look -- what things will look like, but really documenting and then taking account any changes that I've been made will only be more informative to us when reviewing submission.

MS. BENT: Does anybody else have anything they

would like to add before we move on? Okay. Oh, go ahead. Sorry, Elektra. Go.

MS. PAPADOPOLOUS: I was just going to say that, you know, I think you all recognize that this is a really fluid situation and that we're learning as we go in real-time. None of us could have anticipated the situation and so there was some flexibility built into the guidance process allowing us to do the periodic -- the updates as we needed to.

And some of the Question 13 that I discussed earlier at the beginning was one of those and it actually was done in, sort of, an iterative manner as we were facing the challenges and we saw the need to put this out in the public. So that's a good thing about how this is set up is that that, you know, obviously, we can do these updates as the need arises.

MS. BENT: Thanks so much. Sorry, I muted and unmuted inappropriately. Thanks so much. I see that we have a little bit of time and I think that we're -- I'm really excited because I think that we're going to hear from a colleague of ours on the NUCOAT team and I'm going to turn the mic over briefly to Dave Cella to kind of talk about what we're -- what he's going to talk about. Thanks.

DR. CELLA: Hi again. So when Kimberly was referring to SEG and her work with us, Kimberly is working

with us on the Northwestern project, NUCOAT, her reference to SEG is the Stakeholder Engagement Group and George Greene, who's joined the panel for this few minutes, is the person, is the co-investigator on our team who's leading, or maybe better put, facilitating the Stakeholder Engagement Group. It's a very, very engaged and active group.

We have brought them, and as Kimberly has advised, we've we brought them in from the very beginning and all along the way they have participated with us including requesting to be able to attend these meetings with us, which we were happy to and the FDA was, happy to oblige.

So George, could you just tell us a little bit about what we've learned from the SEG, as Kimberly put it?

MR. GREENE: Absolutely. Thanks for the opportunity to speak as well and Kimberly, thank you so much for again sharing with us your experiences. We really appreciate it and you're a good example of why stakeholder engagement is really important for the research that we're doing.

First, I need to acknowledge that, you know, we're working with a team here at Northwestern and I do have a co-chair that's helping to facilitate our work and that's Katie Benjamin it AbbVie Pharmaceuticals. So she has been a good partner to me in helping us think about the structure, and the coordination and the functioning of our group. But

we've, you know, learned a lot from our stakeholders both from our patients and our patient's caregivers.

We've got four patients representing both sarcopenia and related conditions as well as patients with rare disorders, and we've also been very fortunate to have their caregivers involved because they also offer another intimate perspective on what life is like for the patients and their loved ones, really the people that are caring for.

Our stakeholders have been incredibly important for us. Most recently, we had a meeting with them in -- I think was July or -- yeah, end of -- middle of July, and we talked a lot about the things that Kimberly and Sharon both talked about here. We wanted to learn about how COVID-19 has impacted their lives. We want to know how it's impacted their health care and what we were trying to follow down to is there really learn about what their thoughts were about engaging in research as we move forward out of this research lockdown at the university setting.

So we wanted to know from them what would be acceptable and what would not be acceptable when it comes to doing research. Would you be willing to come to our university offices to, you know, do a grip assessment or do a gait speed test? So we really learned about what our stakeholders needed to -- what they needed to see in place before they felt safe coming to our offices.

And for the most part, I think our patients still have a lot of concern about possible exposure out in the world. As safe as we like our offices to be, there are concerns about, you know, taking public transportation or getting in a car and driving through a parking garage, taking the elevator up. You know, what are we doing as researchers to ensure their safety moving forward to part in research.

So that's helped us, you know, to think about what we need to do to relaunch our research for in-person data collection but fortunately, as Dave mentioned, we've been able to do a lot of our work online and remotely, so. And thanks to, you know, collaboration with FDA to letting us do some of screenings using paper and pencil measures so we don't have to do these in-person as that potentially with people at risk.

So, you know, that's sort of, you know, sort of the big, you know, contribution I think that we've seen from the stakeholders thus far, but I want to add that, you know, we have conversations, you know, in and out of our meetings with our stakeholders and we had a nice conversation with Kimberly following one of our meetings where she gave us really great input on our interview guide and wanted clarification on some of the questions that we're asking and, you know, suggested ways to better ask these questions.

So it's really been a joy doing the work. I love doing stakeholder work. As a community psychologist, this is very important to me and it means a lot to see people engage in this discussion as well, so thank you for that.

MS. BENT: Okay. If you don't mind, I think to follow up with a question, is there anything that you've learned in the past six months that would impact how you would -- and maybe not just to George to put him on the spot, but to also some of -- to the rest of our grantees -- is there anything that you've learned in the past six months that would impact how you would plan future studies and trials including contingency measures or unexpected -- for unexpected disruptions? I mean, I don't think anybody expected, anybody could have ever seen a public health emergency of the scope coming, but is there anything that you've seen or learned that you think will impact how you do things going forward?

MR. GREENE: Just right off the top of the bat, and to keep it brief because I know that other folks probably have suggestions as well, and this is something that we learned is that our, and Dave mentioned this, is that our stakeholders want to be more engaged, right? We have meetings bi-monthly to quarterly, but our participants, our partners in this, really want to contribute to other aspects of our work. They want to, you know, know what

we're doing with the FDA, what are those conversations like. We want to know, you know, be in communication with the technical group, the technical experts, and the clinical experts as well because they really want to have a voice in sharing their experiences.

So I think, you know, that's important. It's just, you know, if we can meet more frequently and have our participants engage more, I think that's been hugely important. And the idea of ongoing communication to have, you know, people feel like they're a part of something, they're part of, you know, our NUCOAT family. I think that's also been important as well. It's a sense of you know camaraderie or the sense of community in the work that we're doing. So those are a couple of things.

MS. BENT: Thanks. Kanecia, did you happen to have any thoughts about this?

MS. ZIMMERMAN: I think most of it's been said. I don't have anything, you know.

MS. BENT: Okay. All right. What about anybody else? Does anybody -- do any of our grantees have any thoughts about kind of lessons learned? If not, then just a forewarning to my FDA colleagues, I'm coming to you next.

MR. WIRTH: If I may, and this is really just reiterating what's already been said, but as we move into the UH-3 phase and start thinking about data collection, we

obviously, and I think I can speak for everyone, we need to think about how do we move, (indiscernible) or if, you know, we can. We may be in a very good situation in which we can, which may not have been the way that we approached the study in the past. I doubt we would even have thought about sort of contingency plan to move everything to a remote environment, but I think going forward not just for this project, but, you know, for how long into the future, that's just going to be sort of standard practice (indiscernible). Thank you.

MS. BENT: So FDA, do we have any thoughts about how this changing paradigm, what we may be -- for -- as we plan for the future or as we talk to people about planning trials, do we have -- do you have anything that we would share with them beyond -- I mean, obviously, we've already done a lot of work with the questions and answers and the guidance, but is there anything else that you would like to add?

And I -- it does look like we're kind of wrapping up on our last five minutes, so if there's any, like, key takeaways that you would like people to hear, this would be a great time to share that as well.

MS. CAMPBELL: I think, you know, people often hear us say, "Come engage with us early. Come have these conversations with us," and we really mean it. You know,

while this grant is a cooperative grant so we get to work with our grantees and meet with them on a pretty regular basis, I think the conversations we had to handle the challenges we are facing during this phase were done as early as possible.

You know, when they came up we were thinking about them and trying to find workable solutions so we could keep the trial, these programs going and the data collection going. I think, you know, in my prior-to-FDA-life and having done research in academic setting, I take Scott's comment to heart of just documenting everything. So if something changes, something happens, just building in documentation so we can understand the story that was occurring, the unexpected parts, the expected parts of data collection.

It helps us understand what's going on so instead of losing data or making it missing or having to do some type of crazy statistical test to the data, we have a better understanding of what's going on and it gives us a better fuller picture of a trial, of a study, of qualitative work, of the psychometric trial. Whatever aspect of data collection, it just tells us a better, a better story of what was going on.

MS. TARVER: (Indiscernible) innovation, I think that, you know, we have seen a lot very creative ways that

people are looking at putting together information to better understand how patients are operating in a (indiscernible) agreement. And in the trial setting, we see creative (indiscernible) of new tools. And I say "tools," because they were things that were meant for a different purpose that they're looking at how they can adapt it to measure or capture things that are critical to (indiscernible).

So I think that, you know, to Michelle's point, come talk to us early about these things, because I think that we can do a lot of troubleshooting, figure out where there may be challenges and opportunities to use that data and give more balanced approach to how they decide to proceed so that we can have, you know, help them move towards success in the end.

MS. PAPADOPOLOUS: I'd like to echo these comments and also add that, you know, this is something that -- the ability to do remote assessments can have, you know, huge advantages in terms of any type of clinical research with participants. And some of those are really that, you know, that they long-recognized even before the pandemic such as, you know, sort of allowing a more diverse and heterogeneous population to participate, for example, or just reducing burden on patients in general and perhaps even allowing us to assess things that we couldn't previously assess using our traditional methods.

And so, you know, I think this is even further highlighted during the setting of the pandemic, but is something that we've been long thinking about.

MS. BENT: (Inaudible) much. So it looks like we're coming up on 10:00 a.m., so I'd just like to extend a big thank you to all of our panelists for sharing their experiences and their -- for their thoughtful responses to our questions. We really hope that this panel discussion about the many different factors that researchers should consider when deciding to change their protocols during COVID-19 public health emergency to include remote assessments and also as Kimberly and others on the panel pointed out, this can benefit research participation beyond the current public health emergency.

And so I'd like to thank you for all your questions and at this time, I would like to invite Dr. Richard Lipton professor at the Albert Einstein College of Medicine to turn on his video and audio to discuss the progress of the Migraine Clinical Outcome Assessment System, MiCOAS grant. Dr. Lipton?

DR. LIPTON: Well, good morning. That was certainly a fascinating session. Would you like me to share my screen or where you're going to project centrally which is what my expectation was?

MS. BENT: Yes, the screen -- the slides are being

run by our producer so we are good to go. Thank you.

DR. LIPTON: Okay. Great. So if I can have -- are my slides currently being projected, because I don't see them? Oh --

MS. BENT: They are, yes.

DR. LIPTON: Oh, beautiful. Okay great. So I'm very happy on behalf of my co-principal investigator, R.J. Wirth, and the rest of our team to tell you a little bit about the Migraine Clinical Outcomes Assessment System.

One of the things that struck me while listening to my colleagues present both yesterday and today is that our project differs from the other two in an important way. Our project is actually focused on a particular disabling disorder, migraine, whereas other -- the other projects are focused on measuring pain in young children or focused on measuring physical disability, which is a very different kind of challenge.

