

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION (FDA)
 CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
 OFFICE OF NEW DRUGS (OND)

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EVALUATING THE NEGATIVE SYMPTOMS OF
 SCHIZOPHRENIA IN CLINICAL TRIALS

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PUBLIC MEETING

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FRIDAY
 AUGUST 16, 2024

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The public meeting was convened at
 FDA White Oak Campus, Building 31 Great Room,
 10903 New Hampshire Avenue, Silver Spring,
 Maryland, at 9:00 a.m., Dr. Bernard Fischer,
 Deputy Director, Division of Psychiatry, Office
 of Neuroscience, CDER, presiding.

PRESENT

BERNARD FISCHER, MD, Deputy Director, Division
 of Psychiatry (DP), Office of Neuroscience
 (ON), OND, CDER, FDA

ANTHONY O. "TONY" AHMED, PhD, HSP, Associate
 Professor of Psychology in Clinical
 Psychiatry, Vice Chair for Psychology, New
 York-Presbyterian/Westchester Weill
 Cornell Medicine

RACHAEL BLACKMAN, MD, PhD, Clinical Reviewer,
 DP, ON, OND, CDER, FDA

JACK J. BLANCHARD, PhD, Associate Provost for
 Enterprise Resource Planning and
 Professor, Department of Psychology,
 University of Maryland

STEPHEN BRANNAN, MD, Chief Medical Officer,
Karuna Therapeutics
TERESA BURACCHIO, MD, Director, ON, OND, CDER
MICHELLE CAMPBELL, PhD, Associate Director of
Stakeholder Engagement, ON, OND, CDER, FDA
CHRISTOPH CORRELL, MD, Professor of Psychiatry
and Molecular Medicine, Feinstein
Institute for Medical Research
TIFFANY R. FARCHIONE, MD, Director, DP, ON,
OND, CDER, FDA
WILLIAM P. "BILL" HORAN, PhD, Professor, UC Los
Angeles, Chief: Psychosis Section, VA
Greater Los Angeles Healthcare System
ERIC JARVIS, MD, Associate Professor of
Psychiatry, McGill University
BONNIE KAISER, PhD, MPH, Associate Professor,
Department of Anthropology; Global Health
Program, UC San Diego*
RICHARD S.E. KEEFE, PhD, Professor Emeritus in
Psychiatry and Behavioral Sciences, Duke
University School of Medicine
DEANNA KELLY, PharmD, BCPP, Acting Director,
Maryland Psychiatric Research Center,
University of Maryland School of Medicine
BRIAN KIRKPATRICK, MD, Professor, Psychiatric
Research Institute, University of Arkansas
for Medical Science
STEPHEN R. MARDER, MD, Professor, David Geffen
School of Medicine, UCLA
MARK G. OPLER, PhD, MPH, Chief Research
Officer, WCG, Inc.
MATTHEW RACHER, CRPS, Certified Peer
Specialist, CuresZ Foundation
ROBERTA RASETTI, MD, PhD, Clinical Reviewer,
DP, ON, OND, CDER, FDA
DAVID REASNER, PhD, Director, Division of
Clinical Outcome Assessment, CDER, FDA
MICHAEL SAND, PhD, CEO, S2 Consulting, LLC
NINA SCHOOLER, PhD, Professor of Psychiatry and
Behavioral Sciences, SUNY Downstate Health
Sciences University
BRANDON STAGLIN, President, One Mind
GREGORY STRAUSS, PhD, Franklin Professor of
Psychology, University of Georgia
LAURA SWETT, PhD, Reviewer, Division of
Clinical Outcome Assessment, CDER, FDA

SOPHIA VINOGRADOV, MD, Department Head and
Professor, Department of Psychiatry &
Behavioral Science, University of
Minnesota Medical School

HEIDI WEHRING, PharmD, BCPP, Clinical Reviewer,
DP, ON, OND, CDER, FDA

PEILING YANG, PhD, Office of Biostatistics,
CDER, FDA

*via videoconference

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1 P-R-O-C-E-E-D-I-N-G-S

2 (9:01 a.m.)

3 DR. CAMPBELL: Good morning,
4 everyone, and thank you for coming. My name is
5 Michelle Campbell and I am the Associate
6 Director of Stakeholder Engagement and Clinical
7 Outcomes in the Office of Neuroscience. On
8 behalf of my FDA colleagues, I would like to
9 thank you and welcome you to our public meeting
10 on evaluating the negative symptoms of
11 schizophrenia in clinical trials.

12 We are really looking forward to
13 today's great discussion and learning from you.
14 We'd like to quickly go over some housekeeping
15 items and then we'll get started. You should
16 all have a copy of the agenda. If not, it is
17 located on the FDA's website, under CDER, under
18 meeting and events.

19 We'll be spending the first half of
20 our morning hearing about the lived experience
21 as well as talking about the circuitry in
22 relationship with the brain. We'll then be

1 breaking for lunch around 11:40 and we will
2 have an hour for that. The second half of the
3 day we're going to be focusing on clinical
4 meaningfulness, outcomes, and trial design.

5 Just as a reminder, this meeting is
6 live and is being recorded. To our people who
7 are online, thank you for joining virtually.
8 We will be having someone who will be
9 monitoring the question and answer portion
10 online and we'll do our very best to make sure
11 to incorporate your questions into the live
12 discussion.

13 Also, for our attendees online, we
14 will be taking back your questions if they're
15 not asked, so we can learn from them and see
16 how we can incorporate your questions and
17 thoughts into our everyday work. Additionally,
18 to our audience that is live and in the great
19 room with me today, if we do not get to your
20 questions and you really have some comments and
21 thoughts, you may send an email to O&D public
22 support at FDA.hhs.gov, and in the subject line

1 please put, negative symptoms of schizophrenia,
2 in there and that mailbox will filter those
3 emails to us in the Office of Neuroscience.

4 Real quickly for some more practical
5 logistics, the restroom is out of the hall,
6 down the hall and to your right. There is a
7 kiosk available for lunch and coffee.

8 So, at this time I would like to
9 invite my colleague and Director of the Office
10 of Neuroscience, Dr. Teresa Buracchio.

11 DR. BURACCHIO: Welcome, everyone.
12 So good to have those of you here in person,
13 and I understand there's quite a contingent of
14 people online as well, so welcome to you all
15 for our workshop titled, Evaluating the
16 Negative Symptoms of Schizophrenia in Clinical
17 Trials. I'm sure many of you are experts on
18 this already, but I'll just briefly provide a
19 little overview of the day, that we're going to
20 start off with a discussion of negative
21 symptoms, which are flattened affect, poverty
22 of speech, lack of motivation, anhedonia, and

1 social withdrawal.

2 And we are well aware at the FDA
3 that there is a great unmet need for therapies
4 to treat these symptoms, we understand that
5 these symptoms cause a substantial impact on
6 patients with schizophrenia, their ability to
7 function in daily life, and in their quality of
8 life, and current antipsychotic therapies are
9 maybe effective for positive symptoms and can
10 treat some factors that contributed to negative
11 symptoms, but negative symptoms can persist and
12 are disabling even in patients who are
13 adequately treated with antipsychotics for
14 their positive symptoms.

15 We also recognize that there is a
16 great challenge to developing new therapies and
17 conducting clinical trials in these
18 populations. Some of the challenges, we're
19 going to touch on many of them today, but to
20 highlight a few are the use of concomitant
21 therapies with antipsychotics, either at the
22 time of a clinical trial or past history of the

1 use of these drugs which can impact negative
2 symptoms and potentially blunt treatment
3 effects of therapies, appropriately defining a
4 population to be enrolled in clinical trials
5 that could be anticipated to be responsive to
6 treatments, and developing clinical outcome
7 assessments that are sensitive to change and
8 are capable of measuring clinically meaningful
9 effects on negative symptoms.

10 The goal of our meeting today is to
11 have an open dialogue about these challenges
12 and identify areas where we can advance drug
13 development and regulatory science in this
14 space. We really have a fantastic agenda for
15 today, I will say that Dr. Bernie Fischer who
16 will be giving our opening comments really was
17 a lead on planning this and he just did a
18 fantastic job, so thank you Bernie. So
19 initially we'll have some introductory overview
20 from Dr. Fischer, who will go through the
21 background on negative symptoms, and this will
22 provide some clinical context and stage-setting

1 for the sessions that will follow. We will
2 also hear from Mr. Brandon Staglin with One
3 Mind, who will present the perspective of lived
4 experience with schizophrenia and the impact of
5 negative symptoms.

6 Session one will then present an
7 overview of the current science on
8 neurotransmitter systems and brain circuits
9 related to negative symptoms and overlap with
10 cognition, session two will focus on challenges
11 in designing studies to assess the
12 effectiveness of negative symptoms, session
13 three will focus on the cultural considerations
14 of assessing negative symptoms and how to
15 establish a clinically meaningful change, and
16 then session four will focus specifically on
17 clinical outcome measures for negative symptoms
18 of schizophrenia.

19 We have many outstanding speakers
20 and panelists today, I really think that we
21 have a fantastic day set for you, and so now I
22 would like to turn to Dr. Bernie Fischer, who

1 is our Deputy Director of the Division of
2 Psychiatry in CDER, and he will begin with our
3 initial session on providing an overview of
4 negative symptoms. Thank you.

5 DR. FISCHER: Okay, and then to
6 advance the slides. So, I am going to just do
7 a quick introduction to negative symptoms just
8 to make sure that we're all on the same page.
9 I know many of you are experts in schizophrenia
10 or experts in negative symptoms, but maybe not
11 everyone. So, I do have a number of references
12 at the end of the slides, and they'll probably
13 be best viewed when the slides are posted
14 online after the meeting.

15 Let's see. All right. So just as
16 an outline of what I'm going to talk about
17 today, I'm going to talk about some early
18 descriptions of negative symptoms, the origin
19 of the terminology, what are the negative
20 symptoms of schizophrenia, why they're
21 important to public health, and why FDA is
22 interested in this, and then I'm going to talk

1 a little bit about how you describe populations
2 of people with negative symptoms for possible
3 enrollment in a clinical trial. And for that
4 I'm going to focus on the three Ps, predominant
5 negative symptoms, primary negative symptoms,
6 and persistent negative symptoms.

7 So, in the early 1900s, late 1800s,
8 we had some astute clinicians that were trying
9 to make some sense of mental illness, and they
10 were describing the symptomatology and
11 prognosis to define certain disorders. And the
12 negative symptoms were a fundamental part of
13 early descriptions of schizophrenia, which was
14 at the time called dementia praecox. So, if
15 you look at Kraepelin and what he had said, he
16 said that schizophrenia included a weakening of
17 emotional activities that formed the wellspring
18 of volition, which is a very poetic way of
19 saying that people had problems expressing
20 affect and problems with motivation. Bleuler
21 also noticed the same thing, saying when affect
22 is lacking, there's a lack of drive. So,

1 people were noticing that diminished emotional
2 expression and diminished motivation.

3 In 1974, Strauss, Carpenter, and
4 Bartko published a series of landmark articles
5 that were informed by the WHO's international
6 pilot study of schizophrenia, and they looked
7 at the phenomenology of schizophrenia and
8 drilled down on symptoms. They borrowed some
9 terminology from some English neurologists from
10 the 1800s, John Russell Reynolds and Hughlings
11 Jackson, who had used the terms positive
12 symptoms and negative symptoms to talk about
13 brain pathology. When Strauss, Carpenter, and
14 Bartko looked at symptoms, they noticed that
15 some had the appearance of being an active
16 process, like hallucinations and delusions, and
17 they referred to those as positive symptoms.
18 Then there were other symptoms that seemed to
19 involve an absence of normal function, and they
20 called those negative symptoms.

21 So, what are the negative symptoms?
22 There's been some, a little bit of change over

1 the course of decades, but for the most part
2 there's five symptom domains that encompass
3 negative symptoms. The first one is blunted
4 affect, which can take the form of unchanging
5 facial expression, decreased spontaneous
6 movement, lack of expressive gestures, the
7 affective non-response can take the form of --
8 in a clinical interview you tell somebody a
9 joke and they don't crack a smile, they don't
10 laugh, they're just kind of flat. There can be
11 poor eye contact or lack of vocal inflection.
12 Then there's alogia which is poverty of speech,
13 people don't talk spontaneously very much.

14 There's the avolition and apathy
15 domain, where people may have poor grooming and
16 hygiene, they may have difficulty keeping up
17 with those tasks, they may have physical
18 inactivity, they may stay at home on the couch
19 watching TV all day, they may stay at home all
20 day on the couch with the TV on and not even
21 watch the TV. There's also difficulty seeking
22 employment, keeping employment, succeeding in

1 school. Then there's anhedonia, where people
2 can demonstrate few interests or hobbies,
3 there's maybe decreased sexual interest, and
4 it's not because of not necessarily finding an
5 appropriate partner. Then there's the
6 asociality domain, where people seem to have
7 few close relationships even among family
8 members, they seem to have few friends, and in
9 social situations they may appear isolated.

10 So, when you think about negative
11 symptoms, are they best viewed as a single
12 construct, as these are the negative symptoms,
13 they all kind of move together? Well actually,
14 there's a variable presentation that people
15 have with negative symptoms. Some people have
16 a lot of negative symptoms, some people have
17 few negative symptoms, and even within people
18 that have a lot of negative symptoms, they may
19 have different patterns, some people may have
20 more difficulties with motivation, other people
21 may have more difficulties with emotional
22 expression. So, some work has identified two

1 distinct factors that the negative symptoms can
2 map onto, and they seem to be emotional
3 expression, which would include the domains of
4 blunted affect and alogia, and motivation and
5 pleasure, which would include anhedonia,
6 asociality, and avolition.

7 More recent work has found that the
8 best fit might actually be thinking about those
9 negative symptom domains as each one
10 representing a separate factor, so that would
11 be the blunted affect, the alogia, anhedonia,
12 asociality, and avolition. And maybe the best
13 way to think about these concepts is that these
14 domains represent a primary order of the
15 factors, where they may map onto those in a
16 hierarchal way, those other two factors of
17 emotional expression and motivation and
18 pleasure.

19 So, why is it important to think
20 about this? One reason is because the
21 different negative symptoms domains may have
22 different underlying neurobiology, they may

1 represent different treatment targets. And we
2 know from some studies that they seem to have
3 different impacts on prognosis and course of
4 disease. For example, the avolition factor
5 seems very much related to poor functioning in
6 school and work.

7 So, why are negative symptoms
8 important for public health? Why is FDA
9 interested in negative symptoms? Well, one
10 reason is because when you look at people with
11 schizophrenia and you see the poor functional
12 outcome that many people experience, it's more
13 closely related to the negative symptoms than
14 it is the positive symptoms. You see people
15 have trouble persisting and work and at school
16 and trouble managing a household including the
17 household finances and keeping the house in
18 good repair, and that may be tied-in some
19 studies it has been tied-to the amotivation
20 symptom domain of the motivation and pleasure
21 factor.

22 When you look at recovery from

1 schizophrenia, which has been defined in the
2 literature in various ways, but when I talk
3 about recovery I mean something along the lines
4 of no major symptoms or hospitalizations for
5 the past 12 months, people have some school or
6 part-time work that they're doing, and there is
7 some social engagement with people. When you
8 look a recovery from that point of view, people
9 with high levels of negative symptoms have low
10 rates of recovery. And then when you ask people
11 with schizophrenia what matters to them, people
12 with negative symptoms have poor quality of
13 life, so people are expressing that negative
14 symptoms impact their quality of life. So
15 that's why it's an important treatment target.

16 So, now I'm going to shift gears a
17 little bit and talk about how you might think
18 of populations that have negative symptoms for
19 inclusion in a clinical study, and there's
20 been, over the course of years there have been
21 lots of different ways to think about people
22 with negative symptoms, but I'm going to

1 summarize that by talking about the three Ps:
2 Predominant negative symptoms, primary negative
3 symptoms, and persistent negative symptoms.

4 So, to take them one at a time,
5 first to talk about predominant negative
6 symptoms. When you think about the diagnosis
7 of schizophrenia, positive symptoms are
8 required for the diagnosis. In order to get
9 diagnosed with schizophrenia, there are
10 positive symptoms, but the positive symptoms
11 tend to wax and wane over the course of the
12 illness. There are periods where the symptoms
13 are exacerbated, and then periods where the
14 symptoms are maybe a little quieter. Negative
15 symptoms on the other hand, they tend to be,
16 they're independent of the positive symptoms,
17 they tend to occur earlier in the course of
18 illness, people that have negative symptoms—
19 about 70% of them have the negative symptoms
20 before they demonstrate positive symptoms—and
21 they tend to be kind of stable over the course
22 of the illness.

1 The concept of predominant negative
2 symptoms means negative symptoms that are
3 greater in severity than the positive symptoms,
4 and that definition requires two things. You
5 have to consider the baseline negative symptom
6 severity, then you also have to consider the
7 severity of the positive symptoms at the
8 moment. So, to illustrate this, if you have a
9 graph with symptoms severity on the Y axis and
10 course of illness on the X axis, when you plot
11 out the negative symptoms, you see that they
12 tend to start in the prodrome or clinical high-
13 risk state, and then they tend to go on during
14 the course of illness and be somewhat stable.
15 When you overlay the positive symptoms, you can
16 see that there's the first episode of positive
17 symptoms and the diagnosis of schizophrenia,
18 but then you see over the course of the
19 illness, they tend to wax and wane, there's
20 some variability there. The period of
21 predominant negative symptoms would be that
22 period where the positive symptoms are less the

1 focus of treatment than the negative symptoms,
2 or the negative symptoms are more severe.

3 Now I'm going to talk a little bit
4 about primary negative symptoms. Primary
5 negative symptoms are negative symptoms that
6 are due to the neurobiology of schizophrenia;
7 the schizophrenia is directly causing the
8 negative symptoms. Secondary negative symptoms
9 are caused by something else, but they have the
10 appearance of negative symptoms. Some examples
11 of causes of secondary negative symptoms are,
12 one, positive symptoms. Positive symptoms can
13 cause secondary negative symptoms, and an
14 example of that is someone who has high levels
15 of paranoia. They may have social withdrawal,
16 they may have poor eye contact or rapport with
17 an interviewer, but it may not be because of
18 primary negative symptoms, it may be due to the
19 paranoia. Antipsychotic effects can present
20 secondary negative symptoms. And this could be
21 something like Parkinsonism, where you have a
22 masked face or decreased spontaneous movement,

1 but you can also have sedation, causing
2 somebody to maybe have less drive or less
3 social engagement.

4 Other mental illness can cause
5 secondary negative symptoms. Examples of that
6 are, depression causing anhedonia or a lack of
7 motivation, or PTSD causing social avoidance.

8 Environmental factors can be a big cause of
9 secondary negative symptoms. If you live in a
10 resource-poor environment, you may not be able
11 to develop a hobby or engage with people, it
12 may not be safe to leave your house and go
13 walking in the neighborhood and make friends.

14 Then there's stigma. People with mental
15 illness face a great deal of stigma, and people
16 with schizophrenia probably more than most.
17 Some people with schizophrenia can internalize
18 that stigma and start to believe what other
19 people say of them, and that can affect them,
20 they could withdraw socially.

21 So, I want to drill down a moment on
22 the picture of negative symptoms, secondary

1 negative symptoms, and antipsychotics. Because
2 as we talked about in the last slide,
3 antipsychotics may be a cause of secondary
4 negative symptoms, but antipsychotics may also
5 treat some secondary negative symptoms. For
6 example, antipsychotics may improve depression,
7 they may improve someone's paranoia. If you
8 have experience with doing clinical trials in
9 people with schizophrenia, then you know that
10 if you have a group of people that have an
11 exacerbation of positive symptoms, and you
12 enroll them in a study, when you do clinical
13 ratings, over the course of the study you will
14 see their negative symptoms reduced, but it's
15 the antipsychotic effectively treating the
16 positive symptoms and other secondary causes.
17 We know that after effective antipsychotic
18 treatment people still demonstrate negative
19 symptoms.

20 And that leads me to the third P,
21 persistent negative symptoms. So, negative
22 symptoms often persist after you treat the

1 causes of secondary negative symptoms that you
2 can identify. When somebody presents to you
3 with negative symptoms, it can sometimes be
4 difficult to tease out whether those are
5 primary negative symptoms or whether those are
6 secondary negative symptoms that just haven't
7 responded to treatment. And this can be
8 especially the case when you have a short
9 screening visit to enroll in a clinical trial,
10 it may be difficult to sort that out, but maybe
11 these persisting negative symptoms, after
12 you've tried to treat secondary negative
13 symptoms, maybe that is the treatment target.

14 You can operationalize that
15 population by saying people with persistent
16 negative symptoms have some degree of negative
17 symptoms, with low levels of positive symptoms,
18 low levels of co-occurring mental illness, like
19 depression, low levels of Parkinsonism on
20 rating scales, and some clinical stability
21 prior to enrollment in the clinical trial, so
22 something along the lines of no

1 hospitalizations or changes in medication
2 recently.

3 So, I'm going to bring up a few
4 questions that I'd like you to keep in mind as
5 we discuss things throughout the course of the
6 day. First question is, what is our target
7 patient population? Should clinical trials
8 enroll people based on predominant negative
9 symptoms, primary negative symptoms, persistent
10 negative symptoms, or is there some better way
11 of defining a population of interest? How
12 should clinical trials ensure that we optimize
13 treatment of secondary negative symptoms before
14 enrolling in the clinical trial? Another
15 important question is, how should development
16 programs for drugs account for real-world
17 antipsychotic use when designing clinical
18 trials for negative symptoms? Thinking about
19 this afternoon's talks, where we talk about
20 clinical outcome measures, what's the best way
21 to measure improvement? We have a number of
22 scales out there, which one might be the best

1 choice? Are there several that might fit what
2 we're looking for as far as an outcome measure?
3 Should clinical trials measure negative
4 symptoms as that single construct of negative
5 symptoms? Or should we start to look at
6 various factors and symptoms domains
7 separately?

8 Should we account for cultural
9 differences when we look at negative symptoms?
10 I'm sure it's occurred to you as we were going
11 through the negative symptoms that things like
12 eye contact can be very culturally bound.
13 People can have poor eye contact because that's
14 how they were raised or that's part of their
15 culture, not necessarily because of negative
16 symptoms. So, when we have development
17 programs that look internationally, how do we
18 ensure that we account or those differences,
19 and make sure that the results of those
20 clinical trials are relevant to the United
21 States population?

22 This is an important concept here,

1 how do we determine what amount of change is
2 meaningful to a patient? So, we can see a
3 statistical difference on a clinical rating
4 scale on negative symptoms, but does that mean
5 something to somebody with schizophrenia? Do
6 we need to see some kind of a co-occurring
7 functional improvement to put the results of
8 that scale into a context? And then finally,
9 how do we incorporate new technology into
10 assessing our endpoints? Is it possible to use
11 technology as a primary outcome measure, rather
12 than a clinical rating scale, or is technology
13 best used to inform the clinical rating scale,
14 and we can decide what's relevant and how much
15 change is meaningful by incorporating this
16 technology?

17 So those are some questions to keep
18 in mind. I'm going to quickly show the
19 reference slides, but again, those reference
20 slides are probably best looked at when the
21 talk is posted online, and I'd like to now take
22 a moment to introduce Mr. Staglin who's going

1 to talk to us about lived experience. Mr.
2 Staglin is the president of One Mind, and he
3 will be talking to us a little bit about his
4 journey and why negative symptoms are important
5 as a treatment target.

6 MR. STAGLIN: Hello. And thank you,
7 everyone, for being here at this important
8 meeting and for the important work that you do
9 on behalf of people with schizophrenia. I'm
10 Brandon Staglin, and as co-founder and Chief
11 Advocacy and Engagement Officer for One Mind,
12 I'm here to talk to you today about negative
13 symptoms of schizophrenia.

14 So, I believe all people facing
15 psychotic illness deserve chances to thrive.
16 Why isn't that the common outcome? Like about
17 24 million of us worldwide, I live with
18 schizophrenia, and I'm very grateful to have
19 recovered from the darkness and debilitation
20 and devastation that entailed for several
21 years, however about two thirds of us don't get
22 that privilege, two thirds of us who live with

1 the condition. This shouldn't be the case.
2 Many of us live lives in limbo, recovery limbo,
3 unable to engage with the world, unable to
4 work, unable to engage socially with people
5 around them, these can be lonely lives that end
6 far too young. We need to address this. As a
7 person with both professional and personal
8 experience with schizophrenia care, I believe
9 negative symptoms are the primary impediment to
10 recovery for many, many, many people. Today
11 I'll share how negative symptoms have impacted
12 my life and the people I know, and also talk
13 about ways to address negative symptoms that
14 are derived from the experiences that I've had,
15 that others have had, and also research.

16 I survived two schizophrenia
17 episodes over a six-year span throughout my
18 life. The first episode was essentially a
19 vortex of psychotic dread. The positive
20 symptoms were predominant in that episode. I
21 experienced the conviction that if I made any
22 moral mistakes over the course of any day

1 throughout the first six months of my
2 psychosis, that demons would jump out of the
3 shadows and drag me kicking and screaming into
4 the abyss to spend eternity in misery and
5 damnation. Needless to say, this provoked a
6 lot of terror within me and worry and constant
7 hypervigilance not to make any mistakes, so to
8 speak, like stepping on a crack or eating too
9 much food at a meal, but I'm very thankful to
10 have recovered from that first episode thanks
11 to my family's loving support and early
12 science-based medical care like you all are
13 delivering and improving, and staying involved
14 with the community to rebuild a sense of agency
15 and purpose. That was the first episode.

16 My second episode took place six
17 years later when I was working as an engineer
18 in Silicon Valley, and I had got into graduate
19 school and I went off my medication in order to
20 sleep less, as the medication had that as a
21 side effect. And this episode was a
22 devastating setback, and it took much longer to

1 recover from than the first episode, primarily
2 due to negative symptoms. Although I
3 controlled my psychosis pretty well, the
4 negative symptoms dug in.

5 For three years I mostly played
6 video games at home and drove around aimlessly
7 throughout the countryside, not working, not
8 motivated to be social. And while I was
9 content with this for a while, because I wasn't
10 embroiled in the turmoil of psychosis anymore,
11 it was dawning on me gradually that there could
12 be more to my life, there could be more that I
13 could accomplish and achieve and experience. I
14 began to fear this might be a dead end for me
15 in my life, this limbo, these doldrums that I
16 was in. I would give up easily on pursuing
17 complex goals due to self-doubts and
18 rumination. So, sometimes these self-doubts
19 still haunt me today. Research indicates that
20 avolition may be the result of dysfunctional
21 reward anticipation. What if enhancing reward
22 anticipation and calming rumination could

1 revive volition? Are there ways to do this?
2 Something to consider. We'll come back to
3 this.

