

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 PAPADOPOULOS, Division of Clinical
Assessment and the Office of New Drugs
KANEZIA 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 measured drug development.

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

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

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

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

1 should be recorded in a clinical trial.

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

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

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

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

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

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

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

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

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

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

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

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

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

25 And finally, because we realize that many of the

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

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

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

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

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

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

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

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

1 Lessons of COVID-19.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 project, but is certainly related to COVID. Thanks.

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

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

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

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

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

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

7 MS. BENT: Thank you.

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

11 MS. BENT: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 MS. BROWN: (Inaudible) everyone.

23 MS. BENT: Good morning.

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

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

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

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

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

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

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

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

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

1 would be taking from there, right?

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

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

9 MS. BENT: Good morning.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 protect us at all levels and -- pardon me. Lung disease.

2 As Sharon was saying, like, we get the chance to contribute
3 and, like, make sure that we're speaking up for people.

4 Like, COVID-19 has bring so much havoc in our world and
5 within all of this, you know, I'm choosing to try to control
6 the things that I can control. So I stay connected with my
7 family, my close friends. I do only things that I love and
8 that bring me joy because I can't control anything else.

9 This I can, and it's super empowering. And I use my voice
10 to amplify for the voice of the people like myself that were
11 often ignored or, like, dismissed. I'm here. We're here.
12 We all have value and I'm just, like, steadily praying for
13 all of us, and that outside is open again next year safely
14 and that we could just all continue forward. So I'm sending
15 everybody good luck and thank you so much for this
16 opportunity.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 question?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 would like to add to what Michelle has said?

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

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

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

25 MS. BENT: Does anybody else have anything they

1 would like to add before we move on? Okay. Oh, go ahead.

2 Sorry, Elektra. Go.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 MS. BENT: They are, yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 people used what things.

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

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. LIPTON: Sure. So --

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

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

18 One of the things that surprised me a little bit
19 is how much variability there is from study to study. So
20 take a construct like pain. Well, do you measure pain on a
21 0 to 3 scale? Do you measure pain on visual analog scale?
22 Do you measure pain at one hour, at two hours? Do you
23 measure area under the pain time curve? There is so much
24 heterogeneity in the way a simple construct like pain is
25 measured and the measurement choices that have been made

1 today really have been disconnected from the patient voice.

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

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

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

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

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

14 MR. MCGINLEY: (Indiscernible.)

15 DR. LIPTON: Yes.

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

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

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

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

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

25 Sometimes I think I took it for granted whenever

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 So as Richard has mentioned, we've conducted

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

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

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

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

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

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

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

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

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

20 (Off the record.)

21 (On the record.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 associated conditions.

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

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

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

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

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

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

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

25 Next slide? So for example, in the mobility

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 Next slide? I think that's it. Thank you very
9 much.

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

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

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

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

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

25 But over time, we might even move to computerized

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

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

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

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

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

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

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

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

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

23 DR. CELLA: Well, the --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 MS. BENT: We can. Thank you.

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

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

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

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

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

25 Now, there are obviously a number of things you

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

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

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

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

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

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

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

1 treatment or medication is effective and safe.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 (Audio interruption.)

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

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

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

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

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

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

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

1 the doctor?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 MR. REEVE: Yeah? Okay. Great.

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

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

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

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

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

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

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

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

1 seeing all three.

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

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

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

1 rating pain for a kid.

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

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

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

1 11:15. So I think we're going to have to end this portion
2 of the presentation now, but I do want to thank the entire
3 COA-OPTIC team for coming out and kind of talking to us
4 about the project and answering our questions. It was a
5 really -- it was a really great presentation.

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

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

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

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

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

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

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

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

9 MS. BENT: Thanks, so much.

10 MS. SMPOKOU: -- and see me okay?

11 MS. BENT: Yes, thank you.

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

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

1 filling in the gaps and meeting unmet needs.

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

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

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

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

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

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

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

25 I have to give credit to one of our experienced

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

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

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

25 And the second piece is really the speech, which

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 So I think that that was one of the important key

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 announcement and my thanks everybody for listening to us
2 today.

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

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

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

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

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

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

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

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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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