So our goal is to incorporate the patient voice into studies that assess the benefits of treatment for a particular disorder rather than measuring a particular very important clinical construct that cuts across a wide variety of diseases.

If I can have the next slide, please? So migraine is an enormously prevalent disorder. It affects 12 percent or more of the world's population, which means that it

affects about 40 million Americans and more than a billion people on a global basis.

If I can have the next slide? Migraine is a symptom complex defined by head pain and various combinations of nausea, sensitivity to light, sensitivity to sound, sometimes vomiting and in about 20 percent of cases, of phenomenon called aura where people experience focal neurologic symptoms that usually include a mix of positive and negative features. For example, scintillations in sparkling wines and a graying out of vision.

If I can have the next slide? So in clinical trials, generally for acute treatments we meticulously measure many of the features enumerated on this slide in preventive studies as a broad approach. We've counted headache days and the features listed on the side are actually the ones that are included in the diagnostic criteria for migraine, which are known as the International Classification of Headache Disorders.

But, of course, the question this project invites is is that all that's important to people living with migraine and also are these really the most important things to people living with migraine? Because in addition to the cardinal diagnostically defining features of migraine, migraine is a frequent cause of disability, migraine causes cognitive impairment, changes in mood, food sensitivity.

Migraine has a well-documented burden that extends beyond the acute attack and we call the acute attack the ictus and we call the burden between attacks the interictal burden.

If I can have the next slide, please? So to determine what's really important people with migraine, in Phase I of our project, our goal is to develop endpoints and their measures that accurately reflect patient experiences. And so there are two, sort of, issues here. One is what's the construct that we're trying to measure. It could be pain. It could be cognitive impairments. It could be sensory sensitivity.

And then the other issue is given that we know what's important to patients, how do we define that in a rigorous way so that it can be measured in the context of a clinical trial and that's why our second goal is to develop these endpoints and measures using patient input, collaboration, and gold standard psychometric measurement.

So this project has a number of people who are experts in measurement. I'm a clinical neurologist/epidemiologist, but it's really been great for me to work with a group that has so much measurement expertise as we try to solve these problems.

Can I have the next slide please? So our first aim is to build a team of advisors and to develop an initial list of endpoints based on our knowledge of what's been done

in the past. Our second aim was to conduct a systematic literature review and refine that list of endpoints and we've accomplished aim one and aim two.

Our third aim in the first phase of this project was to talk to people with migraine and make recommendations for new endpoints and outcomes. And at the moment, we're really about halfway through. Well, a little less than halfway through that third phase as I'll -- that -- the achievement of this third aim of the first phase. I'm sorry.

Can we go on to the next slide, please? So we've assembled an External Technical Advisory Committee. You see Robyn Bent, our host today, is a member of this committee and our committee, our advisory committee, has representatives from industry leading academic, neurologists, headache specialists, researchers. We have a patient-advocate, Katie Golden, on our committee and Katie is in a leadership position in an organization called CHAMP, the Coalition for Headache and Migraine Patients, which is a, sort of, meta organization of patient support and advocacy groups for people with migraine and that partnership has been essential to the work we're carrying forward.

Kelly -- I'm sorry, Kelly McCarrier from Pharmerit, is leading our qualitative work along with Maya

Gersten, not mentioned on the slide, and then our final advisor is Walter Stewart who is a leading epidemiologist of headache who has run outcomes research both in the Geisinger Health System and the Sutter Health System, so his role is to help us get a health plan perspective as we -- and a payer perspective as we develop these endpoints.

Next slide, please? Provide support to people with headache, migraine and cluster headache. Though the majority of the patient members of CHAMP have migraine, their goal is to bring together stakeholders to more effectively help people, to identify unmet needs for those with headache, migraine and cluster, and to work better to support people and their caregivers with this broad range of disorders.

So the leadership of our project has a collaboration with CHAMP that extends beyond the project. We've collaborated on some surveys of their members. We currently have in the field a survey examining the impact of COVID on migraine and on other headache disorders and this has really been an incredibly valuable partnership for us.

Next slide? So in terms of literature reviews, we undertook to review the acute and preventive literature on migraine. So acute treatments are treatments given at the time of the attack to relieve pain and restore function. We identified 705 eligible acute treatment trials and then

conducted an in-depth analysis on 451 of these papers which used standardized case definitions of migraine and were conducted more recently.

On the prevention side, we identified 757 potentially eligible articles and did an in-depth analysis of 268 of these publications again focusing on, you know, more recent publications that used currently accepted methods.

Both of the reviews found tremendous variability across publications and the outcomes used, a lack of standardization and the definitions of outcomes and endpoints a large variety of patient reported outcomes used across studies, though many studies included no patient-reported outcomes at all.

And on the basis of these literature reviews with our internal team and with a couple of our external advisors, we have manuscripts that we plan to submit, you know, over the next four weeks and we will also post these reports once the papers are accepted on our website.

And, you know, certainly the way the literature review was conducted, on the one hand it didn't reveal any tremendous surprises. On the other hand, we can actually quantify how many studies used migraine-specific quality of life questionnaire as an outcome, how many use the migraine disability assessment scales as an outcome, and how often

people used what things.

And in general, the lit review both provides us with guidance in terms of measures for future study, but also underlines the need for this project because of the tremendous heterogeneity among studies.

Can I have the next slide? So we've also undertaken a qualitative study, which you've already heard about from R.J. The initial recruitment through CHAMP generated a pool of 400 people with migraine who are eligible and willing to participate in the study. Our target is to do about 40 qualitative interviews. There's tremendous diversity among the 400 people who volunteered, so we're endeavoring to get a broadly representative group of people with migraine that includes people that vary in income, race, education, background.

We conducted an initial set of four interviews and a couple of practice interviews before we started, and the goal of those initial interviews was to see if people could distinguish their headache experience before the time of COVID from their headache experience in the time of COVID. And, of course, our goal is to make sure that what we learn in our qualitative interviews doesn't in some way exclusively idiosyncratically reflect experience in the current environment which all of us hope will be short-lived.

We pause to assess the interview guide and the participant's ability to differentiate their pre-COVID and post-COVID experience, how COVID impacted patients and the implications of COVID for our ability to collect data. And broadly, although COVID had an impact, people were well able to distinguish their experience prior to COVID from their experience after COVID and that corresponds very well with my clinical experience as well.

Incidentally, some people with migraine reported their headaches got worse due to stress or got worse because they couldn't go in and receive injectable therapies that required in-office administration. Many people reported feelings along the lines of what Kimberly so eloquently expressed in terms of everyone else being restricted made their lives feel more normal. They felt a relief of the stress of having to go to work, appreciated being able to work from home. So some people actually reported benefit from COVID as well.

Next slide, please? So the key points from the first wave of the interview were that impact of COVID on experience, you know, two people said they didn't notice much impact at all when changes occurred. They were bi-directional as already noted and no participant said -- cited fundamental changes in their symptom profile disease impact or treatment priorities.

We've now completed nine interviews and are in the process of doing the detailed assessment of the other completed interviews. We're about 25 percent of our way through this process.

Next slide, please? So people were able to characterize minor changes in their treatment priorities and the second wave of interviews, as I mentioned already, is well underway.

Next slide, please? So for Phase II of the project, our aim is to talk to people with migraine to determine how we can best capture the recommended outcomes and end points that will emerge from both our literature summary and the wave of qualitative work in which we're currently engaged. We're planning on conducting two rounds of data collection in acute and preventive endpoints to study the psychometric quality of new measures and then once these measures are established and validated, our plan is to disseminate the measures.

Next slide, please? So with that I would like to thank you for your attention and thank this group for a very stimulating and interesting morning, and a very stimulating day yesterday. Thank you so much.

MS. BENT: Great. Thanks so much. That was a really interesting presentation and I think now we're going to open the floor, or the virtual floor, to questions. And

I don't know if you would like to call on some of your team to -- some of your team members who are, kind of, here but hidden to answer some of the questions.

But to start out, I think we -- the first question is have you learned anything from the literature review or qualitative work? I know you touched a little bit on it, but can you tell us a little bit more or can somebody on your team talk a little bit more about what's been learned --

DR. LIPTON: Sure. So --

MS. BENT: -- as part of the literature review?

DR. LIPTON: Yeah, so -- sure. So yeah, so I'll go first. I mean, we -- you know, obviously, I've been working in this field for a long time and conducting clinical trials in migraine for a long time, so I was pretty familiar with the literature and was aware that it was heterogeneous.

One of the things that surprised me a little bit is how much variability there is from study to study. So take a construct like pain. Well, do you measure pain on a 0 to 3 scale? Do you measure pain on visual analog scale? Do you measure pain at one hour, at two hours? Do you measure area under the pain time curve? There is so much heterogeneity in the way a simple construct like pain is measured and the measurement choices that have been made

today really have been disconnected from the patient voice.

You know, so those choices, you know, the standard regulatory endpoint for acute pain trials these days is you ask people before giving a drug, “How bad is your pain right now on a 0 to 3 scale?” None, mild, moderate, severe. You don't let people treat until their pain is moderate or severe and then you measure the proportion of people who achieve pain freedom two hours later and that is one of the two regulatory endpoints for acute pain and it’s a basis of approval for medications.

It's actually served us incredibly well on the one hand. On the other hand, when pain doesn't need to go away completely to restore function and we -- and people care about what happens to their pain not just at two hours, but before that and after that as well. So seeing the heterogeneity in measurement really makes me want to incorporate the patient voice into determining the best way of measuring pain.

In addition, in clinical practice, we often instruct patients to treat while pain is mild. So there's a disconnect between the way clinicians advise patients to use medications and a way -- the ways they're studied in a regulatory context. So understanding if that's a gap that needs to be closed is something we hope to do with the qualitative work.

You know, we, you know, learned that on the prevention side while patients tell us and, you know, we're still doing our qualitative interviews so this is something that remains to be determined, but on the patient side, many patients say, you know, if you say to patients, “What's your most bothersome symptom,” they may say, “Well, I can't think when I have a migraine. I can't work when I have a migraine because I can't think when we have a migraine,” and so it may be depending on what else we hear from patients that a focus on cognition will be very important as well.

So the literature summaries were led by some of my colleagues, so I don't know. Jim, Carrie, do you have anything you'd like to add?

MR. MCGINLEY: (Indiscernible.)

DR. LIPTON: Yes.

MR. MCGINLEY: Okay. I'll start my videos. So I'm Jim McGinley. I've done a lot of the work with Carrie and Dawn with the lit reviews, and just kind of adding to what to what Richard said, I think the thing is surprising to me the most -- surprised me the most was not only the number of outcomes using variety, but also even within what you consider sort of the same outcome, there is variability.