4 Later I had the opportunity to use a
5 new medication, aripiprazole, a partial
6 dopamine agonist, that re-ignited my volition
7 big time, it made me very ambitious, it made me
8 want to be more physically active, and want to
9 grow my social status, and I'm sad to say that
10 I made some reckless decisions and comments to
11 people that I loved, during the early period of
12 my time with aripiprazole, mainly because I
13 didn't have the cognitive control needed, the
14 executive function and the attention to manage
15 my volition effectively and to govern that for
16 healthy relationships and productivity. I
17 still regret some of the comments that I made
18 to family members, telling them that they were
19 terrible people, when I was in the throes of
20 these symptoms and the medication's effects.
21 So, it was very, very important to improve
22 cognition while you improve the volition of

1 people dealing with these symptoms. Can
2 enhancing cognition help to guide volition?
3 Another question to consider as we progress
4 through our day today.

5 Later, I had the ability to
6 participate in a study conducted by our very
7 own Dr. Sophia Vinogradov, seated there on the
8 front, of a neuroplasticity-based treatment
9 called cognitive training. This improved my
10 cognition dramatically. Cognitive training is
11 a treatment that uses the brain's ability to
12 remold its neural pathways in response to
13 targeted, gradually increasing in intensity,
14 challenges that can improve people's ability
15 to, say, pay attention, to focus better in
16 conversation, remember what's being said. I
17 benefitted from this treatment by doing it for
18 about two months, and by the time I was done I
19 was enjoying time with friends again and
20 working again, it was a turning point in my
21 recovery. This improvement in cognition
22 dramatically unlocked my sociality, can this be

1 something that happens for people in the
2 general population? Something to consider.

3 What else can enhance sociality and
4 cognition? So, the studies of Dr. Nina Kraus
5 at Northwestern University have shown that
6 musical training can act very much like
7 cognitive training in enhancing cognition, and
8 in essence it can enhance the ability of the
9 brain to be plastic, to change, to mold itself,
10 and improve people's ability to do various
11 cognitive tasks. But I've been through this
12 dramatically in my recovery later on. When I
13 was about 35, becoming more social, I decided I
14 wanted to have a new hobby that would help me
15 be more social, so I took up guitar. And
16 another member of our audience, a speaker
17 today, is Matthew Racher, also plays guitar. I
18 had the opportunity to compose a song and
19 perform it in front of an audience several
20 times, actually, in 2017, about schizophrenia
21 recovery. And when people sang along to the
22 final chorus in my performance, it was like

1 such a thrill, and it gave me such a sense of
2 satisfaction that my creativity could inspire
3 joy and hope in other people.

4 And this was a huge motivating
5 factor, huge boost of motivation, put it that
6 way. It enabled me to do much more in my
7 career, that boost in motivation enabled me to
8 get a Master's of Science in healthcare
9 administration from UCSF and took a yearlong
10 program to do that, and become president of One
11 Mind shortly thereafter. I'm very proud of
12 what I did during that six years tenure as
13 president of One Mind.

14 So, I believe music enjoyment is
15 very important, because it's mediated by
16 dopamine function, important for schizophrenia.
17 Because it's mediated by dopamine function, and
18 especially in the mesolimbic pathway, and by
19 enhancing this dopamine function repetitively
20 through musical enjoyment, I believe we can
21 actually help people with schizophrenia
22 neuroplastically to reduce their anhedonia and

1 improve their ability to enjoy things again as
2 well. So, not only has musical training helped
3 my sociality, it's also helped my motivation.
4 Can musical training treat multiple negative
5 symptoms? Question to think about.

6 Practicing sociality has also made
7 me feel whole, so after the benefits I received
8 from cognitive training and musical training, I
9 became much more social. My adult social life
10 and my ability to interact with people socially
11 as an adult began to grow with my relationship
12 with my grandmother, who you see pictured at
13 the top right. Her name was Darlene, she was
14 my close friend and confidant while I was
15 recovering from my second episode of
16 schizophrenia, and she was a great support for
17 me during that time. As she got older and more
18 frail, her needs began to outweigh mine, and I
19 began to care for her, helping her relocate to
20 a new assisted living facility near where my
21 family and I lived, helping her to organize her
22 time and her belongings at home, et cetera. I

1 learned from this relationship to care for
2 people in general, to take care of others.
3 This was a huge benefit for my growing
4 sociality as I began to develop more
5 relationships. Over time, sociality can
6 develop into intimacy, where people understand
7 and accept one another without having to have
8 too many words used in communication for
9 meaningful enjoyment mutually, and I'm happy to
10 say, and grateful that I've attained such a
11 state with my wife and our animals. My wife
12 and I, who you see pictured at the lower right,
13 have been happily married for 15 years, it's
14 better every year.

15 So, I believe to strengthen
16 sociality, it helps to practice it, once you
17 have the tools needed to start. So, some take-
18 home strategies for us to remember today are to
19 strengthen volition, increase reward
20 anticipation, and decrease rumination, okay?
21 How can you do this? Well, there are some
22 treatments that address this directly. For

1 example, one thing Dr. Vinogradov is working on
2 in her EPI-MINN program, the Minnesota arm of
3 the EPINET program for early psychosis care and
4 research, is an app called PRIME, personalized
5 real-time intervention for motivation
6 enhancement. It addresses this directly, she
7 can tell you more. Musical training can also
8 help, as I mentioned earlier. Secondly, to
9 improve volition successfully, also strengthen
10 cognition, keeping it managed, keeping the
11 volition in healthy channels. Cognitive
12 training can help with this, as can new
13 medications coming down the pipeline, from
14 large pharma companies as well as smaller
15 biotechs, like One Mind helps through its
16 accelerator program.

17 And then thirdly, to improve
18 sociality, enhance cognition, and follow up
19 with opportunities to socialize with family
20 members in ever-widening circles. How can you
21 do this? Well, community clubhouses are one
22 way that people can engage if they live with

1 serious mental illness with others, like the
2 Fashion House, for example, in New York,
3 coordinated specialty care programs often
4 involve group therapy sessions and family
5 focused therapy that can help with this,
6 another group called Students with Psychosis is
7 a group that connects young people with
8 psychosis with each other and communities and
9 for advocacy. Also, another upcoming One Mind
10 at Work program may soon address this for young
11 people in the workplace.

12 So, we're faced today with a shadow
13 crisis of negative symptoms, I know so many
14 families whose sons or daughters are trapped in
15 recovery limbo due to their negative symptoms,
16 not working, not being social, spending all
17 their time at home, and this is a great source
18 of consternation and turmoil for these
19 families. I know one family whose son has
20 overcome the avolition but still has the
21 blunted effect of alogia, and very sadly,
22 although he's very talented and skilled and

1 motivated to work, when he goes through the
2 interview stages of his job applications, he
3 fails because the employers can't see past that
4 blunted affect to the great person that he
5 actually is, and he doesn't get the jobs. So,
6 loneliness as well due to negative symptoms is
7 a huge problem. Not only is it corrosive to
8 health, it's also a source of torture for so
9 many people, just being alone so much. And I
10 experienced this myself while I was recovering,
11 but also Jeremy Novell, a colleague and friend,
12 believes that this could be a cause of the
13 early death of so many people with
14 schizophrenia, the loneliness and the corrosive
15 health effects.

16 As clinical scientists, you must
17 deal with many people who have these symptoms
18 and are in these situations. What can we do?
19 As a scientist, you have the tools to discover
20 solutions. You have the caring, the
21 compassion, and the know-how to make a
22 difference in millions of people's lives. This

1 is our task today, to tackle negative symptoms
2 using the inspiration that I've delivered, that
3 others will deliver, and the idea that many
4 that will speak today will offer. Our job
5 today is to figure out how to address these key
6 obstacles to recovery at scale and to develop
7 and employ these solutions to meet the needs of
8 the community.

9 If we can keep young people healthy
10 through our preventative and early care,
11 leveraging innovations inspired by what I've
12 suggested today, I believe we can save lots of
13 lives and transform lives for the better. This
14 is essential for the future of so many people
15 as well as for our society. Thank you. Are
16 you with me?

17 I do have a minute left. May I take
18 questions if there are any? Any questions?
19 Yes. I can hear you, although I'm not sure the
20 mic is on.

21 DR. KIRKPATRICK: This has
22 implications for clinical trials.

1 Can I whisper now?

2 MR. STAGLIN: I can hear you.

3 DR. KIRKPATRICK: Okay great. This
4 has implications for clinical trials, if we
5 think broadly, and that is there are a lot of
6 reasons why even if someone had a medication
7 that was effective for negative symptoms, there
8 are going to be so many obstacles for that
9 becoming obvious, and for people to have good
10 outcome, to have good level of function. Some
11 people have these problems begin in childhood
12 and adolescence, and they may not have acquired
13 the skills that they need, and certainly if
14 someone has had this for ten years, I think
15 it's going to be very normal for many of them
16 not to have much confidence to go out and do
17 these things.

18 So, if we have a medication, even
19 with a small effect size, that makes them able
20 to respond to the psychosocial treatments that
21 they really need, social skills training,
22 cognitive rehabilitation, et cetera, that may

1 be a really big deal, and we should keep that
2 in mind. Also, it's just going to take a long
3 time for people to show these results, to
4 improve their function. Thank you for the
5 talk, it was great.

6 MR. STAGLIN: Great comment, thank
7 you, very true. Thank you. Okay, we're out of
8 time, but --

9 DR. CAMPBELL: Brandon? We're here.
10 I've got some web thoughts. So first of all,
11 someone says, 'we're all with you, thank you
12 for your remarks.'

13 MR. STAGLIN: Thank you, thank you.

14 DR. CAMPBELL: I have two quick
15 questions if you're okay with answering them,
16 if you feel okay. Is that okay Bernie? Okay.
17 So, the first question is, did you find any
18 benefit of musical treatment to your ability to
19 discriminate and process sounds, and do you
20 think that helped with cognition as well?

21 MR. STAGLIN: I found the musical
22 treatments, primarily, yes, they helped my

1 ability to appreciate the nuances and
2 complexity of music, so yes, I think as an
3 auditory phenomenon, music is something that I
4 was able to appreciate a lot better thanks to
5 musical training, yes.

6 DR. CAMPBELL: I have one last
7 question if you're okay. All right. You did
8 not mention the lack of awareness of negative
9 symptoms we see in many patients. Can you
10 speak to this behavior barrier to treatment?

11 MR. STAGNIN: Yes, I can. So during
12 my second episode, I can't remember if I
13 mentioned this, but I was fairly content to
14 live a life of not engaging in work or not
15 engaging in social activities, and I didn't
16 really care that much about it, I wasn't aware
17 that I was missing anything at that time, I
18 didn't feel like I was missing anything, but it
19 took a while, I began to think that there could
20 be more to life again, there could be more that
21 I could accomplish, remembering how I used to
22 be, basically, and the achiever that I had

1 been. And so yes, for quite a long time I
2 wasn't really aware the negative symptoms were
3 affecting me, but eventually I did become
4 aware. Thank you.

5 DR. RASETTI: Good morning,
6 everyone. Can you hear me, can you see me?
7 Welcome to Session 1. My name is Roberta
8 Rasetti. I am a psychiatry and a clinical
9 reviewer for the Division of Psychiatry in FDA,
10 and I will be moderating session one, session
11 one is on the brain circuits and relationship
12 to cognition.

13 This session will be a brief
14 overview of the current science on the
15 neurotransmitter system in the brain circuits
16 related to negative symptoms. This session
17 will last 30 minutes, we will have the first 20
18 minutes with the presentation, by the speaker,
19 and then there will be 10 minutes of a Q&A.
20 After this session, we will have the first
21 coffee break that will last an hour and ten
22 minutes.

1 Okay, so now it is my pleasure to
2 introduce our speaker, Dr. Sophia Vinogradov.
3 Dr. Vinogradov is Professor and the Department
4 Head of the University of Minnesota Department
5 of Psychiatry and Behavioral Science, and she
6 leads the Translational clinical neuroscience
7 lab focused on the cognitive dysfunction in
8 psychosis, and also she leads a network of
9 early psychotic clinics in the State of
10 Minnesota. The title of her presentation is
11 Negative Symptoms, Cognitive and Neural System
12 Features. Thank you.

13 DR. VINOGRADOV: Good morning, what
14 an incredible gathering of individuals, and you
15 may not believe this, but Brandon and I
16 actually did not talk before today, and we
17 somehow had some mind meld going on, because
18 Brandon, set me up perfectly for my topic. The
19 other thing I want to say is that the topic of
20 the interplay between negative symptoms and
21 cognition and underlying neural circuitry could
22 be a weeklong workshop in itself at the end of

1 which we would come to no conclusions.

2 So for those of you who are not
3 researchers in this field, and I have really so
4 many incredible colleagues, I feel like I'm
5 standing on the shoulders of giants, but for
6 those of you who do research in this area,
7 please forgive me, I beg your indulgence,
8 because I'm really simplifying, I'm going to
9 simplify for the sake of 20 minutes today a
10 really complex set of topics. For those of you
11 who are new to this area, I'm going to beg your
12 indulgence, because it's going to appear much,
13 much simpler than it really is, but perhaps
14 this is a starting point just for kind of
15 shaping some of our kind of thinking as a group
16 going forward, and as you're going to see,
17 Brandon's personal experiences and the
18 conclusions he has drawn from his lived
19 experience really do fit well with some of
20 these general themes that I will provide in an
21 overview to you.

22 So let's see. Okay, did I go in the

1 wrong direction? Here we go, okay, sorry about
2 that. My disclosures. We've already heard
3 from Bernie about the five negative symptom
4 domains, we've heard about the two factors and
5 I'm just refreshing your memory here, because
6 this is going to be kind of very germane to
7 where the research has evolved recently in
8 thinking about these interplays which I was
9 describing. Bernie already described to us the
10 importance of negative symptoms in terms of
11 functional outcomes, and has already mentioned
12 that we've got this consistent association
13 between negative symptoms and poor outcomes,
14 and what is very interesting and important is
15 that we see this association, that negative
16 symptoms are predicting some additional
17 variants and functional outcomes, even when we
18 start to account for general cognition and
19 functional capacity in individuals.

20 More recent work, Tony Ahmed and his
21 colleagues, who are here today, have done some
22 very interesting, I would say, kind of external

1 validator analyses, and have shown that when
2 you drill down into some of the specific
3 domains, those five domains that we described,
4 we see some strong and consistent domain-
5 specific associations with functional outcome,
6 particularly with the avolition anhedonia
7 factor as you've already heard, and to a lesser
8 extent with blunted affect. And again, this
9 point about these five domains that's important
10 to keep in mind is that, when you do this kind
11 of external validator work, each of these
12 different domains is showing some specific
13 associations with these range of external
14 validators that aren't accounted for by the
15 two-factor approach, and that includes
16 functional outcome, as I mentioned,
17 psychological measures, such as defeatist
18 beliefs, which Brandon has alluded to,
19 cognitive function, and neural system findings.
20 So another kind of, in a sense,
21 accepted [concept], now, with decades of
22 research, is that we see a consistent

1 association between negative symptoms and
2 disrupted cognitive functioning, but as you
3 look historically at the research and then kind
4 of fast-forward to where we are today, there's
5 some inconsistencies, and this is because in
6 the earlier body of studies, there were aspects
7 of measurement overlap and clinical compounds
8 that again, you've already heard partially
9 alluded to. So for example, in some of the
10 earlier rating scales of negative symptoms,
11 cognitive observations were a fundamental part
12 of how negative symptoms were rated, and so
13 then of course we start seeing these
14 relationships between more severe negative
15 symptoms and more severe cognitive functioning.

16 There was a recent systematic review
17 of about 3,000 individuals with negative
18 symptoms, this was first episode psychosis, and
19 the interesting thing about this sample, of
20 course, is that this is going to be individuals
21 who have not yet necessarily had a long amount
22 of chronic exposure to some of the impoverished

1 environmental resources, the accumulating
2 effects of medications and so forth, and in
3 this sample, there was a consistent association
4 between negative symptoms rated more generally,
5 using a range of different ratings scales, with
6 lower executive functioning and poorer theory
7 of mind. So what's interesting about that?
8 Executive functioning, right, generally
9 cognitive capacities, certainly strongly pre-
10 frontally mediated, poorer theory of mind
11 social cognition capacities. And then in Ahmed
12 et al.'s study which I mentioned to you,
13 avolition, across three different samples, was
14 showing the strongest and most consistent
15 association with disrupted cognition. There
16 were also some associations seen in a couple of
17 the samples with anhedonia, blunted affect, and
18 alogia. So again, sort of the take-home
19 messages, yes, we do see this association with
20 negative symptoms and cognitive functioning,
21 there is some of these confounds with
22 measurement and other environmental exposures

1 likely contributing to that, avolition seems to
2 certainly be playing a central role.

3 One of the other consistent findings
4 in this field is that when we look at samples
5 of individuals with more persistent negative
6 symptoms, we see in those samples a fairly
7 consistent association with structural and
8 functional changes in prefrontal and temporal
9 cortex. So, for example, again, looking at
10 early psychosis samples, when we see
11 individuals with these patterns of prefrontal
12 disruption, such as progressive cortical
13 thinning in prefrontal cortex, in these
14 individuals we see a more severe course of
15 illness, worse functional outcomes, and
16 increasing negative symptoms over time.

17 So there certainly seems to be this
18 kind of picture that emerges, that when you
19 look at persistent negative symptoms, perhaps
20 persistent and more predominant negative
21 symptoms in individuals, over time we see this
22 relationship with disruptions in prefrontal and

1 temporal cortex, which of course is the central
2 executive network, right. This is the network
3 in the brain that is responsible for
4 essentially integrating information, coming
5 from all different, kind of sensory perceptual
6 memory inputs and so forth, integrating them in
7 order to be able to carry out abstraction,
8 problem solving, anticipating the future,
9 creating value representations of future
10 behavior.

11 More recent research, though, and
12 this has been sort of a really exciting
13 explosion in the field, is that as more recent
14 research has drilled down into some of these
15 specific domains, what has been sort of kind of
16 emerging, again, in a fairly robust way, is the
17 relationship between anhedonia and neural
18 system findings. I'm sorry, avolition and
19 anhedonia. So again, that sort of often, it's
20 often considered that motivation factor, and
21 very specifically again with avolition,
22 avolition has been associated with lower

1 glutamate and GABA concentrations in anterior
2 cingulate cortex. Avolition has also been
3 associated in a very recent study with
4 amplitude of low-frequency fluctuations, which
5 represents intrinsic neural activity across
6 multiple cortical regions, prefrontal, even
7 more posterior, anterior cingulate, and again,
8 avolition as a domain showed this association
9 in a more specific and enveloping pattern than
10 some of the other domains did, although some of
11 the other domains were showing, again, drilling
12 down, some very interesting specific
13 associations.

14 And then looking at the motivation
15 factor for avolition and anhedonia, the patter
16 that is, again, consistently emerging is that
17 it's associated with reduced ventral striatal
18 activity and disrupted connectivity between the
19 ventral striatum and other regions of the
20 brain. And so now we're talking about the
21 reward processing circuit, right? So ventral
22 striatal, mPFC, again, new to some of you,

1 medial prefrontal cortex, very important in
2 valuation, reward processing, social cognition
3 as well, orbital frontal cortex, anterior
4 cingulate cortex, and this network, again, we
5 kind of, in a sense, call the reward processing
6 network.

7 I want to come back to the idea of
8 functional outcome, because there's been some
9 interesting analyses, path analyses, structural
10 equation modeling, kind of, that give us some
11 of these clues about the relationship of
12 neurocognition to negative symptoms, and you're
13 going to see some of the themes that Brandon
14 was alluding to emerging here.

15 We know that neurocognition has a
16 direct relationship to functional outcome, but
17 we also know that it is partially mediated
18 through the effects that neurocognition has
19 (fundamental neurocognitive capacities have) on
20 the brain's ability to carry out social
21 cognitive operations. Social cognitive
22 operations are, even at the most simplistic

1 level, are things like eye gaze detection,
2 emotion recognition, vocal emotion recognition,
3 theory of mind, in terms of a higher order
4 social cognition capacity. So, we know about
5 this relationship, that's been well established
6 in the literature for several decades now.

7 What more recent work has shown, out
8 of Giordana et al.'s lab, is that if you kind
9 of elaborate upon this analysis now with
10 measures of negative symptoms, we also see that
11 the effect of neurocognition on functional
12 outcome is being partially mediated through
13 negative symptoms, both the kind of domain of
14 motivation, anhedonia, avolition, as well as
15 the domains related to blunted affect and
16 alogia.

17 However, when you look at the
18 relationship of social cognition to functional
19 outcome, it is partially mediating -- the
20 relationship of social cognition to functional
21 outcome is being partially mediated
22 particularly by this domain of avolition and

1 anhedonia. But there's a final kind of piece
2 to this puzzle, which, again, shows you a
3 little bit about its complexity and about how
4 we still have not fully resolved kind of where
5 all the pieces in the puzzle fit together, and
6 that's the fact that, and again, in a number of
7 different studies, if you just look at the
8 right hand part of these paths, this
9 relationship of neurocognition and social
10 cognition to functional outcome is strongly
11 mediated also then by their effects on
12 motivation.

13 And we know that, again we see this
14 over and over in a number of studies, that if
15 we have -- that we can both target these as
16 treatment targets, and we've done that in my
17 lab around targeting social cognition,
18 targeting neurocognition, we can see
19 improvements in motivation, and distal
20 improvements in functional outcome, as Brandon
21 alluded to. And yet at the same time, we know
22 that some of these relationships are being

1 partially mediated through the effect of
2 negative symptoms, and yet negative symptoms
3 contain within them this motivation factor,
4 right, of avolition and anhedonia.

5 So, I want to say a few more
6 thoughts about motivation and avolition, and
7 kind of, again, sort of summarize some thoughts
8 about it. So, now we're talking about
9 motivation as a concept, and maybe talking a
10 little more generally than we had about just
11 avolition, but motivation as a general concept,
12 as it's been increasingly studied in cognitive
13 neuroscience for the last 10, 15 years. Again,
14 it is really understood as arising from the
15 interaction of two major neural systems, and I
16 underline the word "interaction."

17 You know we as researchers, as
18 people trying to sort of put together complex
19 ideas, we like to pull things apart and say oh,
20 there's a module here, the central executive
21 module, there's a module here, the reward
22 processing module. That's not, of course, at

1 all how the brain works, but in terms of the
2 circuitry, again, that central executive
3 network, dorsolateral prefrontal cortex, dorsal
4 caudate, - I'm simplifying a great deal of work
5 here - but, essentially, again, as part of what
6 central executive functions do, they're
7 encoding the relationship between actions and
8 potential outcomes, that contingency, it can be
9 representing the expected value of an action,
10 if I do X, this will happen, and it has this
11 value or meaning to me, and then of course
12 there's really strong functional overlap here
13 with cognitive control mechanisms and
14 intentional control mechanisms, which we know
15 are disruptive in the illness.

16 And if you want to simplify a great
17 deal, you can think of these central executive
18 networks as being really critical for just our
19 capacity to do these higher order functions
20 that allow us to move adaptively through the
21 world, problem solving, a distraction, et
22 cetera.

1 The other major system, as I've
2 already alluded to, is the reward processing
3 network, ventral striatum, and its related
4 projections and connections. These of course
5 are much more kind of taking on the operations
6 that are related to anticipating reward and
7 then valuation of a reward, as one is
8 anticipating it, and as one is receiving it.

9 The representation of stimulus-reward
10 associations as they're happening, and of
11 course this system then talks to the prefrontal
12 cortex and said, "huh, there was an important
13 value based, you know, reward-based association
14 happening here, learn about it, I want you to
15 learn this," right? Those are those dopamine
16 projections to prefrontal cortex. And this
17 circuitry has a high degree of functional
18 overlap with value-based, reward-based decision
19 making, and social cognition.

20 And I'm going to do a footnote here,
21 because again I think it was embedded in your
22 talk, Brandon, which is that our social

1 cognition capacities, our ability to make sense
2 of the social world in which we move is
3 critically important to our survival, right,
4 we're social mammals, and it's very intimately
5 connected to the reward processing system, and
6 in fact, social stimuli are known to be in and
7 of themselves, most of the times, rewarding,
8 right? To see a face, a face that you know, to
9 see someone smiling at you, to smile back at
10 them, to have that reciprocal interaction, that
11 is innately rewarding for the brain, and these
12 are the neural systems that are recruited
13 during those processes.

14 So, again, keeping things super-
15 simple, we have now an important interplay
16 happening between cortical systems, cortical
17 circuitry, and subcortical systems. Thinking
18 about models of schizophrenia etiogenesis,
19 right, this is the interplay between cortical
20 excitation and inhibition balance, glutamate-
21 GABA, and subcortical and cortical dopamine
22 modulations, so dopamine - that's originating

1 in the midbrain -, both in terms of what's,
2 kind of the circuitry in terms of the ventral
3 striatal and dorsal caudate, but also the
4 projections of this midbrain dopamine into the
5 frontal regions.

6 And, of course, as I said, in terms
7 of etiopathogenesis of schizophrenia, we have
8 theories related to models related to
9 excitatory inhibitory imbalance in the cortex,
10 glutamate-GABA imbalance, and of course we have
11 this notion of subcortical hyperdopaminergia in
12 the dorsal caudate, and that these two systems
13 are out of balance, and that's giving rise to
14 the different symptoms that we see.

15 Again, people simplify and say well,
16 it's an EI (excitatory-inhibitory) imbalance at
17 the level of the prefrontal cortex that's
18 giving rise to cognitive and negative symptoms,
19 and it's this hyperdopaminergia at the level of
20 subcortical systems that is playing a role in
21 the development of positive symptoms of
22 psychosis. We know it's much more complicated

1 than that.

2 For example, as I think we are all
3 aware, and we probably will hear a little bit
4 more about today, we know for example, this is
5 just one kind of additional, in a sense, level
6 of complexities, we know that muscarinic
7 modulation effects these symptoms both
8 cortically and subcortically, we also know
9 that, again, as I've mentioned, the dopamine
10 projections, the D-1, D-2 projections, the
11 effective D-3 receptors on what's happening in
12 terms of dopamine modulation of prefrontal
13 cortex can also be targets that are affecting,
14 essentially, the GABA-glutamate interactions,
15 the capacity of the prefrontal cortex to learn,
16 to engage in its higher order cognitive control
17 operations. So, if nothing else, I want to
18 just emphasize that these are useful heuristics
19 for understanding what some of the neural
20 systems and neural transmitter systems are,
21 that play a role in negative symptoms, but by
22 no means should we think that the story stops

1 here.