So how you define a headache day, how do you define a migraine attack, all these things can vary within the study. It's hard to capture it in the literature

review. So I didn't appreciate that. Whenever we committed to doing this literature review, I don't think I really appreciated how hard that is across these studies and I learned a lot, you know, in doing so, but there are things that even going back, we could capture it more information about this.

And from, you know, a research standpoint, I look at things. I review articles a lot differently about the level detail that needs to be provided to understand what is the outcome. Even if you call a headache, a headache day, what is it? You know, there's a level of detail that I learned that you have to think about with this stuff.

And the second thing that I learned, I would say would be the tie between endpoints and the design. So the designs of some of these studies are preventative, there tends to be a similar design. Now for acute, the study designs some differ. You know, so you can have, sort of, like, crossover designs. You can have parallel group, sort of, standard things and then the timing of the assessments and vary. Richard said oftentimes they focus on two hours, but a lot of times studies use different endpoint or different time points for assessing things, and the endpoints and the outcomes depend on the design too a lot of times and it's hard to appreciate how difficult that is.

Sometimes I think I took it for granted whenever

you're looking just at two hours, but you really need to think about these things together, and going through all these studies made that very apparent to me at least and that was surprising to me. But it only took me fifteen hundred articles to realize that, so.

DR. LIPTON: Yes, I -- so just building on what Jim said, to some degree particularly in the acute treatment space there is a component of what I call clinical trial gamesmanship. And so the way that -- just to give you an example of how that works, if you think you have a drug that's really fast then you pick very early time points to get a competitive advantage.

If you have a drug has a long half-life and you think it'll have sustained benefits over 24 hours, then you might prioritize how people are doing 24 hours after taking drug and, you know, people actually shift how they define their endpoints and what endpoints they designate as primary endpoints in ways designed to highlight competitive advantages of their product. And we can talk about whether that's a reasonable thing to do or not, but that's certainly a factor that contributes to heterogeneity among studies.

MR. MCGINLEY: You know, what Richard said about --- there's definitely some heterogeneity in the -- so we kind of split things up in terms of the PROs between migraine or headaches sort of specific versus general PROs.

A migraine or headache specific tool might be something like the MIDAS which means Richard medicines or the MSQUAL (phonetic) or something like that, and there are some that pop up pretty frequently and pretty regularly especially in prevention studies. In a few, it's sort of all over the place.

The other thing that I would point out are in that general PRO bucket, which are things I've said like the SF-36, things that are just kind of generally measuring quality of life, things that, you know, pop up on some of the other projects, you know, on this call, there's so much heterogeneity and there's almost like just -- there are a lot of things that are just made up. You know, like you can't even find the details. Somebody just threw in a few questions and can't even call it really anything. It's underneath anything.

So I think that the other thing that I learned, you know, how outside in PRO realm there's, it's kind of -- it's all over the place. There few instruments that are headache-specific I think that are used, but in, outside of that, it's -- it really varies a lot.

DR. LIPTON: Yeah. So yeah, so I'll add that the most widely used PRO in prevention studies is an instrument developed, an instrument called MIDAS that I actually developed. Now, I developed it for screening for disability

at the time of initial primary care visit. I did not develop this to measure with in-person change over time and so it was certainly not -- it is certainly not fit for purpose and the FDA hasn't accepted it in labeling, with very good reason.

But the fact that so many sponsors choose to use an instrument not designed for the purpose they're using it for, which has no chance of making it into labeling, I think highlights why this work is so important.

MS. BENT: Thank you. I think that was a really, that was a really informative discussion. I really appreciate hearing about that. It looks like we have received a question. So the focus of this grant is on adults. For the future, how can this work helped the unmet need in pediatric migraine?

DR. LIPTON: Yeah, so -- you know, so the unmet need in pediatric migraine is huge. If you look at the epidemiology of migraine, it's actually very common in children, more common below the age of 12 in little boys than in little girls. At the age when young girls start having their periods, risk really takes off in females and remains higher in females at all ages past the age of puberty.

Because migraine half the time begins before the age of 21 and because migraine is sometimes a disorder that

progress has particularly in the setting of poor treatment, I consider pediatric migraine an enormous priority. We would like to extend the work we're doing to pediatric populations.

Pediatric migraine has been studied by treatments that have emerged, you know, under the FDA mandates to study children, but many studies in children have failed. In children and adolescents, migraine attacks tend to be shorter. They tend to be more bilateral. They can be quite disabling, they can disrupt school, and we would love to do the work necessary to move to younger populations given that opportunity because it's so important from a public health and treatment perspective.

MS. BENT: Thank you so much. I don't know if anybody else on your team has anything they would like to add. I'll pause for a moment in case they do.

DR. LIPTON: Well, so -- yeah. So, Maya, do you want to add anything, any observations about the qualitative work? I mean, you speak very compellingly about that work.

MS. GERSTEIN: Sure. Hi everyone. I'm Mya Gerstein and would be happy to share at least some preliminary insights that we have from the qualitative work that we've been conducting with individuals living with migraine.

So as Richard has mentioned, we've conducted

interviews with about 25 percent of the total number of people we plan to talk to you for this qualitative study. By the end, we plan to talk to about 40 individuals living with migraine, so we do still have quite a bit more to go before we reach a point where we feel like we've really captured the full range of experiences and perspectives and before we can be confident that themes we're already seeing emerge are really representative of the shared experience of people living with migraine.

But with that being said, I do think we're starting to see some aspects of living with migraine emerge in the interviews that we've conducted thus far as being at least so far universal and critical pieces of that experience and perhaps not well captured in other studies that have become -- that have come before this one.

So for example, we're hearing a lot about the impact of migraine on cognition and experiences with cognitive interference. So losing words, memory issues, trouble focusing, feelings of disorientation. I mean, we're hearing about this both during the migraine attack itself, but also for some people about the lingering impacts of that in between and how that can be such a major impact on people's livelihood.

So the participants in this qualitative study are really helping us to find this. You know, what does that

look like? What does that feel like? How does that impact or disrupt their life? And we're already capturing some really vivid descriptions of this. I think it's going to lead us to a place by the end of this study where we have a better handle on cognitive interference caused by migraine from the perspective, and I think this is the most important part, of those who are actually living with the impacts of it.

We also -- I just want to know one other thing. We also spend a lot of time during our interviews asking people to think about their treatment priorities. So what are they looking for out of their acute medications, their board of medications, what are they looking for out of their preventivement, and I think we're starting to see some interesting and maybe surprising patterns emerge around how people with migraine think about pain freedom versus pain relief.

So we're consistently hearing people prioritize pain relief over pain absence, you know, citing some of their own pragmatic views on the issue. Their own treatment experience is really framed by their previous experiences with migraine medications and many of them have come to the conclusion that reliable pain reduction is perhaps a more practical and acceptable outcome for them than complete pain freedom.

So it'll be interesting to see if this continues to dominate as a view when we continue to speak with individuals living with migraine about their treatment priorities and we get further into the study, but we've certainly flagged that as an issue that we want to continue to dig into. So I think we'll have likely much more to say and a couple months once we've finished our interviews and our analysis, but it's just a small peek into, I think, a couple of the very key takeaways that we've identified thus far.

MS. BENT: -- so much. I think that we -- that was really informative and I think we're all really excited to hear at our next meeting, or maybe sooner on your website, kind of the findings of this work and really have the opportunity to review it and definitely learn a lot from it. So thank you and thank you for the -- to the entire MiCOAS team. It is 10:32 and I think that we are now scheduled for a break. We'll take a 15-minute break and reconvene at 10:45. Thank you all.

(Off the record.)

(On the record.)

MS. BENT: -- Dr. Dave Cella from Northwestern University to turn on his video and audio to discuss the Northwestern University Clinical Outcome Assessment Team grant, or NUCOAT. Dave?

DR. CELLA: Thank you, Robyn. Can you hear me okay?

MS. BENT: I can, yeah. Thank you.

DR. CELLA: Oh. All right. Great. Well, I have the privilege of representing the Northwestern University Clinical Outcome Assessment Team, or NUCOAT, in this presentation. Several of the team are also in attendance and I hope will chime in during the discussion period. This is a project that focuses on, as Dr. Lipton mentioned, on physical function and across a range of diseases, and I'll explain both diseases and disorders in a moment.

But the focus here is on physical function as measured by patient self-report as well as through performance assessments of physical function capability.

May I have the next slide, please? So there are three aims to conduct this work and the first aim as indicated by the status bar is completed and that's to convene stakeholders, patients, care partners, clinicians, measurement experts, the payers, the regulators across the board including industry representatives around this topic of physical function as it relates to the approval of new drugs, so a specific context of use.

And that (indiscernible) has happened. You heard about some of that earlier, and then the second aim which is ongoing, is to propose model conditions. Three that involve

sarcopenia, which is muscle loss and three rare disorders, that affect physical function and cover a range of that particular concept or domain a physical function, and look at the gaps, if any, to the proposed measures that we would be putting forward.

And finally, the third aim is to is to propose interim plans and final plans for refining and testing these PRO and performance-based measures using PROMISE, which is a National Institutes of Health-sponsored set of tools to -- that measure self-reported physical function as well as using the NIH toolbox, which is also work-sponsored by the NIH, which is across cross-institute effort under the Neuroscience blueprint. It measures motor performance.

And then finally the Short Physical Performance Battery which was developed by Jack Guralnik and colleagues while Jack was at the National Institute on Aging. He's now a consultant with us and is at the University of Maryland. So that's the overview of the aims of this particular project.

Next slide? (Inaudible) that we're focused on in sarcopenia or muscle loss are osteoarthritis, hip fracture, advanced cancer, COPD, heart failure and Parkinson's disease. And we finalized with the FDA in late-February the rare disorders that we will be focusing on in this planning phase, the UG-3 phase. Hepatocellular carcinoma,

facioscapulohumeral muscular dystrophy or FSHD, myositis, idiopathic pulmonary fibrosis and systemic sclerosis.

And as mentioned, the goal is to, from these 11 candidate conditions, select six that will go forward, three in each column. All measuring -- all looking at physical function as the target domain.

Next slide? This is an overview of the project. It kind of maps out the sequence of our plan starting with literature review and scoping interviews that will lead to condition reports. That's work that's ongoing as you'll hear in a moment. And then we will, as we -- as you heard all along the way, you get input from the Stakeholder Engagement Group and other advisory entities, including a clinician expert panel and, of course, with E-Tech and we will then do a gap analysis and propose these measures. And if the proposal is acceptable, we would go forward into UH-3 where we will then test and validate for this particular context of use the proposed physical function measures.

Next slide? So getting into some more detail on this, the first part of the project, which we're in the middle of now and in particular the scoping interviews. If we can go to the next slide? We've got the objective of exploring a range of physical function limitations, severity in quality of life impact for the candidate conditions that, as I mentioned, these five rare disorders and six sarcopenic

associated conditions.

And we're going to use that, the findings from the scoping interviews and the literature review, which I'll say about a bit about in a moment, to look at a gap analysis on what might not be covered in what we are provisionally proposing to inform the selection of physical function measures for these six conditions that will be selected from the 11 starting position conditions.

Next slide? Halfway through the scoping interviews. Planning to go to at least 33 interviews, that is three per condition and we've done around, you know, a little more than 15. And you can see here that there's a pretty good representation of men and women and a reasonable representation of non-white folks, but we're always trying to make sure that we have good representation across the socio-economic spectrum.

Next slide? Just to give you an idea looking at one particular question about physical function, “To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries and moving a chair?” With the middle category of response of 3 being moderately, you can see that, you know, so far we're looking at, you know, people that are kind of in the middle range of physical functioning on this this kind of question where the sort of moderately able, which

reflects some degree of impairment or disability, but also, certainly also some functionality.

So that's good because it means that there is room to measure improvement and there's room to measure worsening as we go forward. So this is encouraging to see people, you know, these small groups admittedly being more or less in the middle range.

Next slide? Narrowly, the themes that are coming through on physical function can be classified into five subdomains, if you will. One is mobility. That's getting up and around. Another central axial function, which is, you know, bending and picking things up and, you know, stooping and kneeling down, getting up from the floor for example, instrumental activities of daily living able to go about your usual activities whether that’s shopping, house work, work, work-for-hire, et cetera.

And manual dexterity upper limb, upper extremity function, and then finally facial function, which is a relatively new one for us that we're learning about new conditions like FSH deviance systemic sclerosis; facial function being physical in the sense that it involves being able to control the muscles and movements in your face area, but it's also got obvious important social implications for these patients as well.

Next slide? So for example, in the mobility

subdomain, you can see the kinds of things that are sort of scoring it with most patients and that includes, you know, basic functions like walking, and climbing stairs, and balance and being able to stand, you know, for periods of time.

Next slide? On the dexterity side or upper extremity issues, you see things like gripping, or holding objects, or raising arms above your shoulder to get things that are coming up as salient for people, or things like fine motor function like typing, or pushing buttons, or buttoning clothing, et cetera. Also important in some conditions like, for example, systemic sclerosis. Thank you.

Next slide? And then facial function. As I said, this has been kind of an interesting and new one for us. You know, we're hearing from FSHD patients that this is really very important to them, you know, in terms of managing, and also to some extent the sclerosis patients, being able to move your mouth in the way that you want to in order to speak or to eat, smiling, which, of course, is very important in social situations and just general facial expression control is coming up as quite important.

Next slide? Now moving to literature review. We're in the middle of this process as well and we're identifying and describing the impacts of these different

conditions on physical function and identifying existing PR -- patient-reported outcomes and performance outcomes that are assessing these in these particular conditions so we get sort of a sense of the lay of the land.

Next slide? The purpose of those reviews are to map these key concepts onto particular topics or research areas to identify these concepts specifically and prioritize them by condition and then look for gaps that have been noted in the research. These are -- these kinds of literature reviews, the scoping literature reviews, are particularly useful when a field as complex as this one is certainly to capture physical function across a range of conditions or hasn't been comprehensively reviewed previously. That's certainly true with rare disorders.

Next slide? So to give an example on the sarcopenia side, we have reviewed over 2,000 abstracts and I've included several hundred in the review process. So I have boiled that down and looking at the -- looking closely at the abstracts to a subset of around 70 or so articles that are included, will be included in the formal review.

Next slide? Patients that we've had so far on the advanced cancer side is that frail advanced cancer patients who report that they have lower physical function aren’t actually also demonstrating low physical performance on objective tests. So that's encouraging to us that we have

some agreement there. The agreement's not really strong. Of course, if it was real strong, we wouldn't need to measure both, but the fact that it's moderately high tells us that we're on the right track with both types of measures. At the same time, you probably need both types of measures to get a full picture on physical function.

In Parkinson's disease, clinicians report that sarcopenic patients have increased difficulty with their activities of daily living and osteoarthritis. We see reports that obese patients with OAA display lower grip strength and poor physical performance, gait speed, and poor timed up and go, and sit/stand tests, et cetera. And the COPD patients to report that lung function is assessed often with digital technology and is related to physical function assessments in COPD patients. So again, we get that relationship between the digital health measures and self-report.

Next slide? So the next steps for us are to complete the rare disorders scoping literature reviews and to conduct analysis of the data extracted from the searches, and this will happen in the fall. We're going to integrate the scoping interview results with the literature review and to condition reports, the Level 11 condition reports that we expect to have available in November.

Next slide? And now we've heard a little bit

about this in the previous session about the Stakeholder Engagement Group, so I won't go into much detail here, but it has been a very, very engaged group, very helpful all along the way. In fact, often, a George Greene mentioned, asking if they can be more involved than we've asked them.

So they actually want to engage in activities that we had not necessarily scripted for them in the planning phase and we've been happy to be able to oblige that with the FDA's permission and encouragement. So these convenings have occurred. There have been three during the COVID era and we've learned quite a bit. If I can go to the next slide, we can talk about some of the things.

Well, let's just first look at the people. Sorry. So the -- we have them clustered into four groups. There are four patients and four care partners. George mentioned that in the previous session. Patient advocacy organizations also represented in our group, both Millard and the Alliance for Aging Research. (Indiscernible) Jay and Ryan Carney. The pharmaceutical industry is mentioned and as George said, Kate Benjamin is actually co-chairing the SEG. And finally, we have a healthcare payer representation.

Next slide? (Inaudible) three meetings since COVID hit and in these three meetings, we've accomplished a range of activities that, as I've said, have already been

discussed so we can move forward to the next slide and maybe have this for discussion, if interested.

In terms of the impact of COVID on care partners and patients, we heard quite a bit about that today, but -- and also through the Stakeholder Engagement Group. Healthcare engagement with cancelled appointments, postponed appointments, converting to remote health care visits, completing in-person health care visits when necessary. So for example, cancer chemotherapy or some primary care screening visits sometimes necessary.

In terms of the potential research engagement as George alluded to earlier, we had people tell us that they would participate in-person as long as researchers adhere to strict and comprehensive COVID-19 safety protocols, and remote participation was more welcome typically. Home visits acceptable in some cases and one person who would just prefer not to participate. So we have a range of willingness during this period of our history with the pandemic to participate in the project.

Next slide? So we will fully transition to UH-3 next year and will be able to then conduct mixed methods research including qualitative and quantitative exploring of the responsiveness of the proposed tools, looking at the evidence in support of that, and then the proposed fit for purpose tools by the end of the UH-3 phase.

Next slide? This is a list of the aims that we have tentatively proposed for UH-3 and rather than read through them because the font is awfully small for me to see on the -- under the panel. You can see them for yourself and I'll just say that, you know, basically the point is that we will be testing these self-report measures along with the performance measures in the six defined conditions that are target -- you know, that target people that would be candidates likely to be eligible for expected clinical trials in these six areas, but also with an eye toward the possible generalizability of these physical function measures beyond these six conditions because the whole idea in discussion with FDA is that we could use this process to build generalizable physical function measures that cut across different rare disorders than cut across different chronic and serious health conditions not just sarcopenia and these conditions, but this is a starting point to do that.

We have the advantage -- I haven't talked about it too much now, but we may in the discussion. We have the advantage with both promise and the NIH toolbox to have these banks of questions, that is large sets of questions or tasks, that are tailored to different levels of physical function. So for example, in promise there are 160 physical function questions and so because of that, it may be that

sarcopenia and osteoarthritis picked one set of six or seven questions, but in advanced hepatocellular carcinoma picks a different set and then hip fracture picks another set.

So the questions that get asked can be tailored to the condition and that becomes a generalizable practice that could go forward, you know, for future trials in areas -- in diseases outside the six that go through this UH-3 process.

Next slide? I think that’s it. Thank you very much.

MS. BENT: Great. Thanks so much, Dave. We're going to now move on to our question and answer period. And I will leave it to you to decide who on your team is the best to answer the question. The first question that we have, and it's a mouthful for me, is are you exploring having your core outcomes that focus on the use of a common metric, not necessarily a common measurement tool, to help create flexibility in capturing relevant content across a range of disease severities?

For example, perhaps having several core clinical outcome assessments that are all co-calibrated on a single metric and that the endpoint that would be derived is expressed on a single metric? This is a twist off of what people have been using -- have done using item response theory, item banks, and computerized adaptive testing to allow reasonable and efficient measurement of all patients

with no mild, moderate, or severe symptoms or functional issues, for example, without 20 questions.

DR. CELLA: Yeah. Thanks, Robyn. I think I may be the best person to address that of the people in the group on the call now and, yeah, this is what I alluded to at the end of the presentation there when, you know, when I was talking about being able to select different questions from a large item bank. That's exactly the thinking. You know, we've had discussions with FDA not just in the context of this UG-3 project, but in other in other contexts as well about this being an aspiration that the Agency has for going forward, and yet it has to be done, as I understand, it has to be done in a way that each step along the -- each condition or each setting, you know, is fit for purpose kind of an internal sense.

So we're working toward this generalizability with this project and elsewhere, and that is the goal. Specifically, the way, you know, we're kind of walking before we run. So we're thinking in terms of short forms that would have different -- likely have different questions or content for different conditions and different settings or maybe for different levels of a trait. You know, levels of physical function; very high functioning or low functioning groups of patients.

But over time, we might even move to computerized

adaptive testing where the computer selects the best question, the most informative question. This is particularly popular in clinical practice where clinicians want brevity. They like to be able to ask three or four questions and not 30 questions to be able to pin down where somebody is likely to, you know, to be on a domain-like physical function, and that CAT technology is also available for the motor test used through the NIH toolbox. So was a long way of saying yes to that really well-crafted question.

MS. BENT: Thanks. I think this brings up maybe the -- a bigger question. I think you've spoken to it, but maybe a little -- maybe you can add a little more or somebody on your team can add a little bit more about how this one physical function measure really can be developed across all of the disease areas when you're talking about disease areas where you have facial weakness versus, you know, difficulty with walking. And I know you've kind of talked about it, but if you have anything more that you would like add about that?