2 I'm going to end with two points I'd
3 like to make, and this is sort of my perhaps
4 solipsistic thoughts about where we might be
5 headed in terms of understanding more about
6 negative symptoms in general, and its
7 relationship with cognition.

8 Our lab, which by no means we are
9 not the only lab, there are other major labs
10 around the world that have been really looking
11 at reward-based trial by trial behavior in
12 individuals and doing computational analyses of
13 this behavior. And what's really interesting
14 about this approach is you can come up with
15 tasks that can be done across species and look
16 at these variations in trial by trial behavior
17 across individuals within a species, in humans
18 who might have illness, who don't have illness,
19 who are on a medication, or not on a
20 medication, and you can start to pick up some
21 of these interesting aspects of "how is reward
22 sensitivity effecting behavior of the

1 organism?" And what we have seen is that when
2 we do these trial by trial analyses, that
3 impairments in reward sensitivity, and that
4 means how much is your decision on a given
5 trial affected by the reward you just saw on a
6 previous trial, and we see a linear
7 relationship between impaired reward
8 sensitivity and avolition ratings in humans,
9 but we can have animals do these same tasks,
10 and we can manipulate the animals.

11 In the monkeys, we can give ketamine
12 to the monkeys and disrupt the GABA-glutamate
13 balance, we can do genetic manipulations of the
14 mice and see how these different genetic models
15 change this reward sensitivity, you can do
16 pharmacologic manipulations, and so on. So,
17 this is a growing area that allows us to bridge
18 the gap between something which is so
19 subjective as motivation or lack of motivation,
20 and actual animal behavior. And we're going to
21 be just seeing lots of exciting results emerge
22 from that kind of work.

1 And I want to conclude with just
2 throwing up some data, because it sort of ties
3 together nicely with what Brandon presented to
4 us. It's really important to remember that
5 manipulation of these systems can happen
6 through behavioral means, not just through
7 pharmacologic manipulations, and we have shown
8 just recently in a trial that was carried out
9 entirely remotely across the world that when we
10 offer intensive social cognitive trainings,
11 we're really training intensively the circuits
12 that have to reliably and efficiently and
13 quickly pick up socially relevant information,
14 again, eye gaze, spatial emotion, et cetera.
15 And we pair that with an app that deliberately
16 creates goal-setting and social network support
17 for goal-setting for individuals with early
18 psychosis. That combination drives changes in
19 motivation measures -these are motivation
20 measures done by blind raters - and these are
21 correlating with changes in defeatist beliefs,
22 which are in turn associated with changes in

1 functioning six months later. So that's just
2 to give you a little bit of a flavor of the
3 different ways one can do behavioral
4 interventions, cognitive interventions. I
5 should also say, we've also seen just doing
6 straightforward cognitive training - just to
7 improve some of these aspects of higher order
8 cognition, as well as lower level kind of
9 perceptual information - we see some
10 associations with improved motivation measures,
11 particularly when we add in some social
12 cognition training.

13 All right, in sum, negative and
14 cognitive symptoms are considered separate
15 domains of psychopathology, but we see these
16 consistent associations, these shared features.
17 Negative symptoms in general, but particular
18 avolition and amotivation, seem to be
19 specifically mediating aspects of this
20 relationship. We have the frontoparietal
21 central executive network, which seemed to be
22 more implicated in persistent negative symptoms

1 or worse outcomes, and of course play a key
2 role in general cognitive capacity.

3 We see the ventral striatal reward network
4 strongly implicated in avolition and anhedonia
5 symptoms. We see the promise of computational
6 modeling of reward-based kind of learning and
7 behavior, as I think this incredible new tool
8 has evolved. And in our work and others, well-
9 designed cognitive training strategies can
10 improve motivation measures and functioning,
11 and, the most important piece, echoing Brandon,
12 is that cognitive and meta-cognitive factors
13 affect the expression and impact and the
14 evolution of negative symptoms over time.
15 Thank you.

16 DR. RASETTI: Thank you very much
17 for that wonderful presentation. So, we do
18 have like 10 minutes for Q&A, and I think we
19 can start. We can open it up to the floor, if
20 there are any questions, and then if there are
21 any, we can open it up to online questions.

22 PARTICIPANT: Hi. Thanks, Sophia,

1 for the great talk. I'm curious in your
2 studies of cognitive training, have you ever
3 looked at what percentage of those patients
4 would meet criteria for having predominant or
5 prominent negative symptoms?

6 DR. VINOGRADOV: You know, that's a
7 wonderful question, and, preparing for this
8 talk today, I realized a big blind spot that
9 I've had as a researcher is lacking a focus on
10 negative symptoms. I would say, overall, and
11 we've focused so much on cognition as our
12 outcome measure of interest, and we've only
13 looked at sort of symptoms secondarily, that
14 it's like a big lacuna, or has been for me, but
15 now I want to sort of go back and see if we can
16 retrospectively take a closer look.

17 So, I could not tell you kind of the
18 percentage or the composition of our kind of
19 samples, our participant samples, their
20 baseline in terms of negative symptoms. I can
21 tell you that we have seen, in one study with
22 first episode patients, that when we do a six

1 month follow up after the cognitive training,
2 we see an improvement in positive symptoms that
3 reaches a statistical significance and a trend
4 towards improvement in negative symptoms. So,
5 we've seen that relationship, but I couldn't
6 tell you at the outset what the relative kind
7 of composition of the sample was.

8 PARTICIPANT: Yeah, I'm curious, and
9 I'll look forward to hearing that. When I was
10 working more closely with Rich Keefe and Phil
11 Harvey, we were looking at some very big data
12 sets, CIAS trials, and I'm saying this because
13 I think this issue is going to come up a lot
14 today. The overlap between patients in CIAS
15 drug trials who met one of these predominant or
16 even prominent negative symptom definitions was
17 typically south of 20%, so it was generally
18 pretty low.

19 DR. VINOGRADOV: And what's your
20 sort of thinking or your interpretation?

21 PARTICIPANT: It's going to be
22 really hard to do trials of patients who have

1 pure predominant negative symptoms, to get them
2 done in a reasonable amount of time.

3 DR. VINOGRADOV: Yeah, yeah.

4 DR. HORAN: So, I was struck by the
5 overlapping neurobiological basis of both
6 cognitive impairment and negative symptoms.
7 So, I have a sort of psycho-pharm question that
8 also bleeds into regulatory to some point,
9 right, so I'll pick somebody else's drugs.

10 You can imagine a kappa-opioid
11 receptor drug, right, could regulate striatal
12 dopamine activity, improve motivation, reduce
13 anhedonia, and have direct effects on negative
14 symptoms, that have corresponding effects on
15 cognitive performance, right? Either directly
16 or indirectly through engagement, task
17 engagement, right, because we ultimately
18 measure cognition through cognitive measures
19 that require you to be engaged. I think Phil
20 talked about engagement.

21 So, you can imagine getting it that
22 way, but you could also look to something like

1 luvadaxistat, right, a DAAO inhibitor that may
2 improve executive function, right? So, in a
3 sense, directly improves cognitive function
4 with a downstream effect on negative symptoms.
5 And so how important is it to disentangle these
6 effects?

7 You know, to Bill's point, you don't
8 have these overlaps that you might expect,
9 although there's correlation there, but you
10 give them this very difficult decision making
11 process of "are you a pro-cognitive agent, are
12 you a negative symptoms agent, are you both,"
13 and how do you really design effective trials
14 and establish efficacy when, realistically, at
15 least from a neurobiological basis standpoint,
16 these functions are so overlapping? There's no
17 answer here, I just wanted to stand up here and
18 spout about this for a second.

19 DR. VINDOGRADOV: You know, and I
20 have to leave the pragmatics of that to my drug
21 development colleagues, I think as a
22 researcher, the geeky side starts to go "That's

1 so interesting, which is causal of which,
2 right?" And "Oh, you know, both are going to
3 be useful targets," and "One is going to, as
4 you say, may be driving -- you know, it is a
5 primary factor to the improvement in executive
6 functioning and therefore the ability to
7 anticipate reward action outcomes, and now
8 with stronger executive functioning maybe
9 you're not having as many ruminations, and now
10 it's easier for you to engage, blah, blah,
11 blah," right?

12 So, I know as a researcher that
13 becomes super exciting and interesting. I
14 think from a pragmatic point of view, in terms
15 of trial design and what are your primary
16 endpoints and so on, I don't want to touch that
17 one, I'll have to let colleagues talk about
18 that later, yeah.

19 DR. HORAN: Thank you.

20 DR. HARVEY: I just wanted to raise
21 a point about the unitary nature of motivation
22 and engagement. We finished a large-scale

1 ecological momentary assessment study, and
2 about 20% of our patients were home and alone
3 during 85 out of 90 surveys that they answered.
4 One would interpret that as being social
5 amotivated, but they answered 85 out of 90 EMA
6 surveys when they were home and alone.

7 So, what this suggests is that they
8 weren't completely unmotivated, because they
9 were doing something when they were requested
10 to do it. Maybe you could say it was because
11 of the dollar they were getting when they
12 answered the survey, but it suggests that there
13 are layers of motivation. And I think your
14 positing the complexity of the interaction
15 between cognition and motivation may help
16 resolve some of those questions, because one
17 would think that you would view some of these
18 digital phenotyping strategies as being very
19 hard to pull off in people with significant
20 negative symptoms, but that's how we know they
21 have such significant negative symptoms, is
22 because they're answering the digital

1 phenotyping surveys.

2 DR. VINOGRADOV: Right, and so two
3 important points there in terms of actual kind
4 of, you know, working in the real world, which
5 is because of some of these motivational
6 deficits, it's challenging to have participants
7 want to engage in these intensive treatments
8 without some sort of very concrete reward
9 attached to it.

10 Abstract reward is difficult. So
11 we, in our first episode work, we find that
12 offering sort of cognitive training and use of
13 the motivation enhancing app, just offering it,
14 the uptake is low. If we offer it along with,
15 "here's a chance to earn a few dollars every
16 time you use it," the uptake is much better,
17 right? it's almost like we have to hijack the
18 motivation system initially to kind of get it
19 jumpstarted in order then for the individuals
20 to engage in these more plasticity-based
21 treatments, right, that eventually will allow
22 for the symptoms to be much more self-

1 perpetuating. So that's point number one.

2 Point number two, and I think I was
3 just hearing from Dr. Strauss about really this
4 strong relationship between the kind of
5 motivation levels, and forgive me if I'm not
6 getting it right, that people are experiencing
7 over the course of their days and their weeks,
8 and where they are in terms of an environment,
9 whether the environment is enriched, not
10 enriched. You know, so it becomes almost a
11 social deafferentiation situation, or a sort of
12 general stimulation deafferentiation, in that
13 there's this again, interplay between
14 environmental impoverishment and motivational,
15 the kind of motivational systems in the brain.
16 Did I get that right? Pretty much?

17 DR. SCHOOLER: So I just wanted to
18 get back to the issue of pharmacologic trials,
19 and from what I'm hearing you say, one of the
20 questions that becomes important is actually, I
21 can refer to the movie Groundhog Day, which I
22 think everybody remembers, and the fact that by

1 the end of it, the character can do all sorts
2 of things that he couldn't at the beginning,
3 because he's repeating the same day over and
4 over. So the question becomes, what would the
5 role of cognitive training be in evaluating a
6 medication that was primarily designed for
7 negative symptoms and improving motivation?

8 And I just wanted to raise one other
9 point, which relates to Bill Horan's comment
10 about the very low percentage of people in
11 their trial, in their study that had
12 predominant negative symptoms, and that's that
13 people with lack of motivation are not
14 motivated to participate in trials. And I just
15 want to link what you've been talking about to
16 what the goal of the session today overall is,
17 and I wonder if you have comments on it?

18 DR. VINOGRADOV: Just that in real
19 world clinical practice, the patients I worry
20 about the most are the ones that are not
21 motivated to come into their treatment, right?
22 And those are the ones who have the poor

1 outcomes, and again it becomes that sort of
2 downward spiral. They have predominant
3 negative symptoms, they don't engage in
4 treatment, they don't engage in studies, they
5 don't engage in trials, et cetera.

6 But in terms of, like, in the ideal
7 world, I mean, I know the focus here is drug
8 development and I don't want to take away from
9 that focus, but we all know that the optimal
10 kind of treatment approach for individuals with
11 psychosis spectrum illnesses is multi-modal,
12 and in my fantasy world we would be combining
13 these motivation enhancing negative symptom
14 addressing medications with kind of evidence
15 based behavioral and psychosocial
16 interventions.

17 And I honestly think the combination
18 together could be done quite efficiently, like
19 I think we could get significant improvements
20 over two to three months, which is something
21 you can sell to, you know, young first episode
22 patients and their families.

1 MS. RASETTI: Thank you very much.
2 I think we are running out of time.

3 We're going to have now a coffee
4 break of 10 minutes, and then we will start
5 with Session 2. Thank you.

6 (Whereupon, the above-entitled
7 matter went off the record at 10:20 a.m. and
8 resumed at 10:31 a.m.)

9 DR. BLACKMAN: We will try to stay
10 as close to on time as possible. I know we're
11 already running a little over, so let me just
12 get started with some introductions and
13 logistics as people sit back down or get back
14 to their computer.

15 I just want to introduce myself.
16 I'm Dr. Rachael Blackman. I'm a clinical
17 reviewer in the Division of Psychiatry here at
18 the FDA. I will be moderating Session 2, which
19 is on study design.

20 So, in this session we will focus on
21 the challenges of designing studies and
22 clinical trials to assess the effectiveness of

1 negative symptoms in schizophrenia. Currently,
2 there is no consensus on the best way to design
3 clinical trials for negative symptoms in
4 schizophrenia, so this is important
5 conversation for us to have.

6 Before we start, I just want to make
7 clear that there are currently no approved
8 medications for negative symptoms associated
9 with schizophrenia. Therefore, any drugs
10 mentioned by the speakers or panelists today
11 are either investigational or being used off-
12 label in any examples you may hear about.

13 Now let me describe the format of
14 the session. We will hear from two speakers,
15 and then we'll have a panel of esteemed
16 respondents. So I will introduce all the
17 panelists after the speakers have finished and
18 we will hold all questions until the end of the
19 session, during the Q&A part.

20 And now it's my great pleasure to
21 introduce our first speaker, Dr. Cristoph
22 Correll. Dr. Correll is a Professor of

1 Psychiatry at the Zucker School of Medicine at
2 Hofstra/Northwell in New York, as well as
3 Professor and Chair in the Department of Child
4 and Adolescent Psychiatry at Charite University
5 Medicine in Berlin, Germany. Dr. Correll
6 completed his medical studies at the Free
7 University in Berlin, Germany, and Dundee
8 University and Medical School in Scotland. His
9 focus has been in areas such as identification
10 and treatment of severe mental illnesses,
11 psychopharmacology, and clinical trials. If
12 you've read any articles in recent years,
13 chances are you've read one of his
14 publications, because he's highly prolific and
15 very well cited. Dr. Correll will be talking
16 about considerations for drugs designed to be
17 adjunctive to antipsychotic medications today.
18 Dr. Correll...

19 DR. CORRELL: Thanks so much for the
20 kind introduction. We're unfortunately 15
21 minutes late, but I'll try to stay on time.
22 I've already been reminded to do so, so that

1 our panelists can really have their two
2 minutes. I was complaining I only have 20.
3 But when I heard you only have two, I'm okay
4 with that.

5 So there are many great minds in
6 this room; there are many great minds
7 listening. And I think it's wonderful -- kudos
8 to the FDA to convene this meeting -- that we
9 try to put our heads together, as has been
10 done, like, over a decade ago. Steve Marder
11 was leading that effort. And the question is,
12 have we advanced since then? And I would hope
13 that out of this meeting we can also have
14 another paper and consensus come out of this.
15 How to not only raise problems, but maybe even
16 solve them, or make some suggestions what the
17 next avenues should be.

18 So this is my disclosure
19 information. And this is what I would like to
20 cover. A lot has already been in my first
21 section alluded to, so that makes it easier.
22 So the negative symptom considerations will be

1 easier and faster, but then treatment
2 considerations and trial design and some
3 recommendations will be the meat of this.

4 Now, you've already heard that we
5 are talking about predominant, primary, and
6 persistent. But there's also been a question,
7 should it be really predominant? Or how much
8 admixture should we allow in order to be more
9 real-world? And where's the pseudo-
10 specificity coming in?

11 Also, there's another question about
12 pseudo-specificity of comorbidities, either
13 dimensionally or categorically. Here is a
14 paper that looked at the transdiagnostic
15 presence of some of these symptoms across
16 diseases. And are we excluding and making the
17 sample squeaky clean? Or are we allowing some
18 of these comorbidities in, especially anxiety
19 disorders, so that we even have a pool of
20 patients and can generalize to the patients out
21 in the real world? But, then, what does that
22 mean? Where does the negative symptom come

1 from?

2 We've already heard about that there
3 are different components in negative symptoms.
4 And here I just took out three studies.
5 Although the negative symptom component -- or
6 the percentage overall was different across the
7 studies, you can see that the distribution,
8 which of the negative symptom domains was most
9 frequent, was consistently the highest in the
10 social amotivation. So, for each of the
11 studies, that was the highest. So should we
12 enrich for that? If we have more patients with
13 these symptoms, would a drug work particularly
14 well if it captures that aspect of it? Do we
15 need to look much more, not just at the
16 outcome, but at the in-come, what the patients
17 look like? And, particularly, do we want to
18 enrich? Do we want to even approve, or
19 consider going for approval, for medications
20 that have specific effects rather than global
21 effects?

22 We've already heard about depression

1 being a potential confounder. And it's
2 interesting that antidepressants, in patients
3 who say they are not depressed and have
4 schizophrenia with negative symptoms, seem to
5 work, with an effect size of about 0.28
6 overall, 0.37 when the primary outcome is
7 negative symptoms.

8 So, should we rule out some of the
9 patients that have depression based on an
10 overall depression scale or specific items in
11 depression? So, should we exclude patients who
12 have pessimism or suicidality, because that
13 might be much more related to depression,
14 rather than the blunting that we see otherwise
15 with schizophrenia and negative symptoms?

16 And already we've also heard about
17 secondary negative symptoms, that we need to
18 rule out potential effects when patients
19 improve on depression, or EPS, or sedation. Do
20 we have a stay or switch design where both can
21 move? Or do you have a drug that has less EPS,
22 or even treats EPS, or less sedation? Does it

1 help with sleep or reduce pain, which can all
2 also mimic negative symptoms? That's all very
3 relevant. And, obviously, with the predominant
4 versus primary or prominent symptoms of
5 negative type, we need to talk about the
6 positive symptom overlay also.

7 Now, negative symptom treatment
8 considerations. What has been done in the
9 past? We did an umbrella review of 42
10 augmentation strategies. And that's my talk.
11 Steve Brannan will talk about monotherapies.
12 And we were quite flabbergasted how many, when
13 you look meta analytically, how many treatments
14 actually are better than placebo. Wow; that's
15 quite a lot here. And they have effect sizes
16 of 0.2, 0.3, 0.8. Really? One, 1.4. This is
17 all our meta-analysis, SNRIs. That's amazing.
18 So we have all these great treatments that we
19 should use in clinical care, but somehow it
20 doesn't seem to work. And they should all be
21 approved. And nothing is approved. So what's
22 going on here? And that's for non-clozapine

1 treatments.

2 And here we have clozapine where nothing
3 seemed to work.

4 And so we thought, wait a second, this is
5 weird, and looked at the quality of the meta-
6 analyses. And, actually, the meta-analyses
7 were done well. Fifteen of the 32 meta-
8 analyses were mine. We weren't doing such a
9 bad job there. But, then, wait a second. Why
10 are they good? Because we have quality
11 metrics. Every meta-analysis now has to follow
12 certain procedures. So they were done well.
13 But, what's going on? There's a disconnect.
14 So we created another quality metric. And
15 that's not for the meta-analyses, but for the
16 studies that enter them, and for the
17 consistency between the individual studies and
18 the overall outcome. And that's where it all
19 fell apart. So, basically, this goes until
20 eight as a quality score. And you see there's
21 nothing higher than five. And all of the
22 significant effects had three or four or two of

1 the quality. And that is because they were all
2 small. There was a big publication bias.
3 Because if you have a small study and it
4 doesn't work, well, then it's not powered. But
5 if you have a small study and it works, yes, we
6 found something, this is a great lead. So, we
7 have a real problem. In none of these meta-
8 analyses, in none, did the larger study ever
9 confirm what all the individual studies that
10 drove the mean effect actually showed. So we
11 need to get away from these meta-analyses that
12 put everything in and celebrate. But it also
13 tells us that the cliff from phase II to phase
14 III is enormous. Because we have a small study
15 with little expectation, that works. And then
16 everything falls apart when we do the larger
17 study.

18 And we also need to consider what
19 happened in prior trials. And there are people
20 here in the room that have driven that forward.
21 So this lack of approval of any treatment for
22 negative symptoms is not for lack of trying.

1 We've tried. So why have failed? Is it the
2 design? Is it the molecules? Is it both? And
3 we're obviously here in order to hone in on the
4 design so that we can make it easier for
5 molecules that could work to actually show
6 this. Now, this is a phase II trial with
7 bitopertin, a glycine transporter 1 inhibitor.
8 A \$1 billion endeavor that failed,
9 unfortunately. And the first thing that I've
10 learned from clinical trials, when your phase
11 II study that has little expectation just
12 scrapes the 'p' less than 0.05, forget it. You
13 don't have any buffer. It will get lower, the
14 effect size. And if you then have to do a sub-
15 analysis on per protocol on patients that
16 actually fulfill the protocol, and only then it
17 works, you have even less of a buffer. So we
18 need to learn from phase II, and maybe do
19 another phase II, to see which of the patients
20 do better. But what was also interesting is
21 that our usual linear, higher dose is better
22 than lower dose, doesn't always work for

1 certain of these mechanisms. So here there
2 seemed to be an inverted U-shaped curve. Do we
3 need to learn from that? But what you can see
4 is that at eight weeks, which is considered
5 relatively short, there was around 6.5 point
6 improvement for drug. And there was about 4.5
7 for placebo.

8 That's basically eight weeks here of 6.5
9 and five points. It's interesting that when
10 you now go for not eight or 16, but 24 weeks,
11 or three times the duration, the effect at
12 eight weeks was much lower. Why was that? I
13 mean, that's weird. Because if at eight weeks
14 you already have so much drug and placebo
15 effect, now people know I have three times the
16 time, so maybe the expectation is it will take
17 longer. And so at the end of 24 weeks there
18 was not much higher, actually, a similar effect
19 for the drug. The drug didn't move. But the
20 placebo effect, obviously, got larger. So
21 that's a problem here. Why does placebo
22 increase and drug doesn't increase? We see

1 that with positive symptoms or total symptoms.
2 Generally, the placebo effect goes up, but the
3 drug also gains.

4 And then the most recent effort to
5 look at pimavanserin, a 5-HT inverse
6 antagonist. And it showed at Week 26 in phase
7 II, again just a barely significant effect.
8 The effect size was 0.21, 11 versus eight
9 points. Yes, there was a dose effect. In this
10 case, the higher dose was better. It actually
11 had an effect size of 0.34. That's something
12 you can rest on and say, okay, 0.34, that's
13 maybe the minimal effect where it can see
14 something, even at a larger study. So phase
15 III study was begun. But should we have
16 trusted these results? How consistent do they
17 have to be? Well, first thing was,
18 unfortunately, the drug again in phase III had
19 the same effect, about 11 points, but drug
20 placebo caught up, and you can see the effect
21 size dwindled from 0.34 for the 34 milligrams
22 now to 0.07.

1 But should we have trusted the phase
2 II effect size and effects? Well, do we need
3 to also triangulate and understand different
4 measures measuring different things of the same
5 construct? I mean, we've talked about
6 confounding. But also it could give us some
7 estimate of robustness of finding. So in the
8 phase II study there was the small effect size,
9 0.21 for the NSA-16 total. And, again, this is
10 not divided by dose. But you can see that it
11 didn't really generalize across different
12 domains in the NSA-16. It only separated with
13 an effect size of 0.26 for one single aspect.
14 So, out of five domains, only one. Is that
15 enough to do a phase III trial? All right,
16 maybe it is, because it all adds up with small
17 effect sizes. But then, does it have any
18 clinical relevance? There was basically no
19 CGI-S effects. So if it has a negative symptom
20 effect, why doesn't it, in predominant negative
21 symptom, move the needle overall? And then,
22 yes, we're not happy with the usual PANSS

1 negative symptom score because two of them are
2 cognitive. But they should correlate, correct?
3 And there was, again, nothing there. So is
4 that enough then to say, yes, we have our
5 primary outcome and need to move forward? Do
6 we need to look at consistency? Do we want,
7 actually, to measure different aspects and be
8 sure that they move in the same direction, or
9 at least carve out subdomains?

10 And we talked already about the
11 placebo effect. So, this is a meta-analysis of
12 placebo effects published in 2019 by Fraguas et
13 al. And you can see that, overall, across
14 different agents with different mechanism of
15 action, the effect size was small, 0.2. But
16 there was huge heterogeneity: studies where
17 placebo beats drug and some studies where it's
18 basically a negative finding, and some where
19 there's a big effect size.

20 So the question, then, is: what drives
21 this?

22 Wait a second, sorry, I forgot about this.

1 So this is the effect size of placebo from
2 baseline. Remember, 0.2 is a small effect
3 size, 0.5 is medium, 0.8 is large. Three, the
4 Cohen's d is three. And it goes from basically
5 0.2, almost nothing in these studies that I
6 just showed with bitopertin, to 14 and 12, if
7 that was calculated correctly. I'm a little
8 bit doubtful that it's that high, but it was
9 calculated and published. But that's enormous,
10 obviously.

11 How can we mitigate the placebo
12 effect? So, here are some regression analyses.
13 And what you can see is multiple factors in
14 univariate analyses drove the placebo effect.
15 Actually, higher study quality drives more
16 placebo effect. That's confounded, because the
17 good placebo control lab studies that have good
18 metrics actually were negative. Later year of
19 publication, our placebo effect has gone up,
20 both for overall effect but also negative
21 symptoms. Longer duration of the trial,
22 interestingly. But what really drives it is

1 higher number of arms in the trial. So if you
2 have too many doses you have a problem. Too
3 many sites. These are all the industry-
4 sponsored studies, obviously. Number of
5 countries. Also number of patients. That's
6 because these are phase III studies.
7 Interestingly, also the mean age, lower mean
8 age, but only in the placebo arm. And also
9 severity of the lower severity of the negative
10 symptoms drove also the placebo effect.
11 Industry funding drove it, because these are
12 the larger studies. When you do a multivariate
13 meta-regression analysis all the other factors,
14 some of them that might sound a little strange
15 are basically driven by these three elements:
16 industry funding so these are large studies,
17 with a higher number of arms, and higher number
18 of sites. So maybe you want to have a small
19 study. But the small studies are usually done
20 when you don't know whether it works. When the
21 drug works, everybody has expectation.