DR. CELLA: Well, just that, you know, that's the -- embedded in that question is something that one of our policy board members, Bill Reilly, mentioned yesterday and that is that we're talking here about a metric not a measure in the sense that the metric is this T-score unit from, you know, the mean of 50 is some deviation of 10. The measure

might be a different set of questions or scale, if you will, different set of questions that get asked in one condition or another.

When you raise the FSHD issue though, it does start to get a little bit tricky because we have one physical function item bank, but as anyone on the call on this -- in this meeting can imagine, being able to walk around, or climb stairs, or, you know, be mobile, you know, sort of lower extremity activity, can be quite different from being able to reach and get something out of a of -- off a shelf or being able to do something fine motor with your hands. And in the general population, all these things do tend to track together and so they're calibrated together as one bank, but we may need to branch out and have specific item calibrations, or information, or statistics if you will, on subsets of questions.

In that FSHD example, you know, we’re not -- we can't promise that, forgive the pun, but we can't promise that FSHD physical function will be scored on the same metric as hip fracture physical function, and we have to look at that. When we look at that there are statistical techniques for looking at that, looking at the item function or looking to see if there are differences. So there's work to be done there, but this is a starting point, you know, with some promise so far.

MS. BENT: Thank you. And I think I'm going to ask you a question that we received when -- during the MiCOAS timeframe, but I think it would be interesting to hear your response to it, which is although the focus of this grant is on adults, for the future how can you see this work helping an unmet need in pediatric populations? I mean, obviously, not on the sarcopenia side, but on -- more on the rare disease side.

DR. CELLA: Yeah, I'd like to ask if Sarah Shaunfield or Robert Chapman -- I see that they're on. I don't know if Devin is on. Maybe you'd like to comment because we have discussed that internally and also with FDA and maybe Sarah you'd like to summarize.

MS. SHAUNFIELD: Sure. Thanks Dave. So I think in terms -- we're developing this currently in adult populations, but I think that there's certainly an opportunity and a need particularly in rare disorders to take the measures that we develop or validate into pediatric populations, explore whether or not they're capturing what is important within those different age ranges and then validate seeing them within pediatrics. (Indiscernible.) I think that -- go ahead (indiscernible).

DR. CELLA: Well, the --

MS. BENT: I'd like to -- go ahead, Dave. Sorry. I was just going to expand my question to say that although

not all your disease areas -- your current disease areas tie into pediatrics, many could, and, like, what steps are really needed to include adolescence and others.

DR. CELLA: There are logistical steps for, like, IRB approval and parent consent. Is that -- you know, with patients that are under 18, and generally we find that, you know, with something like physical function, it's safe, if you will, to bring down the age into the teen, you know, the teen years, but when you start getting below age 14, 13, it's risky to be thinking that you could just downward extend a physical function item bank.

There is a pediatric physical function physical activity item bank that we can link. In fact, Bryce Reeve may have done some work in linking the pediatric to adult physical function item bank. So this is work that can be done technically psychometrically if you will, but in terms of the side of, you know, the content being relevant, that's something that for now we have an eye toward and mindful of certainly in the literature review, and quite interested in extending down into children in a developmentally appropriate way in the future.

MS. BENT: And it looks like we're coming up on the 11:15, so I think I'm going to just ask our -- what's going to have to be our final question. And that question is noting that you have both caregivers and patient

representatives on the Stakeholder Engagement Group and also considering that late stage severely affected patients may not be able to respond on their own behalf, do you anticipate that the proposed item bank would include items relevant to both patient-reported outcomes and caregiver reported outcomes?

DR. CELLA: Yeah, that's a good question. We are anticipating that the typical trial will include people that are eligible and able to sort of respond for themselves. Getting their merging proxy input in is quite challenging. We've learned after many failed attempts to simply replace the patient's report with what a proxy says, but in order to do this in a reasonably correct way, we need to get input from both and then if a patient stops being able to speak for himself or herself to use the information when they were both reporting together.

We have not put that into the scope of this particular work, but it is an important consideration particularly with conditions where you expect that during the time window of the trial you will have patients who lose the ability to speak for themselves. I think if we were working in cognitive function as opposed to physical function, we would have been more compelled to address this head-on in the beginning, but we are actually explicitly excluding people whose -- who have cognitive effects of

their disease and that's after actual discussion with FDA on this one.

And I don't know if George -- I don’t know if there's time, but if there is time, if George wants to add something in terms of what he's heard in terms of similar versus different input from patients and stakeholders in the SEG.

MS. BENT: -- 11:16, but if George could respond in one minute, then we would have to be happy to hear his response.

MR. GREENE: Sure. Very briefly, Robyn. So thank you again for the chance to speak and Dave, for the question. From what I've heard in our conversations and our meetings with our Stakeholder Engagement Group is like patients can speak really well about what their own experiences are with physical mobility, and picking up things, and combing their hair, putting jewelry on and all of the things associated with mobility and physical functions, but we're also hearing a different side as well from some of our care partners and a lot of times it has to do with, sort of, the emotional impacts or the toll of what it means to be living with sarcopenia or a sarcopenia-related condition with a rare disorder.

So they talk a lot more about, you know, mental health and how that relates to being able to live on a daily

basis. They talk more about the processes of accessing, and maintaining, and staying in health care. So I think those are some, you know, the different things that we hear about. Patients might be focused on their day-to-day activities, their daily living, but our care partners and caregivers can talk about, sort of -- sort of, fill in, sort of, the larger context of our patients lives. So I think there's benefit in doing both of possible, but understanding the constraints that daily speaking about it is also very important.

MS. BENT: Thanks so much George, and Dave, and Sarah, and the entire NUCOAT team. We are now going to -- I'd now like to invite Dr. Bryce Reeve to -- of Duke University to turn on his video and audio and to talk about the Clinical Outcome Assessment for Acute Pain Therapeutics in Infants and Young Children, COA-APTIC grant.

DR. REEVE: Good morning, everyone. Can you hear me okay?

MS. BENT: We can. Thank you.

DR. REEVE: Thank you so much, Robyn. I appreciate it. So good day everyone. It is wonderful to be able to have this opportunity to chat with you. I will note if you see my head turning away from the camera, it's only because I have vision problems and I have to project the -- our screens up on a larger screen so I can see it and especially my particular presentation is about the size of

-- about two inches across, so forgive me for that.

But thank you again. It's a privilege to be able to talk to you all today about the important work we're doing and, first, I want to recognize that I couldn't do this without the incredible, wonderful, my colleague and good friend, Dr. Kanecia Zimmerman. And you got to hear from Dr. Zimmerman in the earlier session today. She and I are both leading this project, but we're also supported by a wonderful team and I'll show you some of the names and faces later my presentation.

So our particular project is, like all the projects you've heard about today, is dressing a really important scientific gap and that is focused on newborns, infants, and young children. We don't have an ability to identify FDA approved treatments and drugs that either treat or manage acute pain experienced by newborns, infants and young children who may be experiencing pain from either a traumatic event or due to some type of condition or disorder.

And much -- while there are many reasons why we haven't been able to move this area forward, one of the important reasons and why we're here today is that we have challenge in identifying what is a high quality measure of a child's acute pain levels.

Now, there are obviously a number of things you

probably already identified that differentiates our project from the other two projects. Most importantly is while the other projects are focused on adults, we are focused on the newborns and infants. So our particular scope of project goes from birth up to age 3 years of age, which leads to the second important distinction in that while the other two projects, the gold standard is for the adults to self-report for migraines and physical functioning, while we would love to have these infants to be able to self-report on a questionnaire or survey, unfortunately, they won't have the ability at that particular age up to three.

We hope future studies will look at older kids and allow them to self-report, but again we're focused on zero to three so, therefore, the source and focus of where we gather this information is not while the child is obviously expressing their pain, we will be relying on surveys and questionnaires for which either the parent, or caregiver, or a clinician might complete that evaluates that child's acute pain levels.

So our project is called COA-APTIC, which stands for Clinical Outcome Assessments for Acute Pain and Therapeutics in Infants and Young Children.

Next slide, please? So this is the brief outline, an agenda for today. So I will give you a, a sort of an overall goal for a particular project. I will give you

updates on where we are in our current aims and our methods we're applying to address these important areas. I'll talk very briefly about summation plan as well as the importance of having stakeholder engagement, and then I'll talk about the next steps.

Next slide, please? So our overall goal is to develop or identify existing high-quality clinical outcome assessments. So basically that's a fancy word that says that, you know, these are surveys and questionnaires to which the parent or clinician might fill out as well as how these measures are used as endpoints in clinical trials to evaluate acute pain and other related outcomes for pain therapeutics in infants and young children.

Next slide, please? We have three broad aims of our project. The first two are in what is, you've heard Robyn and others discuss as, sort of, our planning phase, the UG-3 phase and then the last one is in our implementation stage, the UA-3 phase. And importantly, in this first UG-3 phase, what we're hoping to do using a number of methods I'll talk about in a moment, is identify how acute pain and other related are key outcomes in particular studies, what have been to date the existing measures to use to evaluate acute pain related outcomes in these trials as well as how these measures, outcomes are used as endpoints in trials to evaluate whether a drug

treatment or medication is effective and safe.

Following those two aims, our implementation stage is to identify where there are knowledge gaps and then user implementation stage to either, again, develop new med tools or use existing tools and adapt those, and make sure we have all the evidence necessary to make sure that we are in agreement about what should be these outcomes in the space, what should be the measures, as well as what should be the endpoints.

And we're not just doing this alone, but we have the help and support from a broad research team as well as an excellent external Technical Advisory Committee who I'll talk about in a moment.

Next slide, please? So this is a busy diagram, so I won't spend too long on it. Especially, I know that probably for you all as well, it's a hard to read that small font, but I'll just say the main point here is that we are spending two years in our planning phase to make sure we have everything in line to make sure we have an ability to be able to inform our decisions about what will be the measures, outcomes, and endpoints and then use the last three years in our second phase, if we get approved, of course, to go again generate that evidence necessary to make those final decisions about, again, what are the appropriate measures recognizing that we might not have a single

solution, a single measure, that is the same from a newborn who was just born versus someone, a child, who might be two or three years of age. But again, this -- time will tell.

Next slide, please? So I'd like to talk a little bit about sort of our sort of three-pronged approach to help us think about, again, identifying outcomes, endpoints, and measures that are used in trials with infants and young children to assess key pain. And so we're tackling this and getting input in three different ways, at least three different ways.

One is through an external technical advisory committee, second is through a systematic literature review, and the third is through what we call concept (indiscernible). These are in-depth interviews with key stakeholders and my plan is to go through each of those and tell you what our goal is and then where we are currently in this particular project.

Next slide, please? So let's first talk about our awesome external Technical Advisory Committee. And you'll see both their pictures, names and their areas of specialty listed on the slide here. Let's start with those where there are stars because these people are stars for so many reasons. Most importantly, they represent the patient perspective because these are parents of children who have experienced acute pain for a variety of reasons or have

connections to a much larger network of patients and parent advocates as well.

And so these include the awesome and wonderful Ms. Sharon Brown, who you got to hear on the earlier session. So thank you Ms. Brown for your input today and, again, you've been just an incredible help for our particular project. There's Cheryl Siakdia (phonetic) and I apologize if I butchered the last name. Megan Pasco, Amy Ohmer, as well as Liana West.

In addition to our patient advocates, again, who represent almost half of our external Technical Advisory Committee, we have other experts as well in different areas. We have our own Robyn Bent. Thank you for representing the FDA in a regulatory perspective. We have Ernest Kopecki (phonetic) who represents the industry perspective on -- in assessing pain in infants and young children.

Over on the right side at Frank Rockhold, who is just sort of an internationally recognized expert in clinical trials, is a biostatistician. We have Bonnie Stevens and David Warren. These are people who actually are treating kids and assessing their pain and trying to treat their pain. So having their valuable clinical instant perspective is very important when we have Gary Wilco (phonetic) who is a, sort of, at least to academic perspective, and again is an internationally recognized

expert in assessing pain. All these people provide rich expertise and perspective overall.

Next slide, please? One of the important things we wanted to do with our external Technical Advisor Committee and, again, is that we wanted to recognize that this, you know, ideally a five-year initiative where we're going to rely on them to help give us feedback, is that we wanted to make sure everyone, sort of -- is on a sort of level playing field in terms of understanding all the different aspects and components of, sort of, a multidisciplinary or transdisciplinary approach to how we think about identifying measures, outcomes, and endpoints for acute pain.

So each person represents a different perspective and expertise, and so part of our earlier work just before the CVOID shutdown is we had everyone come together in Durham, North Carolina, and each person was asked to share their own perspective and expertise. And so, obviously, for the parents, we had them talk about their own experiences with their children and their perceptions of that child.

We had experts talk about infant and toddler development. We had discussions about how we develop and evaluate surveys and questionnaires, in particular focused on some of what has already been done in infants and young children as well as looking at regulatory and industry

perceptions about therapeutic agents in -- for acute pain in infants and young children.

Next slide, please. Second part of what we were looking at is we wanted to do a systematic literature review. An importance of doing a literature review is, obviously, we don't want to reinvent the wheel, so we wanted to leverage all the great work that's been done to date and so we basically conducted a large literature review.

Next slide, please. And as part of our literature review, we wanted to look at the sort of a combination of three areas to help identify appropriate literature that would inform all of our decisions moving forward. So we were looking at the intersection course of pain or painful events, procedures, and conditions. We were looking at tools of pain, how the assess or measure pain and, of course, limited to children between zero and three years age.

And we have narrowed our search, and I laugh when I say “narrow,” and you'll why in a moment, to all published literature 1980 or beyond and we used various types of databases to conduct our search.

Next slide. So this gives us the progress of our literature review, and here's our surprising number. Is using our -- using even a librarian to help us out, we've identified over 16,000 articles that might be relevant to

our targeted research and we have wonderful research assistants and associates led by Courtney Mann, who will, you might see later, and through that we've been able to narrow that down to a modest 4,500 articles that we need to pull out and view full text screen. So as you can imagine, we're still in the process of reviewing those and again, that would be very helpful for making (indiscernible).

Next slide, please. And so part of what we do once we identify our subset of articles we want to review, we're going to extract some key information. These are just part of the information we want to extract. Obviously, information about the study themselves, including, like, sample sizes, the type of population, their demographics, whether this study was an observational or clinical trial, what was the study intervention and when did they collect data points.

And then, again, most importantly for our project there is what were the outcomes that they assessment study and, of course, pain will be one them, but what measures they use and how was that used in the context of their endpoint as well as other adverse event data that was collected.

Next slide, please. And then the third aspect of what we are looking for. So we talked about the E-Tech input. We talked about the literature review. Now our

third phase of what we're also doing in this planning phase and this is an important here, is the literature review while (indiscernible) what's been done in the past, we want to look --

(Audio interruption.)

DR. REEVE: -- is how it's experienced and how it's assessed.

So what we're proposing -- what we are currently doing this phase is we're conducting in-depth interviews called constant solicitation interviews with key stakeholders. And so these are one our phone-based interviews and these are interviews both with clinicians as well as with parents. And for clinicians, we hope to interview up to 27 clinicians. These include pediatric physicians, pharmacists, nurse practitioners, et cetera.

For caregivers and parents of children, we hope to interview at least up to 40 to parents and caregivers and these are parents of caregivers, again, in for a child between zero and three who their child who experiences acute pain whether it's from a malignant or non-malignant visceral or hematologic disease, or pain from a surgery or some other type of procedure, pain from a trauma or injury, or pain because of a congenital condition as well.

Next slide, please. When we conduct our interview with our clinicians, we're going to ask them a range of

topics to discuss. Some of those include their own approach to how they evaluate pain in children. How is pain typically expressed in newborns, infants, and young children, how pain expression may or may not be different from other types of distress like fear and anxiety. How do they know when and what types of interventions they use to relieve that pain, what surveys or questionnaires they like to use, and what are strengths and limits of current measures, as well as other additional concepts like the aseditive (phonetic) effect of pain itself.

We hope to, in our discussion with clinicians, to make sure that they're -- we're differentiating how pain may be expressed and measured from -- in different age groups from zero to two months, two months of one year, and one year to three years.

Next slide? When we do our interviews with our caregivers and our parents, we're going to ask them a lot of important questions as well, including having the parent talk about their own child's medical history and how their child has experience and expressed pain. We're going to ask the parents how they’re able to differentiate pain expression from other types of stress like anxiety and fear. How did they know or how does a parent respond to the child's pain expressions and when do they know whether it's just a comforting love and hug versus taking that child to

the doctor?

We're wondering if a parent has ever been recommended to use some type of survey questionnaire. We'll get their impact -- perspective on that, excuse me, as well as related concepts. We are purposely stratifying our interviews of parents. The reason why we have so many interviews of parents is because we want to make sure that we're not missing anything from a newborn all the way up to three years.

So we are purposely stratifying are interviewing parents for children between zero and two, two to six months, and so you can see all these different aspects. And again, we want to make sure that we completely have a full story from birth to three years, how pain expression and measurement may vary across that age -- that short age span.

Next slide. If you want any information about our study, we disseminate our information through our website and this is the website address you see on the screen.

Next slide? If you want to hear some of our cross-trainings we talked about, we recorded all those and, again, made those available through our website.

Next slide. Stakeholder engagement is incredibly important to us for a number of reasons. Of course, we're incorporating different stakeholders through our E-Tech and through our own team, but we also want to make sure, because

we know there are so many other research networks out in the North America and globally that we want to connect with and so we are actively working with our NIH partners within our particular project.

We're also trying to recognize that there are a number of organizations and consortiums that have been leading in this particular area, and that includes both the Impact Group as well as the Action Group.

Next slide. So for us moving forward in our planning phase, in the earlier parts of 2021, we hope to finish our interviews as well as our literature review and then bring that to our external Technical Advisory Committee for feedback.

Next slide. Towards the end of our planning, two-year planning phase, we will be able to provide to our team and to the FDA, you know, the type of measures, clinical outcome measures, we've identified for all of the particular outcomes we're including our study. We hope to evaluate what's been done to date in terms of these surveys and questionnaires and then develop plans and protocols for our implementation stage, the UH-2 phase.

Next slide. In our UH-3 phase, again our goal is that we will -- where there are knowledge gaps, we will fill those knowledge gaps by conducting both qualitative and quantitative research as necessary, again, to make sure by

the end of our full project period, if were funded for that phase there, to make sure that we are delivering to the research field a core set of measures, outcomes, and endpoints to help move this bill forward.

And then my last slide. Next slide? I want to recognize more of our team members, and these people will be available for the called answered questions. And so again, I am very honored to have these people to work along them, and Dr. Zimmerman, again, is my co-PI, but we're also joined today by Christy Ziegler, Katie Gustafson, Courtney Mann, and Emily Forgey, and they promise to help me answer all your good questions. Thank you.

MS. BENT: Thanks so much, Bryce. That was a really -- that was a really great presentation and I really appreciate it. I always enjoy how you're able to really discuss complex topics, but in a way that is really understandable to those of us who are not psychometricians. So I do -- I thank you very much for that.

Moving on to our question and answer session, the first question that we have is that digital technology for pain measurement in pediatric studies. What is the role for potential digital technologies to measure pain in infants and young children?

MR. REEVE: -- question and so I will also ask either Kanecia Zimmerman, Courtney Mann, or Katie as well to

put their video or voice on as they think about these things. I'll start, but I would welcome any other thought. In terms of digital measures, you know, I think it's important because I think that can be defined and interpreted different ways, and so maybe Robyn you have your own interpretation of what that question's asking about there.

You know, many -- and Kanecia Zimmer, who is my co-PI, is actually a critical care doc and works in these populations and so she can talk about her use of these particular modes. My guess is many of these measures that are used are easily used by clinicians who might use paper questionnaires and these are, you know, filling out something like the FLACC or something like that, and I think having something that's easily accessible and circle on a paper would be easy.

Digital assessments, I think could be something, especially as COVID-19 stage, where, you know, where if there's some reluctance to have a parent come in to the clinic and so, you know, anything that can be done sort of remotely, and that, "remotely" means electronically, that we can help, you know, move these sort paper questionnaires to electronic platform and the parent is able to fill these out and send that in to the doctor, I think might actually be a good application of digital technology, but I'll stop there.

I don't know if any of my colleagues has any further thoughts.

MS. ZIMMERMAN: My thoughts are consistent with yours with regard to the role of digital technologies here.

MR. REEVE: Yeah? Okay. Great.

MS. MANN: So this is Courtney. Sorry, it’s pitch black in my video, but I thought that one of the things that we can talk about in terms of like digital technologies in general might also touch on a couple of the other questions in much as thinking about, sort of, how we're seeing pain measured via the lit review.

One of the things that is pretty common to see in this age range is looking at physiological parameters, and so there's already, you know, depending on how you're defining digital technologies, we’re already seeing that some of the data that is collected is coming from a digital technology. So it's coming from like a pulse oximeter because we're looking at O2 saturation and things like that.

So in addition to, sort of, like, where our data is coming from, which may be a digital technology, I think there's also room for digital technologies in how we collect additional data from clinicians, and parents, or kids these age, if we're talking about looking at scales.