22 So I want to finish up in the last

1 five and a half minutes by drilling into some
2 of the design issues that are overall relevant
3 for the effect of medications for negative
4 symptoms. And then particularly focus, on the
5 next slide, on what might be relevant for the
6 design of augmentation studies.

7 Some of it will be discussed also in
8 other sessions here, especially Session 4,
9 which is very important, about which outcome
10 measure do we actually use. So, population,
11 which age should it have. Is it inpatients or
12 outpatients or mixed? What's your recruitment
13 frame? How do you get them? Do you announce:
14 do you have negative symptoms and want to come
15 in? Or do you actually get clinically-defined
16 patients? I think that's crucial. Because I
17 have patients call me, are you Dr. Correll?
18 Yes. Do you have a study for me? Do you do
19 clinical trials? Yes. And then they said,
20 well, do you have a study for me? And I say,
21 well, I don't know, tell me what's your
22 diagnosis. And the answer was, what do you

1 need?

2 (Laughter.)

3 DR. CORRELL: And I say, wait a
4 second. That's not how it goes. So what's
5 your diagnosis? Schizophrenia? I say, well, I
6 don't think this is going to work. So, I don't
7 think so. And he said, wait a second, wait a
8 second. Do you need a healthy control? I
9 said, wait, what? You just said that you have
10 schizophrenia. But I was once a healthy
11 control.

12 So we have to be careful with
13 announcing our studies. If I had said, oh,
14 yeah, I have this and this and this studies, he
15 would have said, yes, maybe I fit that one. We
16 have to be, I think, more in the clinical
17 validation of these patients.

18 Cultural differences will be
19 addressed. Who wants to be part of the study?
20 Illness stage. Do we want younger patients,
21 early in the illness, less affected by dopamine
22 blockade or the illness? Do we want more

1 generalizability? What are comorbidities that
2 could also respond to the medication? What of
3 substance use that is maybe ruled out at
4 baseline, but then still has a background
5 effect?

6 Prior treatment. Which
7 antipsychotics? For how long? Will our
8 augmentation studies be different once we have
9 non-post-synaptic dopamine blockers approved
10 and in the mix? Will that allow us to do
11 different studies with different agents that
12 were before dampened by dopamine blockade?

13 How much washout do you want? Can
14 you washout? I mean, that's the monotherapy
15 question that you will have. How do we enrich?
16 Is it the severity? Is it the type of negative
17 symptoms? Will it then have to depend on the
18 mechanism of action of the drug?

19 How long for the stability or the
20 trial duration be? Assessment, I think, will
21 have to be dealt with in Section 4. But I
22 guess we want the persistence. Maybe digital

1 markers are much more important than
2 retrospective recall, how did I feel in the
3 last month?

4 Pseudo-specificity, we talked about
5 that. Also clinical stability. Additional
6 outcomes. They can enrich and enhance trial
7 burden, and maybe also the placebo effect.
8 Because we have tender loving care. There is
9 already an intervention as we get patients into
10 the study. They come often out of rarified
11 environments into environments that are much
12 more enriched. And people want them to come
13 back. Give them coffee and say, please, we
14 like you, come here. And here you also have
15 the reward of remuneration. And then we need,
16 obviously, retention.

17 Data analysis. MMRM is the name of
18 the game. We're basically biasing toward a
19 completer sample, correct? Because we're
20 imputing the outcome from the patients that are
21 the super-responders and stay until the very
22 end. It's maybe a little less severe as in the

1 total symptoms studies. So we need to look at
2 missing, not at random, if that's the case.

3 So, here are some of the highlights
4 for the augmentation. Does the augmentation
5 have to be longer, because the effects are
6 often smaller when you augment rather than
7 monotherapy?

8 What are comorbidities? Can they
9 dampen or enrich the effect if you have co-
10 treatment of them? Do you want less dopamine
11 blockade? What about washout? What about
12 prominent negative symptoms. Do we need them
13 in to be more generalizable?

14 Also, what about lead-in? Do we
15 need a double- or triple-blind placebo lead-in?
16 Variable add on beginning in order to not have
17 people be so expecting of an effect. And then
18 maybe exclude patients that have improved
19 beforehand.

20 There has been a big effort before
21 that already has, I think, guided us. We want
22 severity to be defined. Steve Marder is the

1 first author a decade ago.

2 We want to exclude EPS.
3 Antipsychotics, should first and second
4 generation be there? Should we do
5 stratification based on D2 blockade? A
6 question. Should cognition be co-registered?
7 Do we need, basically, a single global score?
8 No, I think we also need to look at sub-scores.

9 And clozapine is a different kettle
10 of fish because of the treatment resistance.
11 Even in the augmentation meta-analysis it
12 didn't work for clozapine.

13 This was not discussed in the
14 meeting. But this was discussed. And the only
15 lack of agreement, and we should focus on that,
16 is predominant versus prominent.

17 Yes, we want to exclude depression,
18 have a functional outcome, but it's not
19 required as co-primary.

20 Informants. It's nice to have.

21 Trial duration. Should there really
22 be a difference between phase II and phase III?

1 Usually, that can make things a little
2 complicated in the interpretation. We want
3 clinical stability, and also prospectively
4 assess that before the trial for negative
5 symptoms.

6 So I would say we have problems with
7 the augmentation data that have so far been the
8 name of the game. Monotherapy is only recently
9 coming in, because all of our dopamine blockers
10 made these negative symptoms potentially worse.

11 Partial dopamine agonists might have
12 some effect. But is that because when you
13 augment you're bumping off the other dopamine
14 antagonists from the receptor? And in a meta-
15 analysis that was an effect, adding
16 aripiprazole to dopamine blockers, even in high
17 quality studies, not only in low quality
18 studies.

19 So we need to define the underlying
20 treatment very much. So the illness duration,
21 comorbidities. There will be a lower effect
22 size, most likely, than in monotherapy. What

1 about functional unblinding? Keep placebo
2 effects in check.

3 And then, also, we talked about
4 combination treatments. Well, should these
5 drugs be used in order to boost? Or would the
6 drug effect be more clear when you do a
7 psychosocial intervention? Because otherwise
8 you have people who are in rarified
9 environments and can't even execute what's now
10 better in their brains. But, on the other
11 hand, you might enhance a placebo effect even
12 more and wash out the drug difference. So we
13 need to consider that.

14 And symptom enrichment and lead-in
15 options, I think, should be given
16 consideration, and, clearly, how to assess
17 negative symptoms.

18 Thank you very much.

19 DR. BLACKMAN: Thank you so much for
20 that wonderful talk. For our second speaker of
21 this session we will be hearing from Dr.
22 Stephen Brannan. Dr. Brannan is the former CMO

1 of Karuna Therapeutics and a neuroscience drug
2 development expert who has held senior
3 positions overseeing both clinical development
4 and medical affairs for more than 15 years in
5 industry. Dr. Brannan's experience includes
6 drug development registration, medical affairs,
7 launch and lifecycle management in areas of
8 anxiety, depression, epilepsy, schizophrenia,
9 the list continues. He trained in psychiatry
10 at the University of Texas Health Science
11 Center at San Antonio and holds an MD from the
12 University of Texas Health Science Center at
13 Dallas Southwestern Medical School.

14 (Off-microphone comment.)

15 DR. BLACKMAN: So, today he will be
16 talking about the considerations for drugs
17 being designed to be monotherapy. Dr.
18 Brannan...

19 DR. BRANNAN: Thank you.

20 And disclosures.

21 So I'm going to talk about some
22 general issues. Dr. Correll covered a lot of

1 this, and some of the previous speakers. He
2 and I even talked a little bit so we could
3 parse them out a little bit. So, some of these
4 I'm not going to spend a lot of time talking
5 about. The duration of the trial. Negative
6 symptoms purportedly take longer to respond.
7 There's some evidence for that, but it's
8 certainly not universal. And what happens if
9 you have new mechanisms? Is it the same? An
10 issue: how stable do subjects need to be
11 regarding the negative and positive symptoms?
12 So, there's some arguments about that.
13 Certainly, stable and persistent for the
14 negative symptoms. How many recent
15 hospitalizations or symptom changes. So, how
16 OC do we want to be about all these things?
17 There's an issue about relapses and rescues.
18 I'll talk a little bit more about that. And
19 then enrichment, what are the appropriate
20 thresholds for negative symptoms and relative
21 to positive symptoms? So, these are issues
22 that I think that are not quite resolved and

1 probably deserve some discussion. Dr. Correll
2 specifically mentioned, you know, some of the
3 exclusions with depression or EPS. This also
4 comes from ISCTM recommendations that have come
5 out, like, over ten years ago, and then just a
6 couple of years ago. So they've been very
7 consistent. Where do study subjects come from?
8 What is the role of the site and regional
9 differences? And this becomes more important
10 when you get to these large trials. Probably
11 increases variance a great deal when you go too
12 large, by the way. Do you also assess for
13 cognition? Age range? So these are all things
14 that are covered. I'm not going to dive into.
15 I'll say a little bit about placebo issues,
16 because we felt it was important for both of us
17 to kind of chat a little bit.

18 So, let me go to enrichment and
19 relapse issues. General consensus is that you
20 need to exclude the actively psychotic
21 individuals, such as those seen in most of the
22 acute schizophrenia studies, and excluding

1 subjects who lack stable symptoms. Again, this
2 has to do with reasons of variance. Now,
3 there's a question. Should one exclude any
4 subject scoring above a certain threshold for
5 an individual item on the PANSS that's a
6 positive symptom item? So this, I think, is,
7 some people say yes, some people say I'm not
8 sure. Study only stable patients with
9 predominant negative symptoms. Again, how much
10 do we go in this direction? But I think,
11 generally, people are thinking this is the way
12 we want to lean toward. In the studies
13 particularly I'm going to be talking more about
14 on monotherapy, are European sites' patients
15 favored? And there's some reasons for this.
16 In the U.S., a lot of the patients coming into
17 the industry trials are not well-known to the
18 PIs, whereas that is a little different in
19 other parts of the world, such as Europe. And
20 do you add a standardized, here I have
21 vocational rehab and social opportunity, but
22 Sophia and others were mentioning some of the

1 other things that one can do. And is this
2 important to do either prior to the trial or
3 throughout the trial? Would it be synergistic?
4 As Dr. Correll mentioned just in parting there,
5 there are pluses and minuses to this because
6 this could also exacerbate placebo issues,
7 which we know are a difficulty. Let me talk
8 just a second about relapse. So, particularly
9 if you're looking at, and I'll get more into
10 this in a few slides, monotherapy and placebo,
11 you need to have, really, even if you're doing
12 it for all medications, what rules trigger when
13 a subject should be withdrawn? How much
14 fluctuation can one tolerate? So, there's
15 always going to be fluctuation in the trials,
16 especially across the entire population. So
17 you need to start thinking about, okay,
18 sometimes there's fluctuations. We can handle
19 that. And the sites are pretty good at this
20 for the most part. But, in the interest of
21 safety, and even the integrity of the trial,
22 when do you need to start withdrawing subjects?

1 And how do you set that up? One interesting
2 issue and we'll talk more about this, like with
3 the Minerva trial is, is there a subgroup of
4 patients less prone to relapse? And can they
5 be used in these types of trials? And who are
6 they in the general population? What should be
7 the role of a support network and informants?
8 So these are also issues. When I do my trials,
9 I consider myself very pragmatic. So, there's
10 lots of wonderful things one can do, but you
11 shouldn't do it in a trial when you're trying
12 to kind of get stuff done. Keep it simple.
13 And, of course, there's a role need for a DSMB
14 safety board. And this is true for many, many
15 trials. But what is that role here? Is it
16 changing any for negative symptoms in
17 particular?

18 I want to show you just one slide
19 here. This is really from our ISE, not our,
20 excuse me, ex-Karuna now BMS. And it has to do
21 with the KarXT stuff. And it's only looking at
22 the Marder negative symptom scale. On the

1 left-hand side, the full sample, you can see
2 that it looks like there's a drop in negative
3 symptoms, which is pretty common when you're
4 treating the general study population for these
5 acute trials. Then, in a sub-analysis that
6 Bill Horan and others were doing, they looked
7 for predominant negative symptoms, which is a
8 little hard to do. So, it's a small subset
9 within that whole group. And you see it's a
10 little bit more back and forth on the placebo,
11 although it ends up in about the same place.
12 But, you see that group seems to respond even
13 better. And this may just be, you know, you're
14 really finding people with a lot of negative
15 symptoms, so you're seeing more of a drop. But
16 it's an interesting thought, if you're kind of
17 trying to look and see how can we get subjects
18 that are particularly good, or might be good to
19 look at, if you think you might have something
20 useful for negative symptoms.

21 So I'm going to primarily leave the
22 outcome measure issues alone for Session I

1 think it's 3 or 4. I can't remember. So,
2 there's a few things that are still important
3 for the general study design. A relative
4 consensus that functional co-primary is not
5 needed. But should a global scale be included,
6 such as CGI, specific for schizophrenia? And
7 people have already touched on this. Does one
8 look for negative symptoms as entire totality
9 or dimensions? And which dimensions do you
10 look at? I think there is a relative consensus
11 building for depression and EPS scales, mainly
12 to rule out confounds. And then there's the
13 issue of accurate and stable ratings. I want
14 to concentrate on accurate here, one of the
15 bugaboos I have. Is there a need for
16 informants? Do they actually help the
17 accuracy? In the schizophrenia trials, that's
18 not necessarily the case in the U.S. I'll just
19 throw that out. The other thing I was very
20 impressed at, in talking to a number of people
21 while trying to put together this talk, is many
22 of the scales for negative symptoms are not

1 easy to rate consistently. So, based on
2 previous studies, there may be some things you
3 want to do to try to shore that up, and also to
4 know that you add multiple ones of these that
5 can't be done well, that may not be a good
6 idea, either. And then, finally, the use and
7 role of non-rater measurements. So direct
8 speech and facial measurement and the role for
9 ecological momentary assessment, even
10 actigraphy. Now, they're new, they're
11 exciting, but I think, in the next five to ten
12 years, they might be more important as people
13 further refine some of these things. I'm just
14 going to show you some very preliminary kind of
15 stuff that I've seen that I think is sort of
16 interesting.

17 One is, as one looks over the course
18 of six months in just a non-controlled safety
19 study, unproductive versus productive
20 activities. I won't go into the details of how
21 that's all determined. But one can see a very
22 interesting and promising thing here, that it

1 looks like, over time, from the EMA-type
2 information that one is getting, that both the
3 unproductive activities drop and the productive
4 activities increase during this safety study.
5 So it looks like, there are things here that
6 might be of interest in the future.

7 And then this is just very simple
8 daily steps. And so, over the course of six
9 months, again, we don't know how many steps
10 are, important steps or anything like yet.
11 That's a couple of years away I think. But you
12 can see pretty clearly and easily that people
13 are walking more. There's more steps being
14 taken, more activity.

15 So, placebo issues. I am going to
16 concentrate on the middle of the three, the
17 need for rater surveillance. So, I just
18 mentioned a few minutes ago that some of these
19 ratings are not that easy to do, particularly
20 consistency over the course of a trial. And so
21 I'm a big believer that rater surveillance is
22 probably needed. Why have I put it under

1 placebo? It's a lot of non-specific stuff.
2 But, from my experience, this is one of the
3 areas you really need to be careful about rater
4 drift and other sorts of things. And the idea
5 that things are being surveilled, I think,
6 really helps. You sort of get this effect of
7 being watched. And the sites and the raters,
8 in particular, I think, behave differently over
9 time if you have this. Particularly for
10 negative symptom patients, the issue of staff
11 attention is important. If you think of the
12 nature of it, these are people who may not get
13 a lot of attention. And so when you bring them
14 into a place and they're getting a lot of
15 attention, that has some non-specific effects
16 that we also call placebo. And this final one
17 and there hasn't been a lot of stuff published
18 on this, but I think increasingly and I think
19 there's going to be a session coming up at
20 ISCTM in about a year, blinded data analytics.
21 So, there's things that one can watch that can
22 be important to, again, help people understand

1 how to stay...I'll just give a brief discussion
2 of something that I got a call last night from
3 somebody trying to put together a study. And
4 they're like, well, you know, these rescue
5 medications, you know, how much is too much?
6 It had to do with benzodiazepines, I think, in
7 mania. But, it depends on what you're doing,
8 how long, and so on and so forth. But one of
9 the things I said is, well, you should keep
10 watch by site how this is used. Because I can
11 tell you from our schizophrenia studies, some
12 sites never gave a rescue medicine to anyone;
13 other sites gave a rescue medicine to everyone.
14 So, and there's everything in between. So
15 there are things you can watch and talk to your
16 sites during the trial, without perhaps being
17 overly pushy about certain things. But,
18 reminding folks. I did for one site we had,
19 had everybody over the age of 55 for their
20 first three people. And so I called up and I
21 asked how long the geriatric convention was
22 going on in town. And the next three subjects

1 were all under the age of 55.

2 Issues pertaining to monotherapy
3 trials. I think a couple of things here. The
4 comparator arm, are you doing placebo? Are you
5 going to do that against other antipsychotics,
6 in this case, other comparators? And then it
7 also touched on the role of psychosocial
8 interventions. So, you can do a number of
9 things here. And then the idea would be,
10 particularly with the monotherapy, and if
11 you're doing it, is this going to be an
12 additive thing if you're using this? Or is it
13 going to be synergistic? Such that if you
14 actually have something that helps negative
15 symptoms and you have the training or
16 augmentation that is non-pharmaceutical-
17 related, maybe that's the best way to see,
18 actually a signal. So I think all this is not
19 well-determined. If you choose against
20 placebo, there are safeguards. And I'll talk
21 about this in the next slide. For longer
22 durations, you just need to and even if it's

1 not against placebo, define symptom worsening
2 well. You need to have an active safety board.
3 And you will need study subjects who are non-
4 relapsers, for lack of a better term. So,
5 stable, no history of relapse, and probably
6 they also have a good support network. And,
7 again, the number of patients who do that and
8 also are willing to come in to the trial may be
9 small. Against the comparator, you want to
10 have a drug with minimal EPS, or anything that
11 would sort of confound while it was going on.

12 Pragmatically, one cannot use all
13 antipsychotics. So, which one, or ones, do you
14 use are sort of issues. We may not decide
15 today. But important one.

16 So, I'm going to start off here with
17 a placebo-controlled trial. So, there's always
18 a screening period and washout, prior to
19 randomization. So this is important for all
20 the things. Now, I don't have any open label
21 extension on these, but you can clearly use
22 that further on. And all these boxes are going

1 to be very similar. So it's really the stuff
2 in this box here that we'll be talking about
3 that are the differences. So, there is a
4 notable relapse risk. I'll show you some of
5 that. At least if you look at the general
6 population. There's a high potential for
7 symptom fluctuation, and it can complicate
8 treatment benefit. And, of course, this is
9 probably true for most of them. There can be a
10 reluctance to participate, particularly if they
11 know they're going to be on placebo for a long
12 period of time. And this could extend your
13 timelines to enroll.

14 Now, I'm going to talk a little bit
15 about the Minerva trial in a second, about an
16 example of this. Maybe not exhaustive. But,
17 again, we do know that the patients on placebo
18 had an increased risk for relapse. And then
19 you can see again here, in some nice meta-
20 analyses, that if you're looking at this, it
21 does show that these people do relapse. So
22 it's not that you can't find a subgroup. But,

1 overall, this appears to be the data the we
2 know motivates and it's important for why we
3 use antipsychotics in particular. There's
4 ethical consideration really every way you do
5 this. The Minerva trial, 12 weeks duration
6 with a 24-month open label extension. Age
7 ranges, there's 234 subjects, so pretty good.
8 Negative symptom stable for three months. So,
9 how long people need to be stable, people argue
10 about. I found it interesting that BMI over 35
11 you were not allowed to be part of the trial.
12 But I've done mainly U.S. trials and this is
13 primarily European sites. So it probably all
14 fits.

15 You can see actually that in the
16 Figure 2 is really the overall PANSS total.
17 And a low group and a high group. And there's
18 some differentiation. And then, of course, for
19 the PANSS negative subscale here on the right-
20 hand side, you can also see a change starting
21 two weeks or four weeks, depending on how you
22 want to look at it, and then carrying on

1 through. So the other thing that this slide
2 doesn't show is they did have a they had
3 relatively few dropouts compared to what one
4 typically sees in such trials. So it's proof
5 that you actually can carry on such a trial.

6 Another one is, was running a
7 superiority trial versus a comparator. And
8 here, the comparator should be an approved
9 treatment for positive symptoms that is
10 neutral, which I believe is probably all of
11 them. Some them may be a little negative. And
12 then you do have some risk of functional
13 unblinding with approved treatments, from
14 sedation, weight gain, particularly if you have
15 a long-term trial. Only a single drug
16 comparison. If you have only one drug, it
17 could lead to some label issues. But I'm not
18 going to talk about that in front of the FDA.
19 I'll leave that to you guys. And, again, large
20 study meta-analyses suggest that most of the
21 antipsychotics are equivalent in their lack of
22 effects on negative symptoms, although not

1 necessarily in small trials, like Dr. Correll
2 showed.

3 So the cariprazine trial is the one
4 I'm going to sort of use in example here. The
5 fundamental assumption is your comparator
6 adequately controls for positive symptoms
7 without impacting the negative symptoms. And
8 in a positive trial, is it due to both positive
9 effects or is the active comparator decreasing
10 negative effects? There's some things there.
11 But it's probably a very good way to do it. It
12 may be more feasible, practical to run, than a
13 trial just on placebo. And there's some
14 arguments about, at least for the total
15 population, if there's an ethical positive as
16 well benefit.

17 Here, you can see the trial that
18 cariprazine ran. And again it showed some
19 separation. It was run a European sites again.
20 So I think this is both with stability and some
21 other things. Might be an advantage.

22 And it didn't appear...I probably

1 should have changed this slide, I just took
2 theirs. It said no pseudo-specificity. It
3 looks like there's not a lot here. So it does
4 look like the comparator arm was able to work.

5 In the interest of time, I'm going
6 to go through this a little quickly. This is
7 more stay/switch design. So if you're focused
8 on first at a single approved antipsychotic, or
9 you could do it on multiple antipsychotics.

10 So, half your patients would not be at risk to
11 develop clinical instability on a new agent.

12 They would increase your attrition at least for
13 that group. But it probably benefits the stay
14 group because they're used to it. You do
15 increase the potential for unblinding. And
16 when people are looking for new investigational
17 products they're already working against enough
18 problems, they're probably not wanting to
19 benefit the stay group.

20 And then the second one is, you
21 could also not just do it against one, but do
22 it against standard of care. There is an issue

1 here that you would need to talk to our
2 regulatory colleagues about, about sub-analyses
3 of the different groups, because some of the
4 groups would be much smaller than others.

5 So, in summary, there are important
6 issues that relate to both the adjunctive and
7 monotherapy trials. We've tried to highlight
8 some of these considerations. For monotherapy
9 in particular, the choice of comparison, I
10 think, is a big issue that one needs to
11 determine and then decide how you're going to
12 deal with it. One can also envision the need
13 or the use of psychosocial intervention within
14 the trial, prior to randomization, perhaps as a
15 run-in period or even throughout the trial to
16 help augment or sharpen the differences.
17 There's a variety of choices one can take
18 depending on the specific aims of the trial in
19 question and what the mechanism is of that
20 particular NDA. Regardless of choice, concerns
21 about practicality and the threat of high
22 placebo responses should be important

1 considerations when you're designing your
2 trials.

3 And I believe that's it.

4 DR. BLACKMAN: So now I'll ask the
5 respondents to come up. And as they do I will
6 just do brief introductions for them in no
7 particular order.

8 I do have an unfortunate
9 announcement, which is that Dr. Buchanan is not
10 able to participate in the panel today. And he
11 sends his apologies for that.

12 So, for the respondents we have Dr.
13 Farchione, who is the Director of the Division
14 of Psychiatry here at FDA. We have Dr. Yang.
15 She's a supervisory mathematical statistician
16 for the Division of Biometrics I here at FDA.
17 Dr. Michael Sand currently serves as a
18 consultant to a number of pharmaceutical
19 companies and the National Institute of Mental
20 Health. Dr. Richard Keefe is a professor
21 emeritus of psychiatry and psychology and
22 neuroscience at Duke University Medical Center.

1 And Dr. Nina Schooler, who's a professor of
2 psychiatry and behavioral sciences at State
3 University of New York Downstate Health Science
4 Center.

5 So now I'll just give each of the
6 panelists one to two minutes to respond to the
7 talks today. So maybe we could just go down
8 the line and start with Dr. Farchione.

9 DR. FARCHIONE: So I'll just make a
10 couple of quick comments, one general thing and
11 two more specific things. Because I know some,
12 I'm assuming some, of the questions will
13 probably be more pointed. But, the general
14 thing is that it's clear to me that despite my
15 crusade over the last several years to try to
16 banish the word pseudo-specificity from our
17 collective vocabulary, I have failed on that
18 point. I'll let it slide for today. But, you
19 know, two quick things that sort of stood out
20 to me in the presentations. One in Christoph's
21 talk about the phase II studies and how hard it
22 is to replicate things in phase III. And one

1 thing that we see a lot is when Sponsors come
2 in to us and have these meetings and ask us
3 questions, and they'll try to do things in
4 phase II like enriching for younger subjects or
5 fewer prior treatments and things like that to
6 try to enhance signal detection. And it
7 strikes me and we're always like, oh okay,
8 yeah, you know, if you're really, you know,
9 you're trying to identify a drug that might
10 potentially work. But maybe, that's not the
11 best strategy in the end because maybe what
12 you've done is you've detected a signal in that
13 smaller subset of the population and have
14 actually now made it harder to win in phase III
15 where we expect the results to be more
16 generalizable. So, you know, it worries me
17 that now maybe some of the advice we've been
18 giving where we said, yeah, you know, that's
19 fine, go ahead and do that, maybe that wasn't
20 great advice. And I think that will be useful
21 for folks to think about and talk about with
22 the panel. Because now I'm concerned that

1 we've been giving bad advice.

2 But then, Steve, in your talk, your
3 talk was supposed to be about monotherapy. And
4 it struck me that when you described the impact
5 of potentially adding on social and cognitive
6 training and things like that, that you
7 described it as potentially enhancing the
8 placebo effect. But I want to reframe it,
9 because then it's actually you kind of strayed
10 from the script a bit and we're talking about
11 adjunctive therapy instead of just monotherapy
12 in your talk. But I think it's important when
13 we're talking about adding a standardized
14 therapy, one lesson that we have come across
15 very recently is that that standardized therapy
16 should also be standard of care and evidence-
17 based, so that we have some frame of reference
18 when it comes to labeling and things like that.
19 And in that case, when you're designing your
20 study, you need to account for the fact that
21 you expect some improvement in the placebo
22 group because of that intervention. And so

1 maybe that requires a larger study to be able
2 to detect what will ultimately be, unless it's
3 really working synergistically, and then you
4 actually would see greater separation. That's
5 what you would hope for. I mean, that's kind
6 of the whole point in adding it on there,
7 right? So, I don't know. Those were the two
8 sort of specific things that I had to comment
9 on. For the sake of time I can pass it over to
10 Nina, who always has really insightful
11 comments.

12 DR. SCHOOLER: Well, we shall see
13 what we shall see. So, the thing that struck
14 me most strongly was that both Christoph and
15 Steve raised more questions than they answered.
16 And I was hoping for more answers. So, given
17 that, it feels only fair to raise further
18 questions.

19 (Laughter.)

20 DR. SCHOOLER: And the issue for me
21 that's really paramount in terms of all of our
22 studies of negative symptoms is that one of the

1 definitions of being someone with negative
2 symptoms is lack of willingness to do things.
3 And participating in a clinical trial involves
4 doing things. We heard a fair amount of
5 discussion about the issue of once you're in
6 the clinical trial it can be very rewarding.
7 But the fact of the matter is that these people
8 have a lot of trouble coming in to a trial.
9 And my experience in consenting patients, and I
10 regard myself as very good at this because I'm
11 really positive and energetic, has been that
12 there are some negative symptom patients who I
13 dream of who would not enter the trial under
14 any circumstance whatsoever. And so I think
15 one of the really important things is going to
16 be to try to design strategies that work for
17 the consent process, as opposed to, and then we
18 can go on to what we have later. But having a
19 broader population of patients with true
20 negative symptoms may be very important. And
21 I'll just give an example of something that can
22 be used in that regard. The first is the use

1 of some kind of motivational interviewing
2 strategies, which have been shown to be really
3 important in a lot of contexts, as part of an
4 informed consent procedure, which can perhaps
5 enhance the breadth of the patient population
6 that enters in. And the second is that there
7 was really interesting discussion earlier this
8 morning by Sophia which addressed the question
9 of reward, and the idea of the kinds of rewards
10 that you can pay people who participate in
11 trials can be done in different ways. An
12 immediate reward is always going to be better
13 than delayed reward. So the kind of
14 reinforcement that immediate reward can provide
15 may be very helpful to keeping people in
16 studies as well.

17 And I'll stop there.

18 DR. KEEFE: Thanks, Nina. So I
19 thought that...and first of all, I'm not
20 exactly sure what the product of this meeting
21 is going to be and I'm very interested in
22 seeing what that will be. I felt as though

1 both of you raised all of the important points
2 about the methodology of various types of
3 negative symptom trials. My concern, having
4 lived through, day-to-day, the aftermath of the
5 MATRICS consensus process which took place
6 about 25 years ago, we still don't have a drug
7 for cognition and schizophrenia. And that's
8 not the MATRICS process's fault. I think it
9 stimulated drug development. It got a lot of
10 companies trying to do something about this.
11 And I think that the MATRICS recommendations
12 were, in many ways, spectacular about laying
13 down the ways that the proper methodology for
14 clinical trials. However, as everybody knows,
15 I think that industry folks take these
16 recommendations so rigidly and they adhere to
17 every single word. And so what has happened, I
18 think, through the course of that process is
19 that innovation has been stifled. And so I
20 think what we don't want from these
21 recommendations is to leave with a set of
22 incredibly rigid recommendations that don't

1 allow people to take advantage of new
2 technologies, and I hope Greg Strauss and
3 others this afternoon are going to talk about
4 digital assessments for negative symptoms,
5 because my reading of this is they are just so
6 much superior. And we don't want it to be that
7 the only way we can innovate in this space is
8 when all of us up here on the panel have
9 retired or are dead.

10 Thank you.

11 DR. SAND: So as one of the former
12 rigid industry people, I'd like to make just a
13 couple of comments. Other than tremendous
14 presentations, and you really did a yeoman's
15 job, both of you, of identifying the issues,
16 one point I would raise is we haven't talked
17 about, and I think we need to hold our FDA
18 colleagues' feet to the fire on this, is how
19 some of these things are going to affect
20 labelling. Because, at the end of the day,
21 we're in this to commercialize a compound or a
22 device. There are now devices being

1 investigated for negative symptom treatment.
2 But we have to bear in mind that every one of
3 these things that we put into our trials may
4 have a consequence to the label. And that's
5 something that needs to be thought of, and the
6 academicians don't think that way, but we, as
7 drug developers, must. We have to be aware of
8 what does this mean for our label. So if we're
9 looking for the right left-handed, six-foot,
10 redheaded, blue-eyed people, that's great
11 because that's where we have our greatest
12 effect, but unfortunately then our label looks
13 like that and we don't have a drug that we can
14 commercialize. That's one point.

15 Second point is I started my career
16 in human sexuality and I was telling Rich when
17 I walked in here to this building this morning,
18 I was having PTSD from FDA interactions over
19 that over many years, trying to explain female
20 sexual desire to male urologists here was an
21 interesting experience. For some reason, a
22 centrally acting drug for a DSM condition was

1 being reviewed by urology. So that was fun.
2 But one of the things we talked about and
3 needed to make clear to people is when you look
4 at the phenomenon of desire, what's the right
5 level of desire? Well of course, it's very
6 individual. What might be an appropriate level
7 for myself might be completely different for
8 somebody else. Can someone tell me, what is
9 the right level of avolition? Can somebody
10 tell me, what is the right level of social
11 engagement? I have some in-laws I would hope
12 became less socially engaged. So I think we
13 need to be aware at the end of the day that
14 this is a very personal thing. And I think for
15 all of our brilliant work that so many people
16 are doing to parse out the neurobiology of
17 this...Brandon started out by mentioning the
18 word thrive. Okay, and there's a big
19 difference between an improvement on a scale
20 and thriving. And so I don't think we should
21 lose track of what is this meaning to an
22 individual person in terms of feeling better

1 and doing better about in their own lives.
2 Because it is very individual, and what might
3 be an important thing on a mean basis might not
4 be to an individual. And, I think that's worth
5 thinking about.

6 And the last thing I want to toss
7 out, which was not mentioned, is adherence in
8 clinical trials. We know that pill counts are
9 worse than useless, but that's sort of the
10 standard. I conducted a trial and in my last
11 role looking at relapse in preventing relapse
12 in schizophrenia, and used a digital app to
13 assess relapse over the six months. And we
14 found that only about 50 percent of people took
15 at least 80 percent of their drugs. Okay. And
16 in overall trial failed, but in that 50 percent
17 who reached at least 80 percent, there was a 90
18 percent reduction in relapse over six months.

19 I remember Bob Temple, being at a meeting where
20 Bob said "I don't care what happens to people
21 who don't take your drugs. I care what happens
22 to people who do take your drugs." And I think

1 there's a little bit of an elephant in the room
2 when it comes to schizophrenia trials that we
3 don't really know very well what level of drugs
4 people are taking. ISCTM looked at this,
5 AstraZeneca gave the working group data from
6 five failed phase II studies, where they had PK
7 data, and 20 percent of people in those trials
8 had zero detectable drug levels when they were
9 assessed for PK. So if we have almost any
10 signal of effect in the negative symptom trial,
11 it probably means we're onto something good,
12 because a whole lot of those people aren't even
13 taking the drug. And I think we need to think
14 about how we can improve on that in trials.

15 Thank you.

16 DR. YANG: Hello. I am a
17 statistician, so I am going to comment from a
18 statistical perspective. Speaking of the study
19 design, there's a question about what factors
20 could affect the sample size calculation when
21 designing augmentations and monotherapy
22 studies. The sample size calculation many

1 depends on the distribution of the efficacy
2 outcomes in each treatment group. And we often
3 calculate sample size based on the assumptions
4 of treatment effect and the standard deviation
5 of the distribution. And the treatment effect
6 can be affected by patient population, the
7 countries where the study is conducted, placebo
8 response, and other factors that are suggested
9 in Dr. Correll's and Dr. Brannan's talks. In
10 addition, the sample size calculation is also
11 affected by the dropouts. And we know that in
12 the augmentation studies, the dropout rates
13 tend to be lower than the monotherapy studies.
14 In recent years, the implementation of the
15 estimand framework has somewhat affected the
16 statistical analysis of efficacy outcomes. The
17 estimand framework consists of several
18 attributes. One of them is the intercurrent
19 event, which is an event that occurs after
20 treatment starts and may affect the
21 interpretation or existence of the outcome
22 data. Examples include treatment

1 discontinuation and changing the background
2 therapy in the augmentation studies. And so we
3 have been asking Sponsors to include the
4 estimand framework in the protocol,
5 particularly listing intercurrent events with
6 the strategies to handle each of the
7 intercurrent events. These strategies
8 essentially deal with observations, whether
9 observed or missing after the intercurrent
10 events. As a result, these strategies may
11 affect the treatment effect depending on how
12 you handle the missing data or the data even
13 though observed as intercurrent events. So I
14 think Sponsors may consider these factors in
15 their sample size calculations now. Having
16 said that, we need to have good data for this
17 exercise. And especially for endpoint that we
18 have less experience with. And I second what
19 Dr. Farchione just said in the beginning. And
20 the phase II studies, sometimes we see positive
21 results in phase II studies, but a lot of
22 times, my impression is that the result of the

1 phase III studies are not as good as in the
2 phase II studies. And that happens quite
3 frequently. So if you intend to use the
4 results from the phase II studies to design the
5 phase III studies, you want to keep in mind of
6 the variation. Just for example, when you
7 underestimate the treatment effect based on the
8 phase II studies, you want to allow for more
9 variability. So you want to make sure you have
10 really sufficient study power for phase III
11 studies.

12 Thank you.

13 DR. BLACKMAN: Thank you. So now
14 we'll open it up to Q&A before we take any
15 questions. So if people have questions in the
16 room, feel free to come up to the mic. Just in
17 the interest of time, I had just spoken in
18 random order about our presenters, but if
19 anyone needs it, from the podium over is Dr.
20 Correll, Dr. Brannan, Dr. Farchione, Dr.
21 Schooler, Dr. Keefe, Dr. Sand, and Dr. Yang.
22 That's the order people are sitting in today.

1 Similarly, I will ask, if you have a question,
2 if you could introduce yourself and then ask
3 your question. Thank you.

4 MR. MARTIN: Yes. Hello. Steve
5 Martin from UCLA. This is taking off from
6 Tiffany Farchione's talk. I thought that one
7 of the profound things about Brandon's talk was
8 that when he, and I think it's correct, that
9 although you had negative symptoms, you felt a
10 loss and a desire to address that. And what I
11 think one of the problems in negative symptom
12 trials is that many patients don't have that.
13 They don't experience suffering. And I wonder
14 if the people who are indifferent to
15 improvement, whether or not we should be
16 studying them in these trials. Because you can
17 give people dollars in order to participate,
18 but if they don't have a motivation to get
19 better and to reengage in life, as many
20 patients don't, maybe they should be excluded
21 from these trials, particularly early on, when
22 we're looking at signal detection.

1 DR. FARCHIONE: I mean, I don't know
2 if that was so much a question as a comment,
3 but I think it also piggybacks on what Nina was
4 saying in terms of, you may not need to exclude
5 them if you aren't able to recruit them anyway;
6 so.

7 MS. PANI: Luca Pani, University of
8 Miami. Steve, probably I'll just throw this
9 past you, and I'm not a statistician, but when
10 you did the practical analysis and the
11 prominent negative symptoms, the number of
12 patients went from 300 to about 30, something
13 like that, so it's only 10 percent, but the
14 impact was higher. My question is why did the
15 two arms become unbalanced? You had prominent
16 symptoms. You had 31 in one and 22 in the
17 other. Is anybody or maybe Dr. Yang, offer me
18 an explanation of why by doing this you
19 imbalance completely the two arms?

20 DR. BRANNAN: I don't know that we
21 can answer that. This is all retrospective, of
22 course. There may be something there. Again,

1 what I've learned over time is with relatively
2 small numbers, to be somewhat tolerant of the
3 facts of it's not as equally balanced as I
4 would have liked, but it's not too
5 unreasonable...

6 MS. PANI: It's like we're losing
7 the randomization principle somehow. We
8 should...

9 DR. BRANNAN: Yeah. The comment Dr.
10 Correll was saying, it's not stratified. So we
11 didn't stratify subjects...

12 MS. PANI: I see.

13 DR. BRANNAN: ...on predominant, we
14 weren't even thinking about it at the time. We
15 were just doing schizophrenia. So that
16 probably is a good, they weren't stratified, so
17 they weren't necessarily equal numbers to begin
18 with, and then all sorts of things.

19 MS. PANI: So it means the other way
20 around. So you cannot infer from some of those
21 analysis to the generalizability of the general
22 population, or no?

1 DR. BRANNAN: Well, I think if
2 you're looking at that data, you have to be
3 careful because of all the things that you're
4 bringing up. Although to my eye, it looked
5 like you saw a much stronger signal...

6 MS. PANI: Oh, no doubt. Yes.

7 DR. BRANNAN: ...in what already is
8 a strong signal.

9 MS. PANI: Right.

10 DR. BRANNAN: So if it was really,
11 again, this gets back a little bit, I think, to
12 what Dr. Correll was saying earlier. When you
13 have really small things, you have to be really
14 careful. And Michael probably will agree with
15 me that industry people aren't always careful.
16 But especially going phase II to phase III.
17 But I'm not, by the way, don't get too worried
18 about, letting people see signal early on, and
19 I'll get back to that.

20 MR. STAGLIN: Hi. Brandon Staglin.
21 I spoke earlier, One Mind. So questions for, I
22 think, two of you up there. First is for Dr.

1 Sand, partially a comment, partially a
2 question. I applaud how you called out the
3 need to understand what are meaningful outcomes
4 for people who are taking these treatments.
5 What's the right level of sociology? What's
6 the right level of motivation? It's very
7 personal, as you say. And then also about the
8 adherence question to using a drug. Both these
9 can be addressed by talking with people with
10 lived experience directly, obviously. And so,
11 I know that many pharma companies include
12 patient advocacy and patient consultation
13 functions within what they do. But I just want
14 to advocate for more of that, and to ask how
15 can pharma companies and other research
16 entities take advantage of the fact that there
17 are many people with lived experience who would
18 like to help develop new treatments for people
19 like us, like them, and contribute to the
20 process of making lives better for our
21 population, in consultation with treatment
22 developers? So, it may not be something you

1 can answer right now, but how can we make sure
2 that happens on a larger scale?

3 One quick comment. One Mind has a
4 lived experience council, which we just formed
5 this year. It currently involves four
6 individuals, and we're seeking to grow it. But
7 I'd like to see more of these councils grow,
8 and the applicability of them grow, and the
9 trust in them grow. So that's the first
10 question. Any thoughts on that, Michael or
11 anyone?

12 DR. SAND: So I'll comment, having
13 utilized these for years.

14 MR. STAGLIN: Mm-hmm.

15 DR. SAND: I have found it
16 invaluable in our clinical trials to involve
17 organizations such as yourselves or NAMI.
18 Invaluable to have worked with them and have
19 both patient and caregiver panels. We have
20 them review our protocols. We have them review
21 our patient-facing materials. And all of it
22 has a language. I mean, there's so many things

1 that people with lived experience and their
2 caregivers can provide us as drug developers
3 that's valuable. I think anyone who isn't
4 doing that, because again, as you well know, I
5 mean, these organizations are more than happy
6 to help. And I think everyone doing this kind
7 of work should consider, engaging with them.

8 MR. STAGLIN: Thank you.

9 DR. FARCHIONE: And if I can just
10 jump in as well, I know I'm going to call out
11 Steve again, but, you mentioned at one point in
12 your talk that there's a relative consensus
13 about maybe not needing a functional outcome.
14 And, you know, maybe.

15 DR. BRANNAN: Co-primary.

16 DR. FARCHIONE: Well, and that is a
17 co-primary. Yeah, that's true. But I think
18 that we do, to your point, we still need to
19 focus on clinically meaningful change. Like
20 what matters to the person sitting in front of
21 you, you know? If you're not making a change
22 that matters to the person who's being treated,

1 then what's the point of what you're doing?
2 And I think that, if we have a session on
3 clinical outcome assessments, and I think
4 that'll probably come up during that session
5 pretty extensively because one of the things
6 that we really want to do is actually talk to
7 patients and find out what matters to them,
8 how much change. And if we're developing
9 endpoints, are you measuring the things that
10 matter? If you're not measuring what matters,
11 you're not going to see an outcome, even if one
12 exists, right? So...

13 MR. STAGLIN: Very true. And I
14 think that can be a key to improving the
15 adherence to these medications or other
16 treatments. Because if normally, if they meet
17 the needs and interests of people who are using
18 them, then people are more likely to use them,
19 right? And also, simply knowing that they are
20 co-designed with the lived experience community
21 is a way to kind of get in the door with people
22 who might consider taking them, because they

1 know they their interests are being
2 represented.

3 DR. KEEFE: And I think, Brandon,
4 this is for you as well as for the general
5 group. But I think we need to make a
6 distinction between insight about somebody's
7 symptoms and insight about somebody's
8 functioning, and just how they're doing, and
9 whether they're satisfied with their treatment.
10 And the example I'm thinking of is I just
11 started wearing this WHOOP band to sleep,
12 right? And so I'll get up and think oh, it's a
13 pretty good night's sleep I had. And my
14 digital data said uh-huh, no you didn't. You
15 didn't sleep well at all. And so, you know,
16 here are the data. And actually, the
17 variability in the WHOOP is significant. The
18 variability in my perception of my sleep is
19 significant. And they actually don't correlate
20 very well. So my insight...

21 DR. FARCHIONE: That's not that
22 unusual for sleep measures.

1 DR. KEEFFE: Yeah, I know. I know.
2 But my insight into my symptoms is very
3 minimal. However, I think my insight into how
4 my day went the next day, whether I was
5 functioning, whether I was able to pay
6 attention and so forth, those things do matter.
7 And so I think it's insight to symptoms versus
8 insight to what your functioning is like, and
9 whether it's satisfying to you, those are the
10 things that probably really matter to you, not
11 insight about symptoms.

12 DR. SCHOOLER: One more comment. So
13 this actually gets us back to the point that
14 Steve Marder raised about who should be in
15 these trials, and should we not be including
16 people who don't see the problem? And what I
17 would argue is that in many schizophrenia
18 studies, we include many people who don't see
19 what we see as symptoms worthy of treatment as
20 symptoms. In other words, somebody who's
21 genuinely having a paranoid experience doesn't
22 think of themselves as having a paranoid

1 experience. What they're thinking is the FBI
2 is after me, or whatever the experience is.
3 And so I feel that to be a kind of tricky thing
4 to think about in terms of who should be in
5 studies. But I clearly understand the problem
6 in getting people to enter into anything that
7 they don't think benefits them in some way.
8 And so the issue is, what is the hook that you
9 can use that's a legitimate hook that will
10 still engage people who don't necessarily
11 consider what your target of interest is to be
12 their target of interest?

13 DR. BLACKMAN: Thank you.
14 Apologies. I think we probably only have time
15 for maybe one more question. So I'll take the
16 next question in the room here.

17 PARTICIPANT: I was just going to
18 make a quick comment sort of looping all these
19 things together, because the intersection
20 between what Steve said and what Brandon said
21 in his talk suggests that there's not only
22 awareness of the presence of your negative

1 symptoms, but there has to be a motivation to
2 overcome them, which also would imply
3 sensitivity to treatment effects. And we know
4 a tremendous amount about lack of awareness of
5 cognitive deficits, functional deficits, and
6 things like that. But we don't know much of
7 anything about how people with schizophrenia
8 who benefit from treatment, such as cognitive
9 remediation, are aware of the extent to which
10 they improve. And Rich published a paper that
11 involved a successful digital device
12 intervention for major depression, and the
13 people in the active treatment arm who
14 objectively improved in their cognitive
15 functioning didn't report that they were
16 functioning any differently than the people who
17 didn't improve. And so there was this
18 disconnect between objectively measurable
19 improvement on neuropsych tests and the group
20 as a whole's ability to report that that had
21 any impact on them. They found the same thing
22 in a TBI study that was done by Henry Mahncke

1 with BrainHQ. So there's a number of streams
2 suggesting not only unawareness on the front
3 side may be important, but the ability to
4 perceive a gain. How are you going to deploy
5 your new skills if you can't perceive them?
6 And I think the more motivated someone is to
7 benefit from treatment, that may carry through.
8 Can we expect people to develop that over the
9 course of treatment if they're actually getting
10 better? In our view, right? As Nina defined
11 carefully, that we're treating a lot of people
12 who don't think they have symptoms, but we know
13 how to measure what they don't think they have,
14 and we're not asking them to translate that
15 into functioning.

16 DR. BLACKMAN: Thank you for your
17 comment. For just the last couple minutes, I
18 just did want to reserve some time, since we
19 have Dr. Farchione on the stage, and I'm sure a
20 lot of people have this question in their
21 minds, how can they best engage with us here at
22 the FDA in terms of the regulatory process and

1 the drug development process?

2 DR. FARCHIONE: I think that
3 everybody that works in drug development knows
4 about our meeting request and everything like
5 that. So the idea that, you know, you should
6 talk to us early and often, I'm sure you've all
7 heard me say that 65 million times, so I
8 probably don't need to say it again, although I
9 did just say it again. But I think,
10 ultimately, what we've heard so far today, and
11 what I'm sure we'll continue to hear is that,
12 addressing negative symptoms is very complex.
13 And it isn't a matter of, I don't think that
14 there's a single approach that encompasses
15 everything that we're talking about. So
16 ultimately, the way that you design your
17 program really needs to be hypothesis-driven in
18 terms of, what aspect of negative symptoms are
19 you trying to address, are you trying to go
20 from monotherapy, adjunctive therapy? You
21 know, what is your treatment paradigm going to
22 be? All of those things are going to drive the

1 type of study designs that are going to be
2 needed in order to demonstrate an effect, and
3 also to help us to inform labelling. Because I
4 think, you've already mentioned that at the end
5 of the day, we have to be able to write a label
6 that tells people: Who the patients are who are
7 going to benefit from this? How do you use it?
8 What happens if the drug doesn't work; do you
9 stop it, do you not? All of those things. We
10 need to be able to write an informative label,
11 so that people can not only use the drug, but
12 use it safely. So depending on what your
13 hypothesis is, what your proposed treatment
14 paradigm is, what your proposed population is,
15 that's going to affect how you would design
16 your study. And those are the kinds of things
17 that are worth coming and talking to us about.

18 The other thing that I would say is
19 that, again, going back to this idea that it's
20 so hard to see a positive result in phase III,
21 even if you've won in phase II. What I think
22 we see a lot is that folks come in and they've

1 got this like squeaking by p-value and, like
2 you mentioned, they're just barely getting over
3 the line there. But hey, we saw something, so
4 we're going to go after this. I think what
5 Christoph's talk really showed us is that this
6 idea that, like, okay, we won in phase II,
7 let's just do phase III exactly like we did
8 phase II, and we're going to win again, isn't
9 the best strategy. I think looking at why your
10 phase II study won, who the patients are who
11 benefited, and then kind of trying to refine
12 your design. We always talk about how you need
13 to, phase II is exploratory, you need to take
14 what you learn from phase II and apply that to
15 your design in phase III. But a lot of what we
16 see is just let's do the same thing again. And
17 that may not be the best strategy. And in
18 fact, it sounds like it's actually not the best
19 strategy when it comes to negative symptoms.
20 But that is another place where it's going to
21 be really important to engage with FDA.
22 Because now, if you're going to say, "Like,

1 look, it looks like we have this specific
2 population that really benefited," we're going
3 to maybe say, "Okay, well, that's interesting,
4 but now you have to replicate that." You have
5 to demonstrate it. Maybe you might want to do
6 another phase to study, to explore that
7 hypothesis, to make sure that it's a real thing
8 before you jump into these massive studies and
9 invest all of this money.

10 So those are the main points I think
11 I would make. And again, talk to us early,
12 talk to us often. Anything you want to do
13 that's a little nontraditional, it's even more
14 important to talk to us even more often. If
15 you've got questions, we don't really turn down
16 a whole lot of meeting requests, unless we look
17 at it and we say "Oh, that's all review
18 issues." Just send us your protocol. We can't
19 answer it until we see your protocol then
20 sometimes we turn down meeting requests. But
21 mostly, we just want to engage. So that's it.

22 DR. BRANNAN: If I might just add on

1 something, one of the things that I think you
2 do that's very helpful is going to meetings,
3 like ISCTM, even ACNP and stuff like that.
4 Because when the FDA's out there you can...

5 DR. FARCHIONE: We try to go to
6 ACNP.

7 DR. BRANNAN: Well, yes. There's a
8 lot of reasons why you can't go to certain
9 meetings. I'm somewhat aware of some of that.
10 But for, in case your bosses are listening or
11 whatever, it's important. And that engagement,
12 the willingness to engage, I think, is really
13 useful, and it's been very helpful to a number
14 of us.

15 DR. BLACKMAN: And Dr. Sand, if you
16 want to...

17 DR. SAND: Just a provocative
18 question, Tiffany.

19 DR. FARCHIONE: I would expect
20 nothing less.

21 DR. SAND: Good. If someone is
22 being seen for predominantly negative symptoms

1 and they're prescribed olanzapine, do you
2 consider that being prescribed off label?
3 Because I don't think that these D2 blockers
4 have specific indication labels for positive
5 symptoms only. They simply say treatment of
6 schizophrenia. Why, if negative symptoms are a
7 core symptom like the positive symptoms, why
8 wouldn't or should we have or be seeking, as
9 developers, a label for negative symptoms, or
10 should we simply say we're looking for a
11 treatment of schizophrenia?

12 DR. FARCHIONE: Well, but we already
13 have all of these things that are approved for
14 the treatment of schizophrenia. And there's a
15 general consensus that they just don't help
16 that much with the negative symptoms. But the
17 way that the studies are done, you've got these
18 scales that measure everything. And they do
19 move negative symptoms, they just don't move it
20 enough for it to seem to matter, for people to
21 seem to notice. So...