But, you know, I think it would be really interesting at some point depending on what's out there

because I don't know everything about what's out there right now, if there were, you know, for example, like a wireless pulse oximeter that someone could use that would automatically transmit the data to medical record or research database. But those are just things that I think about that would be pretty interesting and helpful in collecting even more data.

MS. GUSTAFSON: And I would add too, the potential for perhaps even looking at infant facial grimacing and some of those other variables that are looked at now by a rater could be perhaps read digitally with some type of a camera.

MS. BENT: Thank you so much. This maybe kind of ties in loosely to what you guys were just talking about, which is what do you anticipate to find in your literature research in terms of the frequency in acceptance of caregiver versus clinician assessments in the pediatric assessment population, and do expect there to be more caregiver or clinician COA?

MS. MANN: That’s probably a me question. I don't have a really good answer for that question at this point. What I can tell you is that, you know, for the age range that we're looking at, which is birth to less than three years old, we are seeing a lot of clinician report, a lot of nurse report, or I guess physician and nurse, their both clinicians, and also a parent report information. So we're

seeing all three.

We're not necessarily far enough into extracting data to know if one is more acceptable than the other, but we are looking at a lot of studies that do look at physiological parameters that come from monitors that look at behavior, which touches on what Katie was mentioning with facial expression, duration of cry, and also, you know, scales are included and a lot of those scales will be either like a 10-point rating system or a clinician completing a VAS or, you know, something like the Premature Infant Pain Profile that actually looks at physiological parameters and behavior and combines them into a score.

And when we are looking at, sort of, what we are considering acute pain therapeutics, we're including pharmacological interventions and also things like sweet solutions and behavioral interventions, which might include something like swaddling or specific ways of, you know, parental interaction with their kids. And so there are there are plenty of studies that we are looking at that are involving parental soothing behaviors and parental ratings.

I don't know in the end, based on the lit review specifically, which one we'll find is generally more acceptable right now, but I do think that it's important that when we're thinking about like holistic measurement, that we're thinking about multiple perspectives when we're

rating pain for a kid.

MR. REEVE: That's a wonderful answer. Thank you, Courtney. The last -- it’s hard to add onto the wonderful comments Courtney just made. I think in many ways this is a very heterogeneous field and at the end of day, we know we're going to need both clinician perspective and parent perspectives and they won't necessarily be hundred percent correlated. They’ll be related, but they provide different perspectives. A lot of it is going to -- you know, at the end of the day when you talk about trials moving forward, it’s going to depend on where that child is. Of course, if that child is that the home, obviously, the parent’s surveyed question on the child's pain will be the prime and be a valuable assessment and that's why we need to make sure we have good caregiver-reported measures.

If that child's in a hospital or acute care setting, you know, having the clinicians have an ability to assess that pain, you know, right there immediately, I think will be important and if that parent’s there, but that sometimes parent might not be there depending on, again, what the contents of where that child is in terms of just getting out with surgery or things like that. So having both will be important and valuable for our group and (indiscernible).

MS. BENT: Thank you all. It looks like it is

11:15. So I think we're going to have to end this portion of the presentation now, but I do want to thank the entire COA-OPTIC team for coming out and kind of talking to us about the project and answering our questions. It was a really -- it was a really great presentation.

At this time. I'd like to invite our panelists for the next session to turn on their video and audio to talk about CDER Standard Core Sets Clinical Outcome Assessments and Endpoint pilot grant program's new funding opportunity. On July 9th, FDA posted a funding opportunity announcement for our new round of grants for this grant program. Grant applications are due on October 14.

FDA is particularly interested in applications focusing on the following areas of development for the Standard Core Set: fluid volume/fluid overload and nephrotic syndrome, age-appropriate domains of pediatric daily functioning, the mechanics of swallowing and speech from infancy to adulthood, and treatment response in systemic sclerosis.

And we're lucky today to be joined by several members of the FDA staff who helped -- who have helped -- are helping and have helped support this program. I'm going to provide a brief introduction of our panelists and please note that at the end of the panel, we're going to have time for questions.

So our panelists are Patroula Smpokou from the Division of Rare Disease and Medical Genetics in the Office of New Drugs at CDER; Raj Nair, Division of Rheumatology and Transplant Medicine in the Office of New Drugs in CDER; Laura Lee Johnson from the Office of Biostatistics here at CDER; and Elektra Papadopoulos from the Division of Clinical Outcome Assessment's Office of New Drugs here at CDER.

And in case you haven't heard enough from me already today, I will be representing my colleagues from the Division of Cardiology and Nephrology. They send their regret, but unfortunately we inadvertently scheduled this session at the same time as an externally led patient-focused drug development meeting for focal segmental glomerulosclerosis or FSGS, which is one important cause of the nephrotic syndrome.

So the team is attending that meeting hearing directly from patients including pediatric patients and adults about the symptoms that matter to them. And really, they propose the development of the Standard Core Set of Clinical Outcome Assessments and Endpoints to assess volume or fluid overload hypervolemia and related impact specifically for use in nephrotic syndrome trials because the development of these sets will ensure that the outcomes that matter to patients are incorporated into drug development in the fields.

But now we're going to hear from Patroula, who will talk to us a little bit about two of our priority areas; the age-appropriate domains of pediatric daily functioning and the mechanics of swallowing and speech from infancy to adulthood. Patroula, can you tell us a little bit about these areas, why FDA thinks that they're beneficial to develop standard core sets in?

MS. SMPOKOU: Sure. Do you hear me --

MS. BENT: Thanks, so much.

MS. SMPOKOU: -- and see me okay?

MS. BENT: Yes, thank you.

MS. SMPOKOU: Great. So thank you, Robyn. My name is Patroula Smpokou. I currently serve as the Acting Deputy Division Director in the Division of Rare Diseases and Medical Genetics in the Office of New Drugs at CDER and I’m really very fortunate to be part of this panel and really give our perspective into why these core sets of COAS and endpoints are important.

So we all know that many of the rare diseases are serious and severely debilitating and many life-threatening. There's really a tremendous knowledge gap in many of those and especially in the area of how best to evaluate clinical benefit and clinical trials. So FDA's in our division, obviously, is very interested in gaining a better understanding of what really matters to patients in terms of

filling in the gaps and meeting unmet needs.

So we are very interested in helping external stakeholders really gain valuable information to develop really some core sets of Clinical Outcome Assessments and Endpoints. You know, why is this important? Because we want to have, of course, a good knowledge base. We don't have methodologically sound and scientifically robust endpoints in Clinical Outcome Assessments. They want to have consistency in using those tools among drug development programs and, of course, want to facilitate this drug development and really push it forward because we know that many of the patients with rare diseases, particularly pediatric patients with rare diseases, have tremendous (indiscernible) that needs new therapies.

The two areas that we have heard are important and we have identified as two areas that have a very high knowledge -- the outcome have to do with daily function in children with rare diseases, and particularly those who are -- which are serious and life-shortening. We are very interested in having Clinical Outcome Assessments and Endpoints that really reflect what those children are able or not able to do in their daily lives.

We know that there's different skills that assess activities of daily living in adults with various diseases. From our perspective, what we hear and what we know is that

there's really no good standardized way to assess those. And even there is no good knowledge of what those domains should be and how those may need to be modified according to the age of the child because, of course, we know that developmental age of the child and their abilities developmentally vary significantly as they get older.

So since there's just such an unmet need in pediatric rare diseases, we feel like having a really a core set that is methodologically sound, scientifically robust, consistent with high psychometric properties would be really critical to really assess what patients, but also their families, think are important to impact with new drugs.

So what are those aspects of daily function? For example, motor function, or speech, or simple things like getting around in the house being able to feed themselves independently and others. So what are those, first of all, and how can we best assess those within the constraints of the clinical trial?

The second area has to do with specifically neurodegenerative and progressive neuromuscular rare diseases. Those again are serious and severely debilitating and there's great unmet need for new therapeutics, but there's also a big knowledge gap in assessing specific areas of function. Those have to do with speech and swallowing.

I have to give credit to one of our experienced

medical officers in our Division, Dr. Dean Mezanno (phonetic) has a lot of clinical experience and regulatory experience in this area in many of our programs. So of particular interest is gaining knowledge and collecting data on what is currently available in terms of assessing swallowing, what tools are out there, how are they being used, what are their psychometric properties, what are their limitations.

The example here is video fluoroscopy, which is currently considerably the gold standard in assessing swallowing in clinical practice. This specific tool is widely used. That's part of the clinical care though, and what we have found in our regulatory experience is that there's many limitations to that when it comes to using it in clinical trials.

So the swallowing piece especially in patients with progressive neuromuscular disease so important because, of course, if somebody loses the ability to swallow either liquids or solids, they're at great risk of aspiration, which is life-threatening, but also it affects their ability to independently feed themselves and to grow well. So that's an area that's critically important to assess and potentially modify or develop new tools to assess that in clinical trials.

And the second piece is really the speech, which

is also impacted in these disorders and really patients are slowly just unable to communicate and, of course, that's very critically important to patients and their families as well. So in terms of the speech, again, what is currently available, what tools are out there, can those be used but first characterize and assess how can we use them or modify them to assess different motor aspects of speech and how can we use those best to assess that as a potential endpoint in clinical trials? So I'll stop there. I'll be happy to take questions later and thank you for the opportunity.

MS. BENT: Thanks so much, Patroula. I think what you're speaking to really kind of helped to set the stage for kind of the complexity of developing these as they as they cross multiple disease areas, but also really the potential rewards that we would see from being able to do that.

Now, I'm going to move on to Raj Nair, who is going to talk to us briefly about systemic sclerosis and why FDA believes that there's a benefit to developing a Standard Core Outcome Set in this area. Raj?

MR. NAIR: My name is Raj Nair. I'm a rheumatologist and I serve as acting team leader in the Division of Rheumatology and Transplant Medicine at FDA. Systemic sclerosis is a chronic multi-system disorder that targets several different tissues with the prevalence of up

to 340 cases per million people. It's well known for the visible and symptomatic thickened and hardened skin that occur in patients. It's further characterized by clinical findings and supported by serologic abnormalities.

There is growing interest in developing treatments for systemic sclerosis, but there are challenges to developing measures to assess the activity of treatment for scleroderma. Systemic sclerosis is a heterogeneous disease as manifested by the varying range of organ involvement disease severity and outcomes. These remarkable differences in patients make the use of one measurement impossible for tracking the effect of the treatment on scleroderma activity.

While there are several measurements available for systemic sclerosis, it's still a benefit to continue to develop instruments that we have and create new ones as we learn more about how systemic sclerosis behaves. As such, it's important to incorporate the patient perspective on the features of scleroderma that most concern the patient.