22 DR. SAND: So if you turn that

1 around and say well, what if I'm developing a
2 compound that I think might have effects on
3 cognition, negative symptoms, and positive
4 symptoms? GPR 52, for example, that has at
5 least a biologic reason to think that it could
6 be plausible. Would I need to do phase III
7 trials in each of those domains, or would I
8 simply do take all comers and get a label? You
9 know, you see what I'm getting at.

10 DR. FARCHIONE: Yeah.

11 DR. SAND: It's hard to...

12 DR. FARCHIONE: Yeah. I mean, and I
13 don't want to get into, like, too many
14 specifics because, you know, we're not having a
15 Sponsor meeting up here at the table. But, the
16 idea that there are areas in schizophrenia that
17 we recognize where there's an unmet need, and
18 even if you were to do, if you had a
19 development program where you were able to
20 improve across the spectrum of symptoms, I
21 think it speaks a bit to the limitation of the
22 current labeling, where everything is for

1 treatment of schizophrenia, and where we have
2 to admit not all symptoms are treated all that
3 well. We would have to come up with a way to
4 still have that broad indication, which is now
5 rightfully earned in a case where you've
6 improved all of those domains, but to also have
7 a description of that improvement in, for
8 instance, section 14 in the clinical studies
9 session that actually addressed it. But I
10 don't think in that case that there would be
11 individual indications.

12 DR. SAND: Yeah. That's why I...

13 DR. FARCHIONE: Yeah.

14 DR. SAND: ...wouldn't think so,
15 but...

16 DR. FARCHIONE: Yeah.

17 DR. SAND: I just wanted to know.

18 DR. FARCHIONE: Yeah.

19 DR. BLACKMAN: Okay. Thank you. We
20 are going to take maybe just one question from
21 the virtual audience. And if it's quick, maybe
22 we'll be able to get two, and then we'll just

1 adjust lunch accordingly.

2 DR. CAMPBELL: I'm going to try to
3 combine a couple questions...

4 DR. BLACKMAN: Perfect.

5 DR. CAMPBELL: ...into one question,
6 because we have a lot of questions. I want to
7 thank the virtual audience for being patient
8 with asking their questions.

9 And so this is going to probably
10 start with Tiffany and Peiling. And while we
11 will be having an entire afternoon session on
12 the outcomes as part of when we think of study
13 design, we have to think about our endpoints
14 and our endpoint hierarchies. And so as we
15 continue our discussions today about trial
16 designs that would work, what are you thinking
17 about the hierarchies in terms of a primary
18 endpoint versus co-primary, or how additional
19 support of secondaries to really inform that
20 overall lived experience? So any thoughts? I
21 want to start with my DP colleagues first. But
22 then if anyone else has a question or a

1 response about that.

2 DR. FARCHIONE: I'm not exactly sure
3 what we would say about that. I mean, you
4 know, in terms of, like, how that would be
5 approached in labeling, or how that would be
6 approached in...I don't know. I guess, I don't
7 know. Christoph, you've got your hand up.
8 Maybe I can piggyback off of whatever brilliant
9 thing you're planning to say.

10 DR. CORRELL: Yeah. I mean, I think
11 the question is whether you go for total
12 negative symptoms or subtypes of it, and where
13 you start. So if you think your drug has a
14 particular affect in an area, and you go for
15 that first, and you know, okay, this might just
16 be subpopulation, but that's my safe bet, and
17 I've enriched for that. And then if I have a
18 positive effect, I do hierarchical testing.
19 But maybe I can get, now, the whole negative
20 symptoms and broaden my indication. So that
21 would be one way of going at it. Or if there's
22 lived experience, you want also, satisfaction

1 or personal recovery aspect in there as a
2 different lower hierarchical outcome.

3 DR. FARCHIONE: All right. I see
4 where that's going now. I mean, it strikes me
5 that that kind of an approach might make more
6 sense, like, in phase II, when you're trying to
7 figure out what your drug does and who it works
8 for, maybe. Because then, if you think it's
9 going to work in the subpopulation, you go for
10 that, because that's your win. And then, you
11 know, you start looking more broadly, more
12 broadly.

13 DR. CORRELL: Right. That's the
14 population. But if you see in this population
15 a particular effect on a subtype of negative
16 symptoms, and that would again be the label,
17 but you could also then, in a second shot at
18 the goal, say well, but maybe we get, actually
19 it's broad enough that we'll also catch other
20 aspects of negative symptoms. That would be on
21 the outcome. But I think group four will go
22 much more into this, I'm sure.

1 DR. FARCHIONE: Yeah. But then if
2 you don't win on that second shot...

3 DR. CORRELL: Then you're just one
4 outcome. That's fine.

5 DR. FARCHIONE: Yeah.

6 DR. CORRELL: But you have a second
7 shot on a broader goal.

8 DR. FARCHIONE: Yeah.

9 DR. CORRELL: Not for the
10 population, but for the outcome.

11 DR. FARCHIONE: Yeah. Yeah.

12 DR. BLACKMAN: Was there another
13 question?

14 DR. CAMPBELL: Yeah. I want to ask,
15 this more a question related to safety. So
16 we've been talking a lot about efficacy during
17 the study design, but obviously safety is a
18 critical thing as well. And so, in the context
19 of requiring patients to have prominent or
20 predominant or stable negative symptoms, is
21 there a risk of relapse? Negative symptoms do
22 not generally lead to hospitalization. But if

1 stable positive symptoms or predominant, would
2 relapse of a positive be a better measure for
3 safety? And my assumption, this is in a trial
4 of focusing solely on negative symptoms, that's
5 my interpretation of this question, that last
6 piece.

7 DR. FARCHIONE: Yeah. I mean,
8 that's the elephant in the room, right? I
9 mean, we're always worried about what happens
10 with positive symptoms. And I think in terms
11 of you were talking about monotherapy designs,
12 if you wanted to...

13 DR. BRANNAN: Yeah. And of course
14 you need to know what the medication is and
15 what it's like. But if you're just talking
16 about relapses, which is the, I think it's the
17 main concern. So we know that there's positive
18 symptoms. We know people off medication in
19 general tend to relapse more if they're on
20 nothing, rather than medication. But there are
21 subgroups, and so it sort of depends on how
22 you're running it and what the subgroups are.

1 I don't know if that's what they're looking
2 for.

3 DR. FARCHIONE: But with those
4 subgroups, how do you identify them a priori to
5 say that this is somebody who isn't going to, I
6 mean, because you need the positive symptoms in
7 order to even get the diagnosis in the first
8 place.

9 DR. SAND: So...

10 DR. CORRELL: No, go ahead.

11 DR. SAND: No. I was just going to
12 make the observation that anyone, I mean, if
13 you were concerned about that, you know, a DSMB
14 would be a way of easily handling that. And I
15 think in any case, anytime you had an actual
16 relapse happening where someone was worsening
17 and hospitalized, that would all be captured.
18 So, it's not like it would escape, even if you
19 weren't focusing on it in your trial, it's all
20 being extensively documented and looked at. So
21 I don't think it's a concern, per se.

22 DR. CORRELL: I think similarly,

1 exacerbation of symptoms, even below
2 hospitalization or relapse, is coded as a side
3 effect. But it's obviously possible that even
4 if you have the underlying medication on board,
5 that you have a stimulatory effect for the
6 negative symptoms that could also stimulate
7 positive symptoms, and we need to look at that.
8 But going back to the adherence, so even if you
9 have an augmentation trial, if people stop
10 everything and worsen, well, we need to know
11 whether that's the drug or they are not taking
12 the baseline medications. So the question is
13 how much does PK inference our reporting of
14 side effects attributed to the drug, and also
15 the efficacy? Is there a possibility to say
16 that we're doing a sensitivity analysis and
17 exclude people at zero blood levels, even
18 thought it might not be fully randomized
19 anymore, but then you correct for this, whether
20 there are any baseline differences? Do you
21 penalize a drug for the 50 percent of patients,
22 20 percent that are not taking any medication?

1 Or could we rescue that trial by using PK to
2 redefine the analysis sample?

3 DR. FARCHIONE: Yeah. But I think,
4 maybe Peiling could even speak to this, too,
5 but that's part of the estimand framework and
6 how you handle those events and everything.
7 And also, if they stop taking it, why did they
8 stop taking it? Is the drug not tolerable?
9 You know, the...

10 DR. CORRELL: Well, not only the
11 drug that's experimental, but also the
12 underlying medication.

13 DR. FARCHIONE: Yeah.

14 DR. CORRELL: But still, I
15 understand why did they stop it? You could
16 look at that, what the reasons are. Are there
17 predictors of this? But are we doing the
18 service and the patient right service by
19 including people who can't improve because
20 they're on nothing?

21 DR. YANG: Yeah. This is related to
22 the intercurrent events. And we are nervous if

1 you want to exclude patients, from the
2 analysis, because of the principle, the
3 randomization principle requires for valuable
4 statistical analysis is lost. But I think it's
5 better to handle this with the intercurrent
6 events framework. Yeah.

7 DR. BLACKMAN: Thank you. This is a
8 great discussion perhaps we could continue over
9 lunch. I just want to give a hand to our
10 panelists and our speakers. This was a great
11 session.

12 For anyone on campus here, the kiosk
13 will be open during lunch. If you think you
14 might need a snack later that you want to
15 purchase, purchase it now, because I'm not sure
16 what time it will close. We will reconvene at
17 12...

18 DR. CAMPBELL: 12:45.

19 DR. BLACKMAN: 12:45, promptly. So,
20 quarter of 1:00. Thank you.

21 (Whereupon, the above-entitled
22 matter went off the record at 12:09 p.m. and

1 resumed at 12:49 p.m.)

2 DR. CAMPBELL: I know we are
3 bringing folks in from outside from lunch. I
4 want to welcome everyone back to our afternoon
5 sessions. And really, I think our goal of this
6 panel is to keep everyone from that
7 postprandial slump, post-lunch.

8 So hopefully, we'll be a very
9 engaging panel discussion on something that is
10 extremely important to us at FDA. It is
11 literally my everyday work, which is a
12 conversation on clinical meaningfulness.

13 We heard it being highlighted from
14 our earlier sessions today, but this is, you
15 know, our everyday world. And so those of you
16 who come and engage with us on a regular basis,
17 you're very much familiar with this
18 conversation.

19 This afternoon, we're going to first
20 start on the conversation in clinical
21 meaningfulness, which will include a
22 conversation on cultural adaptation, diversity,

1 and inclusion, and really understanding the
2 broad spectrum of clinical meaningfulness in
3 the diverse populations, as well as a follow-up
4 conversation, and hopefully we will do a good
5 job to prepare for a very dynamic conversation
6 to end the day, on outcomes. So, how do we
7 take everything we've discussed today and get
8 into the "how do we actually measure this
9 critically important information?"

10 I'm going to ask my presenters and
11 panelists if they can come up and join us
12 already on the stage because, as we've learned
13 from this morning, we are having dynamic
14 conversations. And I don't want to waste time
15 with people walking. So if those folks will
16 come on up. And I will just highlight how
17 excited I am with this panel. I think you will
18 gain a lot from this session, and really be
19 reflective of why we spend so much time
20 focusing on clinical meaningfulness. All right.
21 We will have two presentations. The first
22 presentation will be from Eric Jarvis from

1 McGill University in Canada. And then we will
2 have a presentation from my colleague, Laura
3 Swett, who is a reviewer in our division of
4 Clinical Outcome Assessments.

5 I think it's important to note that
6 any conversation with clinical meaningfulness,
7 I think someone said it earlier today, we could
8 have an entire day, weeks long conversation
9 series on clinical meaningfulness.

10 And so, we will honestly only be
11 scratching the tip of the surface when it comes
12 to clinical meaningfulness. We will probably
13 not be getting into the quantitative aspects,
14 but really the overall importance of this. So,
15 I'm going to turn it over to Eric for his
16 presentation and get this conversation started.

17 DR. JARVIS: All right. Thank you,
18 everyone. Thank you for inviting me to this
19 symposium. I've been really interested in the
20 topics. I'm not involved in clinical trials
21 myself in my work, but most of what I do is
22 consultation on cultural and social issues in

1 mental health, psychosis, schizophrenia. So
2 people will ask me to be part of their grants,
3 or to comment on their programs, or even
4 clinical practices that they're doing. And we
5 -- what we do in our service, the culture
6 consultation service, is we try to identify and
7 find solutions, undo blockages that may be
8 happening because of a person's ethnic or
9 racial or religious or linguistic backgrounds.

10 I'm never asked about my
11 disclosures. I'm asked to give a positionality
12 statement for most of my work, so this is what
13 I do, here. And just to let you know what I
14 do, the kinds of -- I'm an associate professor
15 at McGill. I'm not a member of an ethnic or
16 racial minority, but I am a member of a
17 religious minority.

18 This presentation will -- it's a
19 vast topic, culture, psychiatry, mental health.
20 So I kind of brought down the discussion to
21 these three main groups -it may not entirely -
22 papers published in the United States, members

1 of African American communities, and people
2 with schizophrenia.

3 We've already reviewed these
4 negative symptoms of schizophrenia. I think
5 you know the general categories. I'm just
6 outlining them here so I can give some
7 commentary on some of the problems I think that
8 can arise in anyone -- whatever rating system
9 you're using to number and categorize people.

10 So, just a general overview of the
11 problem, negative symptoms of schizophrenia are
12 not so well-studied in ethnic minorities -- not
13 so well-studied in anybody, I guess, for that
14 matter, maybe partly due to beliefs that
15 negative symptoms are kind of brain problems or
16 biologically driven problems, less than sort of
17 social or culturally influenced behaviors,
18 maybe even less than positive symptoms, where
19 there's quite a good literature on social
20 cultural inputs into positive symptoms of
21 psychosis.

22 We've already talked about this

1 quite a bit, negative symptoms can be
2 misunderstood as -- can be falsely diagnosed
3 instead of other conditions. We've mentioned
4 many here, depression, PTSD.

5 Part of the problem for African
6 American communities in North America is our
7 historical stereotypes; the stereotypes that
8 "psychosis, schizophrenia are linked to people
9 of African origins," that "people in the past
10 have deemed people of African origin to be of
11 less intellectual capacity," that "they may be
12 more prone, for these reasons, to have or be
13 deemed to have negative symptoms of
14 schizophrenia, along with members of other
15 cultural minorities."

16 I just want to read this -- I'll
17 make sure I have the right one -- this is from
18 the APA guidelines from 2004 and were
19 republished in 2010. I'll just read this out
20 to you; "Compared with Caucasians, African
21 Americans, especially men, are less likely to
22 receive a diagnosis of a mood disorder and more

1 likely to receive a diagnosis of schizophrenia.
2 African Americans with schizophrenia are also
3 less likely to receive a diagnosis of a
4 comorbid affective or anxiety disorder. While
5 it is possible that such differences may
6 reflect actual illness variation among racial
7 ethnic groups, there is growing evidence that
8 cultural differences in symptom and personal
9 presentation, help seeking, interpretation of
10 symptoms, and clinical judgments by usually
11 Caucasian clinicians and treatment referral are
12 likely causing race linked biases in diagnosis,
13 and therefore in treatment." That's sort of a
14 traditional position in American psychiatry.

15 Now, Gara and his colleagues
16 published a paper in 2012 kind of confirming
17 these impressions, and another one in 2019 -the
18 references are at the end of the presentation,
19 I'd encourage you to look through those if
20 you're interested - so these -- so excessive
21 diagnoses of schizophrenia and psychosis may
22 predispose African American communities,

1 members of other communities, to be seen as
2 having more negative symptoms if they have kind
3 of doubtful presentations. Cultural mistrust or
4 paranoia, the way we kind of coined these terms
5 about 20 years ago, and they basically talk
6 about healthy suspicion or healthy reticence
7 when interacting with the institutions of
8 society, like, for example, the legal system or
9 the psychiatric mental healthcare system. So a
10 person may come into an evaluation or through
11 the emergency department, and they may appear
12 to be withdrawn or not very responsive or not
13 very engaged for good reason, but maybe
14 misdiagnosed as having schizophrenia with
15 prominent negative symptoms, for example.

16 We know about the literature from
17 Western and Northern Europe about people of
18 migrant backgrounds, especially from the
19 Caribbean, from West Africa, as having high
20 rates of diagnosed schizophrenia.

21 And in the United States, wherein in
22 the past the high rates of schizophrenia in

1 African American communities have been seen as
2 being artifacts of misdiagnosis, like I've been
3 just talking about, there's a new kind of
4 discourse emerging that there may be high rates
5 of schizophrenia in African American
6 communities because of systemic and structural
7 racism.

8 So, the negative symptom literature
9 in ethno-racial communities is a bit mixed.
10 Generally, I would say that in African
11 Americans and Mexican Americans, people tend to
12 report higher rates of negative symptoms in
13 these groups. Chinese Americans, the
14 literature shows -- the reported literature
15 shows that maybe there is fewer symptoms
16 overall in schizophrenia and psychosis. Native
17 Americans are less studied generally, but, as I
18 say, the findings are mixed, and it's hard to
19 draw conclusions at this stage.

20 Let's talk a bit about general and
21 more specific rating problems. The first issue
22 is the nature of psychotic symptoms. So with

1 psychotic symptoms, as most -- as you all know,
2 don't arise purely from brain processes, and
3 then they're sort of displayed to the
4 clinicians, or to the research raters. They're
5 kind of experiences that are filtered and
6 shaped by the context, by the surround. So
7 because of that, it's maybe, under some
8 circumstances, easy to misunderstand what's
9 going on for -- in certain -- in some settings
10 and in some specific populations.

11 The broad ethno-racial categories
12 that we all use, White, Black, Hispanic, Asian,
13 and so forth, really should probably be
14 discarded, because they're not super helpful in
15 a cultural psychiatry context, and they don't
16 really tell us a lot about the people that
17 we're seeing beyond very superficial physical
18 characteristics. But most studies will fall
19 back and use these categories almost
20 unquestioningly.

21 And then there's always the issue of
22 the lack of culturally-adapted instruments and

1 surveys. And I know many people want to adapt
2 instruments and surveys that they're using, but
3 in practice, it can be kind of complicated and
4 expensive.

5 I'm just going to go through a few
6 of the negative symptoms that we see and raise
7 a few issues that could arise. So the first
8 one has to do with negative or blunted -- or,
9 sorry, flat or blunted affect, unchanging
10 facial expression, poor eye contact.

11 I think Bernie mentioned earlier
12 today that these kinds of symptoms have to be
13 taken carefully in the context of the person
14 before you. So when a woman from -- a refugee
15 woman doesn't look at me in my evaluation, I
16 know it's not a negative symptom, I know it's
17 out of deference to me as a male -- older male
18 clinician.

19 Alogia, like, poverty of speech,
20 poverty of content of speech. So if somebody
21 comes from a socially difficult background,
22 maybe a poor educational background, of course

1 the content and quality of the speech will be
2 quite different. So these kinds of ratings may
3 not be so easy to make, especially in very
4 rapid assessments for some kinds of studies,
5 and even in the emergency department.

6 What about avolition and apathy,
7 like lack of grooming and hygiene,
8 impersistence at work or school? So some
9 communities may dress very differently. Some
10 may have different cultural norms for dress and
11 behavior. Some may seem to be maybe a little
12 bit lacking in personal hygiene. We have to be
13 careful before assigning that label to them.

14 There's many, many cases I could
15 talk about, but I'll save just time for one
16 case to review with you, just in a second.

17 Anhedonia and asociality having to do with
18 relations with friends and peers, recreational
19 interests and activities, of course all of
20 these issues can be vastly affected by cultural
21 norms, even family norms and social class
22 norms.

1 Attention, social attentiveness, and
2 inattentiveness during the mental status
3 testing. Imagine if somebody comes to see you
4 who's feeling fundamentally misunderstood.
5 They know there have been problems between
6 their community and the police. They were
7 brought to the hospital or to see you by the
8 police or by the judicial system. You know
9 that they're not going to be comfortable. They
10 might be scared or apprehensive. Of course
11 they're going to be feeling -- they might be
12 coming across as inattentive or disengaged.

13 A quick quotation to read to you as
14 well about negative symptoms in cultural
15 context, the overlap between depression and
16 negative symptoms, by Nancy Andreasen sometimes
17 ago: "Just as manics and psychotic depressives
18 are likely to have delusions and
19 hallucinations, so too depressives are likely
20 to have some negative symptoms, such as alogia
21 or affective blunting."

22 And then the role of social

1 adversity in the production of pseudo-negative
2 symptoms: "Thus, after experiencing the illness
3 for many years, it is possible that indirect
4 environmental factors, like economy, mass
5 media, politics, government, laws, begin to
6 exert a greater effect on their ability to
7 perform recreational, goal-directed, and social
8 activities that are the foundation of negative
9 symptoms."

10 So in conclusion, a quick case
11 example. This just was happening on our
12 service in Montreal, and I just wrote my
13 colleague this morning who is continuing the
14 evaluation. So a young, 18-year-old, African-
15 Canadian man referred to us with a possible
16 history of first episode psychosis in 2020. He
17 had auditory, tactile hallucinations, this is
18 all by report -we didn't see any of this -
19 emotional blunting, avolition, paranoia for one
20 year, and then no symptoms for three years.
21 He's taking no current medication. There's not
22 current substance use.

1 There was a psychiatric evaluation
2 in December of 2023 which diagnosed recurrent
3 depression, but he's not currently depressed.
4 But he went to see a clinic where they began to
5 evaluate him, and let me just give you some
6 quotation from the actual referral, it says
7 "However, though, through multiple subsequent
8 individual psychotherapy sessions, we strongly
9 believe that the patient would benefit from an
10 in depth evaluation to rule out psychosis due
11 to persistent negative cognitive psychotic
12 symptoms."

13 And they go on and say "Since 2020,
14 he began experiencing restrictive affect, less
15 ability and desire to communicate with others,
16 and less anticipatory pleasure about things
17 that he used to look forward to. As a result,
18 he has found it harder to maintain
19 relationships with others. He's also found it
20 more difficult to feel attraction and romantic
21 interest toward others. We would appreciate
22 your expert assessment to help determine if

1 there is enough evidence to appropriately
2 consider that he suffered a psychotic period,
3 and that he continued to struggle with the
4 negative symptoms of schizophrenia.”

5 So, kind of an interesting referral
6 and consultation. Not so different from
7 ratings or assessments you might do in research
8 contexts as well. My colleague has continued
9 the evaluation. He’s convinced that he has
10 depression, this young, African-Canadian man.

11 The clinic had been pushing him
12 toward the traditional trajectory, toward a
13 schizophrenia profile. We felt that it was
14 more depression, but he did think he had a
15 psychotic episode after reviewing the history
16 and talking to the young man carefully about
17 three or four years ago. So that’s kind of --
18 it’s an example of the conundrum we face in all
19 the work we’re doing with negative symptoms and
20 schizophrenia in a cultural context.

21 So, what can be done? This is
22 always the question. I really am, like many of

1 you, raising questions. I don't have
2 definitive answers. But we can -- it's a
3 discussion and an ongoing process. We
4 definitely do need to culturally adapt our
5 surveys and instruments. As everyone knows,
6 it's expensive, it can be complicated and time
7 consuming, but critical.

8 We need to train clinicians,
9 researchers, and raters in what we call
10 cultural humility. Cultural humility just
11 means we don't know everything as
12 professionals. We have limitations to our
13 knowledge, to our understanding. And our
14 patients, our clients, or their family members
15 can teach us a lot about what we need to know
16 to help them.

17 We need to make sure to include
18 diverse participants in clinical trials and
19 other studies, but even maybe more importantly,
20 we should include members of diverse
21 communities in the research process and as
22 members of our research teams, and then follow

1 their recommendations and suggestions. This is
2 often not so easy to do in practice.

3 There is also community outreach and
4 qualitative studies where we can go to hear
5 what people who really have a stake in what's
6 happening to members of their community can
7 tell us about these problems. We need more
8 data, especially ethnographic type data, which
9 is very different from a lot of the
10 quantitative data that we have -- has been
11 gathered, and that is discussed mostly in this
12 field.

13 Cautionary note, practitioners
14 should always evaluate whether psychotic-like
15 experiences, including negative symptoms, may
16 be better explained via ethno-cultural context.

17 So my conclusions for this part of
18 this panel, negative symptoms of schizophrenia
19 are understudied in members of minority groups,
20 which everyone knows. Rates of negative
21 symptoms likely vary by ethnic group. But how
22 much of this is due to cultural variation of

1 illness expression is essentially unknown.

2 Clinicians and researchers need to
3 adopt a position of cultural humility in their
4 work with minority groups. And members of
5 minority groups need to be part of our research
6 teams, and their recommendations need to be
7 implemented to the degree possible.

8 And here are the references, which I
9 think are online. You can consult those in
10 case you have doubts about what I've been
11 saying. Thank you so much.

12 DR. CAMPBELL: Laura, I now turn it
13 over to you to begin your presentation. Thank
14 you.

15 DR. SWETT: Hi, good afternoon.
16 Thank you for being here. What a privilege it
17 is to be a part of this ongoing discussion
18 related to effective ways to measure negative
19 symptoms of schizophrenia from a regulatory
20 perspective.

21 Just wanted to capture a little bit
22 of what we've heard so far related to patient-

1 focused information. We heard about why
2 negative symptoms are clinically important from
3 Bernie. We learned about the lived
4 experiences, how negative symptoms impact
5 people who have been diagnosed with
6 schizophrenia, thanks to Brandon.

7 Sophia made us aware of relatively
8 new and ongoing conversations regarding the
9 interaction between cognitive and metacognitive
10 factors and their interaction with negative
11 symptoms of schizophrenia. And Eric, thank you
12 for your insights regarding the importance of
13 culture and how it influences our experiences,
14 and therefore our interpretations of different
15 signs and symptoms. We can't assume they'll
16 all be interpreted in the same way by different
17 cultures and subcultures.

18 Today, I'll be talking to you about
19 regulatory considerations for assessing
20 clinically meaningful within patient change,
21 and Tiffany nicely set this talk up with her
22 comments just before lunch.

1 This is my disclaimer.

2 The purpose of my presentation is to
3 set up a framework to discuss clinically
4 meaningful within patient change, and today
5 I'll be discussing three topics.

6 The first will be the types of
7 clinical trial measures we see when we're
8 conducting a regulatory review, mostly
9 clinician reported outcomes in this context of
10 use, and how the most popular or well-used
11 measures, which are ClinROs, contain an
12 important perspective, which we rely on, of
13 course, for a diagnosis in clinical management,
14 but there is also, of course, an opportunity
15 for a more comprehensive multi-perspective
16 approach. And this is an approach that is
17 generally laid out in our patient focus drug
18 development guidances and applied also to other
19 therapeutic areas.