By incorporating the feedback from patients as to which features of systemic sclerosis are most important to improve, we can develop core set measures with significant patient input to ensure that what matters to patients is measured in clinical trials. We appreciate your enthusiasm and moving the study of systemic sclerosis forward and

involving patients in the development of additional instruments to measure the activity of systemic sclerosis.

MS. BENT: -- so much. That was really, I think, very informative. Before we move on to questions, we're going to hear from Laura Lee Johnson, who is going to talk a little bit more about the funding opportunity announcement, and then we'll finish up with Elektra Papadopoulos, see if she has anything that she would also like to add. Laura Lee?

MS. JOHNSON: Hi. I thank you, Robyn. And so we spoke about COVID a little bit this morning and another major impact on many lives that are the ongoing struggles that have been mentioned, but many of them were highlighted with protests against incidents of police brutality and racially-motivated violence against blacks. The Black Lives Matter is not new and neither is racism in the history of the lack of diversity in research.

So part of what FDA's patient-focused drug development has focused on early, and as part of our current RFA language, is collecting comprehensive and representative input. We publish final guidance on this topic in June and the RFA, the grant's principal investigators, have the responsibility for developing and implementing a methodologically sound plan to collect comprehensive and representative patient input on what matters most to

patients and identifying important impacts and concepts from patients to develop or modify potential study instruments.

Another important point to look at in this FOA or this RFA is that the product, whether they are de novo or modified Clinical Outcome Assessments and the additional Clinical Outcome Assessment supported evidence that generated through the different grant phases, it should be currently or will be publicly available at the end of the grant period in the public domain at nominal or no cost.

So we're frequently asked, "What does 'nominal' mean?" And so as many people have found out, internet access not free, neither is storage cost. And so we want these (indiscernible) to remain relevant because they're needed.

Many think about the large companies when they think about research coming to the FDA, but a lot of times there are many other smaller organizations, and part of our goals is that people in a group can afford to use these clinical outcomes core sets and that includes non-profits, academics, small one-drug companies and industry. But part of this is that we do need also that these steps are going to be available.

(Inaudible) and that I wanted to point out for you all is some good news from CDRH. And so if you were on the -- here for the morning panel, our colleague Michelle Tarver

mentioned a little bit about what the Center for Devices and Radiologic Health have been doing.

We also, in accordance with FDA's medical device user fee program commitment, CDRH agencies today posted draft guidance entitled Principles for Selecting, Developing, Modifying and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation. So CDRH plans to discuss that document during their upcoming PRO workshop on September 30th. You can find more information on that online and the FDA social media link.

I guess a few other things that may have come up are, you know, there are four topics that are outlined in the RFA that you heard about earlier in the session and those topics are the ones that we are the most interested in funding. So it's not that they're considered non-responsive otherwise, but these are the topics that we'd like to focus on and it's important to read through the entire funding opportunity announcement. Many times a lot of the information is there, but there is a structured format for these to go through and look at.

A few people earlier mentioned proxies and I think Bryce Reeve mentioned some of those weaknesses and typically, and my colleague Elektra Papadopoulos may want to talk about this a little bit more or not, one thing that for regulatory use, FDA typically says no proxies. However, it

is important to think about and focus on what is it, for example, that an observer can observe? What is it that the patient directly can tell you? So we have more information on that and our best guidelines, best glossary, that defines kind of how FDA and also NIH look at many of these words and what we mean when we're using them.

An important element also at the RFA is that we don't stop at the Clinical Outcome Assessment tool. It actually goes all the way to endpoint, and so how you're going to actually bring together this data in clinical trials are also in actual history studies and other types of data that FDA may be looking at is very important.

Also thinking about the global regulatory environment in other areas is important because it's important to us that patients don't have extreme burden as they're trying to answer and have any data collection done.

So hopefully this answers some of the additional technical questions you may have. There is contact information at the end of the RFA that's posted online and for those of you who submitted a Letter of Intent for the RFA, we'll be scheduling a technical assistance call in the coming weeks.

Robyn, I'm turning this back over to you. Thank you.

MS. BENT: Great. Thank you so much, Laura Lee.

And now, Elektra, you've been very involved in the ongoing grant program as well as the development of the current funding opportunity announcement and have been listening as our other panelists spoke. Is there anything that you would like to add to what we have heard here today? Any points that you want to emphasize before we move on to questions from the audience?

MS. PAPADOPOLOUS: Thank you. So I think Laura Lee has really nicely summarized a lot of the key points and I think one thing that has been very powerful throughout this experience is the opportunity for the different grantees to learn from each other's experiences through our meetings, we had meetings yesterday as well as today, because there are a lot of common experiences that are shared that that could really be used to advance their work.

So I guess an example is, you know, the challenges around doing trials and children and trying to address diverse age ranges, and we heard, you know, with assessment of acute pain how the team had to focus on very narrow age bands within that, you know, newborn -- the newborn range up until three, the age of three, and this is a challenge that's, you know, also going to be faced when developing the tools for, you know, for the -- a lot of the rare diseases that impact children.

So I think that that was one of the important key

points that I took away and just also emphasizing what Laura Lee mentioned about multinational trials and being able to have measures that can be not only linguistically translated for use across language groups, but also thinking about cultural differences both around the world and also even within our borders. There are multiple cultures that we also need to consider. So those are just a few points that, you know, I thought -- I took away from the couple of days.

MS. BENT: Thanks so much, Elektra. So it doesn't look like we have any questions right now related to the funding opportunity announcement, but I might just because we have a little bit of time, kind of circle back to a question that came in earlier in the day that we didn't have a chance to get to and I'm pretty much going to take advantage of some of the expertise that we have on the current panel to ask this question and I'm going to ask Laura Lee to start out with the response.

Could you provide guidance whether the change in administration mode needs to be in the ECRF or just the source document? Should additional analyses be performed separately for the PRO data using different modes such as self-administered versus interviewer administered? Thank you.

MS. JOHNSON: Hi, Robyn. Okay. Let's see. So the first question I would have if I was asked this is why

is -- why are you switching to an interviewer-administered PRO and exactly how are you going to administer this? So there are a lot of different interviewer methods and a lot of methodologies that will say that, you know, if people have copy of that PRO in front of them, for example, and it's read exactly to them on the phone, you may not have as much of an issue with how people are responding.

But there are also many times that people are trying to be pleasing. So as I see people in front of me on video, I'm, you know, I'm going to be perhaps a little more worried about their reactions to my answers to them. So there's a lot of variation you're talking about interviewer versus non-interviewer methods.

Now, if the mode of administration was saying you're getting a patient-reported outcome on paper, so a list of questions and responses that you're marking off with a pen and now I'm going to have you do it on a computer or some other electronic method, but that's still self-administered and that's usually not that much of a concern.

So again, it's going to depend exactly on the methodology that's used. So Question 13 of the FDA trial conduct guidance under COVID and also some of our public meeting materials from our Patient-focused Drug Development Guidance 3 meeting that we had October of 2018 has some more information about changes and mode of administration because

a lot of them we don't worry about, but some of them we do.

And I would say, and Elektra may have a little bit more on this, but I would -- especially, if you're moving from self-administered to interviewer administered, it’s wise to perform an analysis to check the potential impact of that change in mode if you're making that change and then again is also in line with the type of information that we have on our COVID-13 guidance because a switch midstream in a protocol for anything is something you want to keep an eye on.

Now, it doesn't need to just be on a source document. As a statistician, if I don't have the data in my data set, it doesn't exist. So this information needs to be on your ECRF. So on that case report form and it also needs to be in the FETM and out-of-data sets for those of y'all who know what those are. But this information needs to show up in the data sets. What mode was used? You need to have a note somewhere of why that change happened and there should be some additional analyses done to make sure that things are reasonable.

And it might be hard to tease out in this case, that change of mode of administration plus all the other environmental contexts around, but again, this is the type of information that you need in order to be able to best interpret your studies at the end of the day. I don't know

if Elektra wants to add onto this or anybody else who's on our panel.

MS. PAPADOPOULOS: Actually, don't have anything to add. I thought that was a really great answer.

MS. BENT: Excellent, excellent. So apparently you guys did an amazing job of explaining everything. We have no questions from the audience coming in. So I guess with that being said, I think that there is a possibility that we can end the meeting early. Before I do that, is there anything that anybody else on the panel would like to add about anything that you've heard here today or specific to anything about the funding opportunity announcement?

MS. JOHNSON: Hi, Robyn. I'd like to thank you for all the work that you and your team has done both for this funding opportunity and for this grant program. Y'all have done great leadership, so thank you and thanks to all my OMD colleagues also and, you know, everybody here and on the other panels and in the other centers. You know, the grantees. You all have done great. Everybody participating in this research, you're doing wonderful job, but it does take a lot of work, so thank you.

MS. BENT: Thanks, Laura Lee. And just kind of building on that, I would also like to extend a big thank you to our panelists for taking the time to be here today and to share your thoughts about of the funding opportunity

announcement and my thanks everybody for listening to us today.

As a reminder, you can continue to share your thoughts to our docket through October 28th, so please consider submitting your comments. There are links to both the docket and to our grantee website on the FDA meeting announcement and, of course, as always, we will work to make our meeting materials available to you.

Moving on to my closing, I would like to just thank everyone who participated in the meeting today, especially our panelists and presenters and particularly our panelists and presenters who were not located on the east coast and who logged in at 5:00 a.m. their time to ensure that they didn't have any technical difficulties before the meeting started.

I'd like to thank all the members of our grantee teams, especially the patients who are working so hard to make these projects successful. I'd like to thank the FDA reviewers who have seen significant increases in their workloads in the past few months and are still remaining committed to these grants and to the grant program as a whole.

And most of all, I'd like to thank you, our stakeholders, who are watching today. Your questions and comments will make our projects stronger. And finally, I

really want to thank my staff who has worked tirelessly to help us get this meeting up and running. This is our office's first virtual meeting and it has it has taken more than we anticipated, but we hope that it was valuable to you today and when we thank you for watching.

Thank you so much. Have a wonderful rest of your day and have a great weekend. Stay safe.

(Whereupon, at 12:15 p.m. the meeting concluded.)

CERTIFICATE OF NOTARY

I, CHRIS HOFER, Notary Public, before whom the foregoing testimony was taken, do hereby certify that the witness was duly sworn by me; that said testimony is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of the action; and that the testimony was reduced to typewriting by me or under my direction.

This certification is expressly withdrawn upon the disassembly or photocopying of the foregoing transcript, including exhibits, unless disassembly or photocopying is done under the auspices of Hunt Reporting Company, and the signature and original seal is attached thereto.

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My Commission Expires: _____

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