20 So I will be discussing also number
21 two, the important concepts from the patient
22 and caregiver perspective. For example, are

1 some concepts considered to be more important
2 to change than others from a patient and
3 caregiver perspective when we're looking at
4 evaluating clinically meaningful change?

5 And then lastly, I'll be discussing
6 other types of clinical outcome assessments in
7 terms of looking at clinically meaningful
8 change.

9 So, this is a snippet here of the
10 clinical outcome assessment compendium, the
11 latest version reflected from June 2021. It
12 captures the schizophrenia disease condition,
13 as you can see, and the second to the right
14 column lays out clinical outcome assessment
15 measures that have been used in clinical trials
16 for approved therapies.

17 And in the context of schizophrenia,
18 as you can see, historically, ClinROs have been
19 used to assess negative symptoms. But one of
20 the questions we want to ask today is "are
21 clinical rating scales enough?"

22 We know that, of course, tools have

1 different uses, and those have been established
2 either through research or clinical practice,
3 may not be sensitive and interpretable in
4 registration trials, even if foundational work
5 on the content has been conducted.

6 So when a COA is used as an
7 endpoint, we ask, "does it reflect how a
8 patient feels, functions, or survives, which
9 defines treatment benefit?" "Has evidence been
10 supplied to demonstrate the patient
11 experience?"

12 Through the CARES Act and PDUFA VI,
13 we have an agency commitment to patient-focused
14 drug development, even as exploratory, to
15 collect patient experiences. So for example,
16 moving beyond a diagnostic construct and
17 utilizing other stakeholders, such as patients
18 and caregivers, to understand negative symptoms
19 of schizophrenia, is a part of this commitment.

20 As we know and have heard, there
21 have been a lot of conversations regarding the
22 most appropriate ways to measure negative

1 symptoms. We've -- are well familiar with the
2 NIMH MATRICS consensus definition and those
3 five domains.

4 However, when we are asked to advise
5 on whether a ClinRO has sufficient validity
6 evidence to support its use in the context of
7 negative symptoms of schizophrenia, we find
8 that direct patient and caregiver feedback, or
9 their perspective, were omitted during the
10 instrument development.

11 We understand that there are
12 challenges in a disease context where self-
13 report is hampered by limited insight,
14 cognitive impairment, or other factors. But
15 potential insights can still be obtained by
16 patients, by caregivers. Our patient-focused
17 drug development guidance 2 lays out some
18 methodologies for collecting that kind of
19 evidence. For example, a focus group with
20 patient and caregivers dyads, or one on one
21 interviews with dyads, or a part -- or an
22 example of one way to collect that information.

1 Looking into literature is another.

2 Before I talk about clinically
3 meaningful change, first we need to understand
4 that meaningful concepts that have been
5 identified by patients and caregivers, and
6 whether or not they are incorporated in to a
7 measure. And then we can discuss meaningful
8 change.

9 So, obtaining these insights can
10 help us to understand - these are listed here
11 on the slide - which concepts of negative
12 symptoms of schizophrenia are important from a
13 patient perspective and caregiver perspective.
14 We heard a lot this morning about increasing
15 drive and decreasing apathy as a point of
16 intervention. What treatment goals are the
17 most important to address in terms of each
18 concept?

19 And then thirdly, which aspects or
20 attributes of these concepts are relevant from
21 a patient or caregiver perspective? And from
22 this, I mean if we look at these aspects of --

1 sorry about that -- look at these aspects of
2 these concepts, we're looking at presence or
3 absence, frequency, intensity, or duration. And
4 so we're wondering from a patient perspective -
5 let's just look at avolition or amotivation -
6 what aspect of that domain would be important
7 to a patient, and what would the MOA be
8 targeting?

9 So for example, would a patient or
10 caregiver consider that duration as important,
11 even if it just moves from a very, like, lack
12 of motivation to mild motivation? Is it
13 important that the intensity of the motivation
14 improves so that, let's just say, the
15 motivation was a zero out of zero and moves in
16 treatment to a six out of ten, is that
17 important? These are the types of information
18 that we find helpful in order to help us
19 understand clinically meaningful within patient
20 change.

21 So, once these concepts have been
22 identified, are they incorporated into

1 currently available measures of negative
2 symptoms, or do the measures require
3 modification or supplementation, or does a de
4 novo measure need to be developed?

5 So in the second part of my talk,
6 I'm going to be discussing aspects of
7 meaningful change that we recommend you
8 consider from a regulatory perspective. And I
9 have these listed just as a series of
10 questions, and understanding, of course, that
11 when you're looking at change, and in a drug
12 development program it's going to depend on
13 your mechanism of action and other factors, but
14 the first consideration is, when observing a
15 change in negative symptoms, can we assume,
16 when change occurs with treatment, that the
17 change is a result of each of the domains
18 moving equally? In other words, do the domains
19 move together? Can we assume the
20 neuromechanism of change impacts all domains
21 equally, or are only one or two particular
22 domains driving the change? We'd like to know

1 what's driving the change.

2 Secondly, regarding the NIMH MATRICS
3 consensus domains, can you demonstrate that all
4 concepts are considered to be important to all
5 stakeholders? In other words, do the concepts
6 identified by patients and caregivers align
7 with clinician observations, or are they
8 different?

9 Thirdly, regarding treatment, when
10 listening to caregivers and patients, which
11 concepts do they consider to be the most
12 important to treat? If I heard Brandon
13 correctly this morning, enhancing reward
14 anticipation would be a treatment goal. Of
15 those most important concepts to treat, which
16 concepts are considered to be the most
17 bothersome?

18 Fourthly, what might be the most
19 meaningful concept of change from the
20 perspective of a caregiver or from the
21 perspective of a patient, which we've heard may
22 differ? Are some concepts more important and

1 more bothersome or less important or less
2 bothersome than others?

3 Fifthly, how does this align with
4 the mechanism of action that the drug is
5 targeting in terms of how a patient feels,
6 functions, and survives? So if a drug is
7 targeting avolition, for example, is this a
8 domain that is meaningful and important to
9 caregivers and patients, or alogia?

10 Sixthly, when we are looking at
11 meaningful change, when is it that we consider
12 clinically meaningful change at the group
13 level, so inferences are made regarding a
14 population which may be of interest to a health
15 system, versus at the individual level, so
16 establishing that a certain proportion of
17 patients benefited from treatment, which may be
18 of interest to a healthcare or treating
19 physician?

20 And then the last two questions
21 we're raising for your consideration when
22 you're looking at measurement and regulatory

1 setting, how much change is considered to be
2 meaningful, improvement or worsening, within
3 each key concept?

4 Worsening, we find, is as important
5 to the patient, caregiver experience as is
6 improvement, particularly if the treatment is
7 impacting that. We'd like to understand what
8 this looks like in order to be able to
9 interpret meaningful improvement or meaningful
10 worsening in the context of a clinical trial.

11 And then, lastly, from a regulatory
12 review perspective, we're interested in
13 evidence demonstrating the link between the
14 improvement of negative symptoms and
15 improvement in functioning as a part of the
16 feels, functions, survives focus.

17 I think the big message to relay is
18 that we are interested in impacts for their own
19 sake as a result of our patient-focused drug
20 development initiative, but also as supportive
21 information for interpreting primary and key
22 secondary endpoints that assess signs and

1 symptoms, even if those impacts are not going
2 to be mentioned directly in labels. And also,
3 we do document in our reviews PFDD (patient-
4 focused drug development) evidence.

5 And then lastly, to address the
6 third aspect of this discussion, if COAs are
7 supplemented with a patient-focused drug
8 development approach, what are other ways
9 meaningful change data can be captured? And
10 there's been some discussion about this already
11 today, and I'll just mention three different
12 aspects that might be helpful.

13 Digital health technology measures,
14 we have a guidance that we put out in December
15 of 2023 called "Digital health technologies for
16 remote data acquisition in clinical
17 investigations" and this helps you in your
18 development or modification of a DHT (Digital
19 Health Technology) to ensure its fit for
20 purpose.

21 And there are examples of DHTs being
22 used in this context of use, which would be

1 schizophrenia, such as a virtual reality
2 functional capacity assessment. So, those are
3 considerations that can be made in terms of
4 looking at meaningful change.

5 The next one is an observer-reported
6 outcome. The caregiver-reported outcome
7 measure would be quite valuable in this context
8 of use, because there will be expected
9 differences between a patient perception of
10 change and a caregiver's perception of change.

11 And so it is important, if using
12 this type of measure, to standardize rater
13 training and to demonstrate adequate test and
14 retest reliability. This would be part of
15 providing the evidence of the reliability and
16 validity of the proposed ObsRO.

17 And then, lastly, videos would be
18 another means of assessing clinically
19 meaningful change in terms of, for example, a
20 task that has been directly linked through
21 patient and caregiver clinician evidence to a
22 negative symptom. And if that task is

1 considered to be meaningfully connected to that
2 system, that can be conducted throughout the
3 clinical trial via video, and centralized
4 raters can be trained to rate that particular
5 behavior, and in changes of that through the
6 course of the clinical trial.

7 So, those are just three examples of
8 alternative methods.

9 I would like to say in closing that
10 identifying clinically meaningful change helps
11 us to interpret treatment benefit, and
12 supplying evidence that the chosen measure in
13 your trial is fit for purpose, including
14 patient-focused evidence, ensures that your
15 clinical outcome assessment will reliably and
16 validly measure the concepts of interest.

17 And then as Tiffany said earlier,
18 whether you're assessing a current measure,
19 modifying, supplementing, or creating a de novo
20 measure, we recommend that you consult with the
21 FDA early and often. Thank you.

22 DR. CAMPBELL: Great. Thank you,

1 both Eric and Laura, for your presentations. I
2 think we are going to have a really dynamic
3 discussion for the next 30 minutes. We also do
4 have someone joining us virtually for our
5 panel. So, they're going to bring her up on
6 the screen to us.

7 But what I want to -- I want to give
8 Laura and Eric a little bit of a break from
9 presenting, and I want to turn to our
10 panelists, and we have a really great
11 representation on our panel.

12 So I'm going to ask our panelists to
13 introduce themselves to the audience, and then
14 provide one to two minutes of reflection of the
15 presentations we've just heard, and I'm sure
16 will also be reflective of our morning
17 conversations. So Matt, may I start with you,
18 please?

19 MR. RACHER: Yes. Thank you so
20 much, and a pleasure to be here today. My name
21 is Matt Racher. I'm an individual living in
22 recovery from psychosis and schizophrenia. I'm

1 also a certified recovery peer specialist and a
2 master's level social worker starting -- just
3 starting a job as a clinician.

4 You know, I'm -- in reflecting upon
5 the presentations today, you know, I think
6 about my own personal experience, you know,
7 kind of what my pathway from psychosis to sort
8 of putting out the fires of psychosis with
9 therapeutic help, medication management,
10 recovery supports, and kind of the long pathway
11 towards my recovery from certain domains of
12 negative symptoms into feeling connected to,
13 you know, meaningful, purposeful activity, et
14 cetera.

15 So in thinking about this, you know,
16 it was a long and challenging journey, and,
17 you know, I think it's important to kind of
18 asses what for me was -- felt like a loss of my
19 former self, and a gradual return to connecting
20 with family, with friends, with close peers.
21 And I think in between that time, that's where
22 kind of this long process of help was needed in

1 a sense of -- so I just wanted to introduce
2 with that topic and that response.

3 DR. CAMPBELL: Thank you, Matt, for
4 sharing.

5 Deana, I'm going to turn it over to
6 you.

7 DR. KELLY: Hi, thanks so much for
8 having me here, and thanks for the great talks,
9 and the talks this morning. I'm Deana Kelly.
10 I'm a professor at the University of Maryland
11 at the Maryland Psychiatric Research Center.
12 I'm also a PharmD, so I have the pharmacy
13 perspective.

14 I've been taking a lot of notes
15 today, so I'm thinking about a lot of things.
16 And I'm -- so I'm going to -- I know you posed
17 seven questions earlier for us to answer, or
18 for us all to think about. I'm not sure I can
19 answer any of those. But I'm going to add,
20 probably, as Nina had said, add more questions
21 to the mix as well.

22 I do think that starting off, like,

1 it's important in the real world for clinicians
2 -- for us to understand that clinicians are
3 short on time, and they will struggle sometimes
4 between negative symptoms, depression, and we
5 don't even talk about it a lot, but catatonia.
6 And so that's an issue that's out there.

7 But also, this idea of primary
8 versus prominent versus persistent is going to
9 be even more challenging for them in the real
10 clinic if we go down these pathways and try to
11 define these symptoms.

12 So how we define research translates
13 into how people are going to have to be
14 thinking about this in the real world. So I
15 think we do have to pay attention to these
16 aspects as we design scales, we think about
17 meaningfulness, we think about outcomes, and we
18 have to, as Tiffany pointed out, put on the
19 labels as well.

20 So -- and Dr. Jarvis sort of spoke
21 to that earlier, about culturally, this does
22 even get more challenging and different in

1 ethnic populations, potentially.

2 I think also, we haven't really
3 talked about this today, but separating domains
4 of symptoms and defining negative symptoms
5 separately has allowed us, as a field, to
6 accept that there's a set of symptoms that we
7 can't treat. And that's how our clinicians
8 feel. That's how, sometimes, we feel.

9 So regardless of how these symptoms
10 actually occur or what causes them, sometimes
11 we just throw up our hands and say we can't
12 treat negative symptoms. So we have to get out
13 of that mindset, too.

14 So I just want us to pay attention.
15 As researchers, we talk about this all the
16 time. But as clinicians, we forgot about
17 treating negative symptoms, because we'll go
18 after depression, we'll go after anxiety, we'll
19 go after other things, but sometimes we're just
20 not going to go after negative symptoms. So I
21 think it's really important.

22 And Dr. Jarvis pointed out, too,

1 like, from the literature about people think
2 there might be brain damage, and there's
3 nothing we can change about that. So it's just
4 important to think broadly outside of our
5 research world on both the diagnosis and this
6 idea that there's no way to treat negative
7 symptoms.

8 I also want to reiterate that people
9 with negative symptoms, regardless if they're
10 primary or secondary, can be helped. If we
11 change our thinking to align with the recovery
12 focus or the recovery model, it helps us set
13 aside just changes on scores and allows us to
14 target behaviors, allows us to target
15 attitudes.

16 Because we can indeed change
17 negative symptoms. We can help people feel
18 better. We can help people function better.
19 And those are the things we want to do, as
20 Brandon pointed out, thrive.

21 We can begin to poke holes in
22 defeatist beliefs. We can increase competence

1 when there's actual performance deficits that
2 are present. And we can assist people in
3 initiating and engaging in goal-oriented
4 behaviors.

5 Our hope is that pharmacologic
6 treatments will be able to improve negative
7 symptoms. But as Dr. Vinogradov pointed off --
8 pointed out, as other people pointed out, our
9 best combinations might be treatments that help
10 with motivation and help change, but also
11 teaching people how to practice that, whether
12 that's through CBT or CBSST or music therapy or
13 whatever that is.

14 Like, I think that we're going to
15 have to have study designs that are going to
16 have to have the basis for teaching the skills
17 or practicing the skills, in addition to
18 improving care.

19 I think about a meaningful change.
20 When we think about that, I think we have to
21 pay attention to limitations. We talked a
22 little bit about self-report negative symptoms

1 measures. And while they're incredibly
2 important, I think about some of my patients
3 and their inability to self-monitor and to not
4 report what's there. So I think having input
5 from clinicians, caregivers, as well as the
6 patient, and take the best approach for all the
7 information, however that may be, could be
8 incredibly important.

9 Also, requiring informants in
10 clinical trials. We really have to think about
11 that. As you brought up, I have a clinical
12 trial, a seven-site clinical trial we're
13 running right now, and we have informants and
14 we're looking at violence and aggression. And
15 it is challenging to actually get reliable
16 informants. So if we require that in clinical
17 trials, we're actually going to diminish our
18 ability to recruit people, too. So thinking
19 about how do we go about getting all the
20 information that we have out there together to
21 inform negative symptoms, I think, is
22 important.

1 And I think leaning towards some of
2 these virtual technologies, as you brought up,
3 are going to be possibly important for looking
4 at some of these measures of functionality.

5 When we talk about what's important
6 for meaningfulness, our team thinks about and I
7 think about improving motivation, initiation,
8 and engagement in goal-directed activities.
9 And that's how we think about it. We think
10 about how can we make someone feel better, how
11 can we make someone function better?

12 I know that Dr. Correll, Christoph,
13 didn't mention this today, but I've listened to
14 him many times, talk about, like, these four --
15 some of these domains, occupational,
16 functional, social, and family, physical
17 health, living arrangements. Like, these are
18 some of the things that really are important
19 for people to function better. It may be what
20 matters the most. But patient perspective, as
21 you said earlier, is really going to matter.
22 There wasn't a lot of discussion around

1 functionality today, but I think that we have
2 to keep that on the table.

3 And cultural considerations, as Dr.
4 Jarvis pointed out, they're extremely
5 important. How do we incorporate this into our
6 measurement of outcomes? How do we ensure that
7 we pay attention to cultural norms, such as, as
8 you mentioned, cultural mistrust, eye contact,
9 dress codes, hygiene, how they differ by our
10 different contexts?

11 And then -- we didn't talk about
12 this, but I think as I heard about it today
13 more and more, it's going to be important to
14 ensure our research teams are diverse to ensure
15 good interpretation and assessment of actual
16 behaviors, roles, and measuring symptoms, and
17 make sure that we're not narrowly focused, just
18 coming from our own biased context, as we all
19 have.

20 So we likely can do a lot better at
21 that, and there's probably a lot more for
22 discussion around how we can improve that. And

1 I loved the input from our lived experiences
2 today. And I think that's critical for
3 informing all of these outcomes that we're
4 going to be talking about.

5 So we all know that negative
6 symptoms impact people's lives. Negative
7 symptoms impact the global functioning, and
8 many different functional impairments in many
9 different areas of people's lives.

10 We may be far too committed to just
11 already the idea of negative symptoms change or
12 this co-primary, as we've talked about off and
13 on. But could we be interested in possibly
14 another outcome of functional improvement, not
15 necessarily co-primary, but another FDA
16 indication, possibly, for functionality? No
17 one's really talked about that. It might be
18 silly. It might be too simplistic. But is it
19 a possibility to think about, can we improve
20 negative, but could we also have indications
21 for medications that could improve
22 functionality.

1 I mean, Dr. Keefe mentioned today
2 about a good night's sleep. We can measure
3 that, but how can you -- and then measuring how
4 he functions the next day after a good night's
5 sleep is something possibly a little bit
6 different. So it's just a thought. So those
7 are my thoughts from today. Thank you.

8 DR. CAMPBELL: No, thank you so
9 much. Mark, I'm going to turn it over to you.

10 DR. OPLER: Thank you. Hi,
11 everybody. Mark Opler, Chief Research Officer
12 at WCG. I want to begin first just by
13 addressing a comment from this morning.
14 Somebody asked, very astutely, how do we know
15 what the right level of volition is for an
16 individual? The answer, actually, is five,
17 moderate severe. That's the appropriate level
18 of volition, if anybody wants to know [
19 audience laughs].

20 You know, I want to -- on a slightly
21 more serious note, I want to start by saying
22 that much like me, our existing rating scales

1 haven't aged well over the last 20 years.
2 They're creaky at the joints. They've lost
3 that certain something.

4 You know, to give you an example,
5 you know, in a lot of debate and discussion
6 these days with folks who want to measure
7 functioning and negative symptoms and the
8 intersect between the two, we're talking about
9 a scale called the UPSA, which many of you are
10 very familiar with and have probably used a
11 lot. Well, when it comes to the UPSA, my
12 question is, you know, I've got folks on my
13 team who probably aren't great at things like
14 check writing, don't know what 411 is,
15 honestly, have never dialed it and never will.

16 Our scales are getting older, and
17 they no longer reflect even the dominant
18 culture that we theoretically live in. That's
19 a problem. So, you know, maybe some of the
20 tools that were mentioned before, like the
21 VRFCAT and other things, will be a better fit
22 for the culture that we actually live in, and

1 also maybe more culturally adaptable. When we
2 have to go to Thailand, we're looking at a
3 completely different set of ideas, norms, daily
4 life patterns. Our tools have to adapt.
5 Otherwise, we're going to miss the boat.

6 The second thing I want to point out
7 is that, you know, in addition to being
8 somewhat creaky, a little culturally
9 inflexible, it's very evidence also that our
10 scales frequently don't measure what matters
11 most. That's a phrase that's been said a lot
12 today. I remember hearing it first in this
13 context in the work of a friend of mine, Dr.
14 Lawrence Yang. Look him up if you don't know
15 him. He writes a lot about stigma.

16 But, you know, he started using the
17 phrase "what matters most in a patient's life"
18 as a way to think about what treatment means to
19 them. A doctor might tell a patient, this is
20 great, your voices are better, you're doing
21 very well. Maybe. But if they're not living a
22 life that feels important to them, have they

1 really improved?

2 The other thing I want to say, you
3 know, there's been a couple of folks today,
4 earlier this morning and recently, who've
5 mentioned informant data, and how onerous it is
6 to gather informant data on the PANSS, and for
7 other scales. This is true. It's another
8 checkbox that has to be checked.

9 Nevertheless, I would like to submit
10 it's a vitally important piece of information
11 and a vital perspective on the patient's actual
12 status. In the PANSS, informant data isn't
13 there by accident. It was put there very
14 deliberately as a requirement, because when the
15 folks who were writing it, sat down and looked
16 at what they needed to rate, they realized they
17 couldn't reliably judge the social performance
18 of somebody they had only known for 20 minutes;
19 they weren't the right person to determine
20 whether or not what they were seeing made
21 sense. They went to informants because they
22 needed that perspective.

1 So, I'm sure folks will be happy to
2 hear we're actually revising some of the
3 informant tools for the PANSS. That is coming.
4 I believe that the need for a better observer-
5 reported tool that's relevant to schizophrenia
6 will be found in the future. It might come
7 from the past.

8 Last thing I'm going to say is, I
9 think, you know, we also need to stop
10 considering all of these measures -- observer-
11 reported, clinician-rated, patient-reported,
12 digital health technologies -- we've got to
13 stop thinking of these things as separate and
14 distinct.

15 Because I have a sense that what's
16 coming in the future will be completely
17 different. It will be a merging of these
18 things in ways that we hadn't previously
19 considered, whether it's the extraction of
20 vocal biomarkers from clinician ratings or the
21 incorporation of a virtual informant to help a
22 clinician get to the right score on negative

1 symptoms. This stuff is coming, and it's not
2 going to look the way we expected.

3 Finally, to just close out and let
4 us get back on with our work, there's a patient
5 that I've gotten to know a little bit in the
6 Bronx, and his name is Corey. He's a wonderful
7 guy. And I once asked Corey, "Corey, what do
8 you really want from the pills that all the
9 doctors are giving you?"

10 And he said, "you know what I'd
11 really like? I just want to look and sound
12 like everybody else. When I'm on the subway, I
13 don't want people to stare at me. I want to be
14 taken seriously. I just want to look and sound
15 like everybody around me."

16 And I've taken that to heart, and I
17 think when we think about negative symptoms,
18 let's not ignore the importance of that idea.
19 So thank you.

20 DR. CAMPBELL: Thank you so much. I
21 want to turn it over to our virtual
22 participants.

1 Bonnie, can you -- first of all, can
2 you hear us?

3 DR. KAISER: Yes. Can you hear me?

4 DR. CAMPBELL: -- unmuted yourself.
5 We can hear you. So can you introduce
6 yourselves and provide some thoughts?

7 DR. KAISER: Yes. And thank you so
8 much for inviting me to participate and letting
9 me join virtually.

10 So, I'm Bonnie Kaiser. I'm at the
11 University of California, San Diego in the
12 Anthropology Department in the Global Health
13 Program. So my main focus of research is
14 cultural adaptation of measurement tools.

15 And so I just wanted to kind of
16 build on that thread that's been mentioned a
17 couple times by folks just the importance of
18 cultural considerations, particularly of when
19 we do global studies, you know, of
20 incorporating rigorous cultural adaptation of
21 our assessment tools.

22 Researchers are sometimes reticent

1 to do a cultural adaptation process rather than
2 kind of a simple translation/back-translation
3 process. One, because it's time-consuming to
4 do more, to do cultural adaptation, and
5 particularly validation. And there's also
6 concerns about moving away from using kind of a
7 strictly translated version of a previously
8 validated scale. Although previously
9 validated, you know, usually means in the U.S.
10 or in Europe, not the kind of local context
11 where the research is going to be conducted.

12 And we've found that there are
13 studies that show that culturally-adapted
14 scales do perform better in subsequent
15 validation studies. When we don't do cultural
16 adaptation and we just do kind of
17 translation/back-translation, and then trust,
18 you know, that that's going to work, we end up
19 with some confusing results. Like one said he
20 found 97 percent of their study population had
21 PTSD. Like, we just don't trust that on face
22 value. That doesn't make sense.

1 And so when we're not confident that
2 we're measuring what we're trying to measure,
3 then it really matches or maps on the lived
4 experience in the context of our study, we
5 can't really be confident in any of our
6 results. We don't really know what our data
7 are telling us. We don't know what we can do
8 with those findings.

9 So, I'm an anthropologist. I do a
10 lot of ethnographic research that then feeds
11 into mixed method studies, cultural adaptation
12 studies, validation studies. So, I see kind of
13 the ways that this research, the kind of
14 preparatory research for these measurement
15 tools can really improve our outcomes.

16 And there's also been, you know,
17 studies that show that this actually ends up
18 saving money ultimately in terms of how we're
19 effectively identifying folks in need of care,
20 effectively referring them for care.

21 And then finally, I just wanted to
22 pick up on one point that Dr. Jarvis mentioned

1 in his study, that, you know, we talk a lot
2 about culture and cross-cultural
3 considerations, but really thinking about kind
4 of the broader context of environment also
5 includes thinking about structures, thinking
6 about systems, and how that shapes
7 possibilities, and how that influences
8 behavior.

9 So, Dr. Jarvis gave the example of,
10 you know, healthy cultural mistrust. But I
11 just wanted to make sure that we think about
12 those issues as well, and consideration
13 alongside, kind of more specifically cultural
14 considerations in global studies and, you know,
15 not just in global studies. Thanks.

16 DR. CAMPBELL: Thank you, Bonnie,
17 for your remarks. So, we're going to try to
18 have a pretty fluid conversation amongst the
19 panelists, and I'm going to start with Matt.
20 And he knows this, so we did prepare for this
21 with the first question.

22 And I want to thank him and Brandon

1 for being here and feeling comfortable to share
2 their lived experience with us today, because
3 it is extremely valuable to us.

4 So, we've been talking about
5 clinical meaningfulness, and one of the most
6 important things that we look at when we're
7 reviewers, and we understand that everyone's
8 lived experience is slightly different. And we
9 have to have this understanding of what is that
10 lived experience, and one of the best ways is
11 through qualitative work.

12 So -- but what I would love to ask
13 you, Matt, is what would clinical
14 meaningfulness look like to you? What would
15 success or improvement from a treatment look
16 like for you in your everyday life?

17 MR. RACHER: Absolutely. Thank you.
18 If I -- I'd love to preface the answer to this
19 question with kind of a quick analogy for the
20 experience of negative symptoms, if that's all
21 right.

22 So, I have this sort of analogy that

1 I came up with over time, and I'd like to share
2 it. It's, you know, imagine there's a
3 beautiful, thriving community within a small
4 town where people work together harmoniously,
5 interconnected in their efforts to support one
6 another, and at the heart of this community
7 stands a central building, a hub that provides
8 vital resources, serving as an essential
9 cornerstone of the town's wellbeing.

10 So, one day, you know, disaster
11 strikes. The building burns down in flames,
12 kind of like psychosis. The fire department
13 responds, extinguishes the fire, and this once
14 vibrant center is reduced to a pile of rubble,
15 almost like the experience of negative or
16 cognitive symptoms.

17 So, this once-lifeblood of the
18 community is now in this state. So this
19 metaphor, I wanted to share it to kind of
20 reflect after a severe episode of psychosis
21 like the one I experienced in 2011, you know,
22 it felt like this profound kind of -- at first

1 it felt like I was going to lose who my former
2 self was.

3 And I really think the pathway
4 towards seeing meaningful change or meaningful
5 outcomes is really having the supports along
6 the way to kind of show that, you know, I still
7 have -- or people with schizophrenia and in
8 recovery from schizophrenia still have the
9 desire to work, to love, to find connection to
10 purpose.

11 And that's a slow process, almost
12 like a light dimmer. Not necessarily a light
13 switch, on and off, but kind of a slow, gradual
14 process to reach those goals and to become
15 connected and to become -- to reinvigorate or
16 re-instill a sense of emotional connection and
17 purpose to passions. For me, that's music, you
18 know, and helping others, and working in the
19 field of mental health and social work, so.

20 DR. CAMPBELL: So -- well, thank
21 you, Matt, for that. And I know when we
22 talked, you talked to me, you gave me that

1 analogy about a light dimmer, and I think that
2 was a really informative way of structuring
3 this gradual aspect, right, of, you know, it
4 may be a low light on that dimmer switch, but
5 you want to increase over time.

6 And that may take time, but there is
7 a range of what meaningfulness could also look
8 like, depending where you are in that current
9 moment. And so I really appreciate that
10 analogy.

11 So I have been taking a lot of great
12 notes throughout the day and throughout the
13 session, and so I honestly don't know where to
14 start, but I'm going to attempt.

15 So I think what we've heard today is
16 that through various lived experiences is, how
17 do we balance -- and something we heard earlier
18 today is how do we balance improvement and the
19 important concepts? So how do we really be
20 able to capture what is meaningful, what
21 matters most, whatever buzz term you want to
22 use?

1 Particularly -- but how do we
2 balance that with when people with lived
3 experience with schizophrenia may not recognize
4 their negative symptoms or the impact it really
5 is having? And others can see it, but when we
6 think about that meaningful change, we really
7 also want to try to have some underpinning of
8 what does that patient think?

9 And this is our struggle in a lot of
10 our diseases and disorders in neuroscience,
11 where lack of self-report can be problematic.
12 And that's why we do have to rely on other
13 informants and reporters to help us.

14 But the heart of it is, is what
15 we're seeing meaningful to patients? And so I
16 was wondering if our panelists had thoughts on
17 that. So I'm going to start with Mark, because
18 I see him head nodding. So -- because I know
19 he's had some thoughts about this when we
20 talked earlier.

21 But how do we really find that
22 balance? Because that is part of this

1 conundrum of how do we then design the trial,
2 and how do we incorporate all of those things
3 into that trial design to be able to find an
4 effective treatment?

5 DR. OPLER: Thank you for that
6 question. I mean, I think two thoughts off the
7 bat. You know, one, we have been trapped in
8 the clinician's office for a very long time.
9 And the more we can do to try to put context
10 back into the work we're doing, especially in
11 early phase and possibly in later phase
12 development, the better off we're going to be in
13 terms of developing treatments that actually
14 mean something outside of the rarified
15 environment of the clinical trial itself.

16 You know, one example that comes to
17 my mind is the classroom study in ADHD. This
18 has been a study paradigm in ADHD research for
19 a very long time in pediatrics, and it's not
20 revolutionary by any means. It's simply
21 looking to see how kids are doing in an
22 environment that matters, the classroom.

1 You know, what's the analogy for us
2 trying to work on negative symptoms in
3 schizophrenia? Is it a clinical interview in a
4 small office? Or maybe it's a structured
5 assessment in a group setting. Maybe the
6 analogy for us in the world of schizophrenia
7 research is group.

8 So, a new formulation of the PANSS,
9 coupled with digital endpoints where patients
10 are interacting with each other and with, you
11 know, other folks in a group setting, might
12 tell us something that we have been missing and
13 introduce clinical meaningfulness and context
14 back into the work we're doing.

15 DR. CAMPBELL: Thank you, Mark, for
16 that. Does anyone else have any other thoughts
17 about that? Deanna, I'm wondering if you may,
18 just thinking about how you were trying to link
19 the clinical practice with the research world
20 and the trial world, and that some of it may
21 have to go back to that practice balance as
22 well, if you had any thoughts.

1 DR. KELLY: Yeah. I don't know the
2 answer. I was hoping to come here and learn
3 from others myself today. But, I mean, I
4 started off talking about -- as I listened
5 today and I thought more about this research
6 context that we're all sitting in, that it was
7 important to make sure we go back to that
8 clinical perspective, that we go back to
9 understanding, like, how people -- how the time
10 that people have in offices with their
11 physicians or their care providers, what
12 they're assessing, what they're looking for,
13 and what they're actually hoping patients -- or
14 their patients might improve upon.

15 And it's going to be very different
16 than, potentially, what we're looking at in the
17 real world. But -- or what we're looking at in
18 the research world. But I do think, like, I
19 agree with what Mark had said. We have to
20 figure out, like, what is meaningful? Like, I
21 think about it as "are people feeling better?
22 Are they functioning better? And how do we go

1 about measuring that?" I'm not entirely sure
2 what the answer is. But I do think that we
3 have to go for some of those outcomes as we
4 think about what's really important. And I
5 really, really think this time around, negative
6 symptoms, including people's lived experiences
7 and listening to people talk about what matters
8 is going to be incredibly informative, and it's
9 going to be critical for us as we think about
10 that more. Thank you.

11 DR. CAMPBELL: Okay.

12 DR. OPLER: I can't help myself.
13 I've got to throw myself in here.

14 DR. CAMPBELL: Go right ahead. And
15 then I'm going to turn it over to Eric.

16 DR. OPLER: Very quick.

17 DR. CAMPBELL: Go right ahead, Mark.

18 DR. OPLER: You know, something that
19 Deanna was saying prompted me. There's a
20 fascinating old technique that's not used very
21 much anymore called goal attainment scaling. I
22 won't go into it now. If you don't know what

1 goal attainment scaling is, you should. It's
2 coming back. We've used it a little bit in
3 depression, and I think it's time to think
4 about using it for negative symptoms in
5 schizophrenia. I'm going to shut up now.

6 DR. CAMPBELL: Eric, do you have any
7 thoughts to add?

8 DR. JARVIS: I do. I was talking in
9 the break with Stephen about how we have our
10 research protocols and our research structures
11 and hierarchies, and we have to kind of follow
12 things that are sort of in a certain way that
13 will produce the -- or produce a result we hope
14 will be replicable, and I think respected by
15 our colleagues.

16 But I think from a cultural
17 psychiatry perspective, it's all about
18 adaptations, modifications, person-
19 centeredness. It's about making exceptions.
20 It's about trying to be flexible in how we
21 apply the protocols and procedures and
22 practices that we've learned and that we've

1 created.

2 So, it's a tension, and I think it's
3 hard to implement often. But I think this is
4 maybe going along with what you were saying,
5 Mark, about group processes to try to find out
6 how can we modify what we're doing to get a
7 little different kind of input.

8 You know, so it kind of goes along
9 with mixed methods ideas as well. Are there
10 ways in our work that we can include a more
11 person-level, or a life world kind of a
12 reaction, or a life world input that can really
13 nuance the findings that we're having? And I
14 just worry that we haven't been able to do it
15 so well, so.

16 DR. CAMPBELL: Well, thank you for
17 that. I'm going to invite the audience, if you
18 have questions, to start heading up to the
19 microphone. But as I've been reflecting today,
20 this conversation, and kind of bringing this
21 back to drug development. So we know that most
22 drug development's global, right? And so my

1 industry colleagues in the room will all head
2 nod when I say they also have to work with
3 other health authorities with their endpoints
4 in their study design. But I think we would all
5 agree that the hallmark of cultural adaptation
6 and translation of these instruments that
7 support those endpoints are sometimes thought
8 about last, right? And unfortunately, I think
9 it does -- the example that Bonnie gave, where
10 we're not really investing in actually doing
11 the qualitative work to make sure we're fully
12 understanding that population we're going to go
13 try to study in, in that country or that
14 region, and enough time to have it be
15 incorporated into trial design and endpoint
16 selection.

17 So -- before we transition to the
18 questions, how do we want to think about making
19 sure we build in, and in the spirit of patient-
20 focused drug development, early into that
21 process of designing the trials, thinking about
22 where our study sites are going to be, where do

1 we have to understand that meaningfulness to
2 build that in early adaption?

3 And I know, Mark, you've got to have
4 thoughts. Because we've talked about it a bit,
5 and I think Eric's got some thoughts as well.

6 And then Bonnie, I'm not sure if you
7 do?

8 DR. OPLER: Yeah. I'll try to be
9 quick. I mean, I think in addition to other
10 things, I also tell people a lot, don't
11 overload your protocols. You know, the more
12 measures you load in, the less likely you are
13 to get data that means anything. I'm going to
14 reverse that very slightly and say, you know,
15 whatever we can do to strip away unnecessary
16 endpoints that, you know, tell us stuff we
17 already know, and replace them with
18 opportunities to collect things like cultural
19 formulation, information on, you know, what do
20 you want to get out of this treatment? Things
21 that are more culturally meaningful and more
22 person-centric are a better bet than another

1 PRO that already measures something that you're
2 capturing elsewhere.

3 DR. CAMPBELL: Eric, do you have any
4 thoughts?

5 DR. JARVIS: I do have some. So in
6 the current research we're doing, we spend a
7 lot of time reaching out to communities, making
8 connections to communities, the people we're
9 going to be actually asking questions of, and
10 try to figure out what's at stake to them. So
11 this is, I think, it's a time consuming
12 direction. I won't say it isn't. But I think
13 it really changes the tone and the direction of
14 the work you're doing. And once the
15 communities you're working with, the people
16 you're going to be studying trust you, and you
17 can have real, honest discussions, they will
18 really change what you'll be -- what they want.

19 They'll tell you that you have to
20 change a lot of what you're doing. And it can
21 be all the way from the title of your project,
22 all the way down to the kind -- how you talk to

1 people, who needs to be in the room when you
2 talk to people. I mean, it's major
3 differences.

4 But the problem is, it takes time to
5 get there, right? So people don't just come
6 out with these problems quickly. It's a kind
7 of a relationship.

8 We were just invited to an Afro-
9 Caribbean parade in Montreal, and I was asked
10 to give a talk on mental health at this parade.
11 It was a really unique opportunity, but very
12 different from what I was used to. So I
13 realized that I was put into an unfamiliar
14 position, like our patients are put into an
15 unfamiliar one when they come to see us in a
16 study setting or in a hospital setting. So I
17 learned a huge amount from that one invitation.

18 Anyway, these things will happen
19 slowly over time if you try to nurture those
20 relationships.

21 DR. CAMPBELL: Bonnie, do you have
22 anything you want to add? If you don't that is

1 okay. I don't want --

2 DR. KAISER: I agree.

3 DR. CAMPBELL: -- to put you on the
4 spot.

5 DR. KAISER: Yeah. I agree with
6 what everyone's been saying. I really
7 appreciate those points. And I guess I'll just
8 share, there's, like, a, I don't know, kind of
9 trope in anthropology that we always get
10 invited to join studies once they've gone wrong
11 to try to explain why things are wrong. And I
12 think there's increasingly a shift towards
13 inviting anthropologists to the team earlier to
14 try to avoid that happening. But yeah,
15 obviously I'm biased.

16 But like, one way to approach it is
17 that including anthropologists, including folks
18 with, like linguistic expertise, you know,
19 local clinicians that join the team from the
20 planning stages.

21 DR. CAMPBELL: Thank you for that.
22 So Heidi, really quick, do we have any online?

1 Okay. So here's how we're going to do question
2 and answer. I'm going to start with an online
3 question, and we have three people in the room
4 that we -- I will come to you. And I just ask
5 if you ask one question, if you have multiple,
6 figure out what's the most -- the burning one
7 you have. But Heidi, what is our question from
8 online?

9 DR. WEHRING: Okay. Thank you to
10 all our online participants. There are a
11 couple that came in that I think might meld
12 well with the next talk, but I have one here
13 that's really, I think, impactful.

14 As mentioned by an audience member
15 in the previous session, patient and external
16 perceptions of functional outcomes don't always
17 correlate. So from a regulatory perspective,
18 how would you evaluate the discordance between
19 outcomes resulting from patient observer and
20 clinician raters. And of course, from a
21 cultural and from a meaningfulness perspective,
22 I think there might be some kind of rich

1 thoughts here.

2 DR. CAMPBELL: Yeah. So I also
3 think that may be a good question for some of
4 our next panel as well, or I'll take staff for
5 you if you want me to.

6 So I think, you know, number one, I
7 don't expect to have exact correlation among my
8 different reporters. That is not the reality.
9 I think what is important when we do see that
10 discordance is the understanding of what was
11 that perspective that they were providing.

12 So I think Mark gave a really great
13 example of why that clinician perspective is
14 important for certain things, because it helps
15 with that perspective.

16 I think this is why it's important
17 to do qualitative work and talk to Matt and to
18 Brandon and those folks who can talk about what
19 that experience was like for them and where
20 they are at right now, to kind of give a way to
21 help interpret and attribute the data we're
22 seeing.

1 So I think that's really important
2 for us to understand. I think when we take and
3 review this data, we're looking at all of it
4 coming in. But the more details behind how the
5 attribution or what was really going on or
6 things that are better defined in a protocol is
7 extremely helpful when we're interpreting all
8 that data that we get that comes in.

9 And this is why we have these -- ask
10 and encourage for this early conversation with
11 us, and frequent conversation, so that when a
12 sponsor starts seeing that too in our trials,
13 that -- what do we need to think about? Was
14 this expected? Is something happening? Do we
15 need to think about this further? Is there
16 adjustments needed?

17 Or maybe this is just actually the
18 reality of the treatment, and we need to make
19 sure we have good documentation with that data
20 for that interpretation piece. So Laura, and
21 then I'll go to Eric.

22 DR. SWETT: Yeah. I just -- thanks,

1 Michelle. I just wanted to add to that, that
2 this is such an interesting disease in terms of
3 there's some constant symptoms and there's some
4 ebbs and flows or waxing and waning, and
5 there's some great benefit to getting
6 information from patients, like Matthew had
7 mentioned, that you had an episode in 2011, and
8 then you have the different perspective now
9 than perhaps if we had gotten your insight as a
10 patient at that time.

11 And there's some real value to
12 getting the post-evaluation of that and what
13 would have been helpful now that somebody is
14 back in their -- maybe just their normal sense
15 of self. That would also be really helpful
16 information to capture.

17 DR. CAMPBELL: Thank you, Laura.

18 Eric, did you want to -- go ahead.

19 Go on.

20 DR. JARVIS: Very quickly. So in
21 our studies, which are not clinical trials, but
22 discordance is an opportunity for a discussion.

1 And it's -- it does take the time. But like
2 you were talking about, it's a different kind
3 of reporting from one stakeholder or a patient
4 or a family member.

5 You're trying to triangulate data in
6 qualitative studies often, and that's -- it's
7 just the beginning of a very rich, sometimes
8 very productive negotiation, I guess, of what
9 the meaning is.

10 DR. CAMPBELL: Thank you for that.
11 So, I'm going to start the first person up at
12 the front microphone. I please ask if you can
13 introduce yourself, so our online audience
14 knows who's talking. Thank you.

15 DR. STRAUSS: Hi, everyone. Great
16 panel. This is Greg Strauss from the
17 University of Georgia. We've been doing a lot
18 of research on culture just over the past year
19 that we haven't published, and negative
20 symptoms, and I wanted to make one comment and
21 ask you all one question.

22 Comment: there are a few reasons why

1 there have not been cultural adaptations
2 created for negative symptom assessment. So,
3 one is that it's thought to be built into the
4 assessment itself. So, raters are instructed
5 to do is rate someone in relation to that
6 person's demographic, age, sex, ethnicity. And
7 that assumes that the rater has proper
8 knowledge of those things, which is not always
9 the case, of course. And their own cultural
10 identity and awareness, which can interact with
11 them.

12 There's no training that I know of
13 to train raters to develop the type of cultural
14 awareness and understanding of factors related
15 to motivation, emotional expression, social
16 behavior related to different ethnicities and
17 other aspects of culture. And to increase
18 validity, that needs to happen.

19 The second comment in relation to
20 that is, the literatures lags behind because
21 people assume that a deficit is a deficit, that
22 the absence of a behavior comes from the same

1 process, regardless of what the absence is.

2 But there can be active cultural
3 processes that differ across cultures. I'll
4 give you one example, the strong Black woman
5 schema. We have found that that is positively
6 associated with the severity of all five
7 negative symptom domains in people with
8 schizophrenia.

9 And it's an active cultural process
10 that occurs in that community that's very, very
11 normative, non-pathological in general, but can
12 contribute to some symptoms like depression and
13 anxiety. But there can be active cultural
14 processes that contribute to negative symptoms.

15 And here's the question I had for
16 you guys. We're finding that context matters a
17 lot. So for example, when you have
18 incongruency between the ethnicity of a rater
19 and the ethnicity of a patient, you see an
20 increase in symptom severity.

21 We've even had the same patient
22 interviewed by a White rater and a Black rater

1 -- for a Black patient, for example -- in the
2 same week, and you find differences based on
3 who is interviewing them. And the question is,
4 are those genuine differences in the behavior?
5 Do the people behave differently in the
6 interview depending on the rater, or is it that
7 the raters are rating the person differently
8 because of their own culture?

9 So the question that I have for you
10 is: how do you tackle that question, and how
11 would you account for?

12 DR. CAMPBELL: Oh, wow. I'm going
13 to -- I mean, that's a fascinating question in
14 general, and we can apply it -- let's go global
15 and all of that. I think that's a fascinating
16 question.

17 I don't know if anyone had a quick
18 thought about that? Okay. So, Mark, and then
19 Eric. I mean, I'm sitting here rattling ideas
20 off my head, and I'm like -- I've got a lot of
21 thoughts. But Mark and Eric --

22 DR. OPLER: I'll be quick. You

1 know, back in the 50's, they did a big study in
2 Manhattan, the Midtown Manhattan Study, like,
3 one of the big first, you know, epidemiologic
4 studies of mental illness on a population
5 level.

6 And the doctors who were running it
7 at Cornell realized a lot of folks there
8 weren't necessarily from America. There are
9 all kinds of languages and cultures. And for
10 the first time in history, they said quick,
11 call an anthropologist. Until today. We've
12 got Bonnie.

13 Well, that was my grandfather that
14 they called back in the 50's. And, you know,
15 he realized a couple of things. You know, one
16 was that there's social distance between the
17 researcher and the subject. And we've stopped
18 recognizing that.

19 Wouldn't it be interesting to start
20 measuring that again, the level of social
21 distance, you know, the cultural milieu of the
22 sites where we do this work in? It's not that

1 hard to do.

2 To collect it as part of a meta-
3 study would be an incredibly valuable thing for
4 the question you're talking about. And I think
5 it's -- this is data. We can't answer these
6 questions until we start collecting data on it,
7 and I would love to see that happen.

8 DR. JARVIS: Okay. That's really
9 fascinating what you're saying, and the
10 findings that you were just describing, I hope
11 you can publish them. I think I may have cited
12 one of your papers. The -- you're the Strauss.
13 I said -- okay, excellent. I'll come and talk
14 to you.

15 So anyway, the thing is that the
16 finding you had about the strong African
17 American woman, I would just run those ideas by
18 members of the community and see what they say
19 and what they think, and get a wide -- go out
20 and get a wide -- that's just one idea.

21 The other one is that we work with
22 culture brokers. There's linguistic

1 interpreters, and there's cultural interpreters
2 as well. So it's kind of what Mark was saying.
3 In this case, Bonnie is kind of like -- as an
4 anthropologist, could be kind of like a
5 cultural interpreter for certain kinds of
6 things. But sometimes you need somebody much
7 more specific to the community to help you
8 understand what you're finding. You know,
9 maybe an anthropologist wouldn't know or
10 wouldn't have that kind of inside information.
11 You know?

12 So those are a couple thoughts, just
13 listening to the work you're doing, so.

14 DR. CAMPBELL: All right. So I'm
15 going to take a question in the middle, and
16 then I'm going to end with Nina up front. So
17 person --

18 DR. KIRPATRICK: Comment based on --

19 DR. CAMPBELL: And who -- can you
20 please introduce yourself?

21 DR. KIRPATRICK: Yes. I'm sorry.
22 I'm Brian Kirkpatrick, University of Arkansas,

1 and with Quantic Innovation. I have reached a
2 conclusion based on experiences with my wife,
3 who is from a different country, has a strong
4 accent, different ethnicity.

5 Watching her maneuver in her
6 country, watching her maneuver in this country,
7 I've come to the conclusions that Americans --
8 that a lot of things that we think are involved
9 with ethnicity are really about social class,
10 education, money. And I think that in our
11 country, they're very confounded, and a lot of
12 other countries, they are as well.

13 But I think that a lot of what we
14 tend to attribute to one thing is really from
15 another. And I think that we, in this -- in
16 the research I'm hearing, I haven't heard that
17 addressed. And I think it would be useful.

18 I would hasten to say, she came from
19 -- she married down. So --

20 DR. CAMPBELL: Well, I think that --

21 DR. KIRPATRICK: I come from a bunch
22 of rednecks, and she definitely does not.

1 DR. CAMPBELL: Well, I think that it
2 actually kind of goes to the conversation that
3 we just had about that, adding that on. And I
4 think when we had our prep call, when we talked
5 about cultural adaptation, and just diversity
6 is, you know, we think about drug development
7 globally, but within the U.S. ourselves, we
8 have so much diversity, cultural adaptations,
9 different thinkings that we need to -- we need
10 to really be taking this account early.

11 DR. KIRPATRICK: Cultural adaptation
12 is one thing. I'm talking about class.

13 DR. CAMPBELL: Yeah.

14 DR. KIRPATRICK: I'm talking about
15 education and money.

16 DR. CAMPBELL: Yeah.

17 DR. KIRPATRICK: And I think for the
18 people in this room, including me, to some
19 extent, we tend to be blind to that in a way
20 that people who are lower social class are less
21 so, is my guess. So --

22 DR. CAMPBELL: Does anyone have a

1 quick thought on that?

2 DR. OPLER: Just that, you know,
3 there's a culture of money and class as well.
4 And I think, you know, we're talking about
5 different sides of the same dice, if you will.
6 It's part of social distance, and I think
7 you're right, we overlook it. We like to
8 pretend it's not there because it's
9 uncomfortable.

10 DR. CAMPBELL: Okay. And last
11 question, Nina.

12 DR. SCHOOLER: So I'm going to end
13 on a more mundane note. This is a question to
14 Dr. Jarvis. I was really fascinated by that
15 little vignette you presented of the example of
16 somebody asking for guidance, first of all, by
17 the degree to which that person was really
18 comfortable with the jargon of negative
19 symptoms and so forth. And so my question is,
20 what's your recommendation?

21 DR. JARVIS: To the referring
22 clinician?

1 DR. SCHOOLER: Yeah.

2 DR. JARVIS: Well, I mean, we often
3 don't give the recommendation right away. We
4 kind of say "let's talk -- we need to discuss
5 what your issues are." This is a new referral
6 to our service. So I -- our impression is it's
7 not psychosis, right? That's our impression.
8 So we're going to have to find a way to talk to
9 the team that's very convinced it is, you know,
10 and we'll have to start a negotiated sort of
11 resolution about how to treat the client.

12 So this is often the way -- we look
13 at our work as mostly centered on the referring
14 team, not on the clients or patients
15 themselves, because it's more of a consultative
16 model, you know?

17 So that's the answer I can give you.
18 My recommendation is going to be that we're
19 going to wait a while and then talk to them
20 about some of our impressions and see if
21 they'll accept that maybe -- part of it might
22 be the patient as well. The patient may be

1 unhappy. I can't remember the full story. He
2 may have been unhappy with the initial
3 evaluation of depression. So that may be
4 partially driving this kind of a -- what do you
5 call it, sort of settling into a psychosis
6 diagnosis.

7 But it's a good question. And the
8 way we work usually, like I say, is we kind of
9 -- we take our -- a bit of time, and we try to
10 hear the needs of the referring team and see
11 what may be driving the referral and making
12 them have such a strong -- take a strong
13 position.

14 Then we'll talk a little about
15 stereotypes as well, and how, like, a lot of
16 people from African communities are pushed
17 toward the schizophrenia, you know, world. And
18 we'll say we often -- we just want to try other
19 possibilities, because he's very young and new
20 to this psychiatric system.

21 So we might try an antidepressant
22 trial and see if that's going to be helpful.

1 And that way, if it is depression, maybe we'll
2 kind of clear the decks and he'll improve. You
3 know?

4 DR. SCHOOLER: And just to clarify
5 why I asked the question, I was thinking this
6 person might be a candidate for a negative
7 symptom study and wanted to negotiate that.
8 Thanks a lot.

9 DR. JARVIS: That would be true if I
10 was running one, you know?

11 DR. CAMPBELL: Well, I want to thank
12 my panelists. I want to thank Bonnie for
13 joining us virtually. I want to thank you for
14 asking questions. So we're going to end our
15 session. We are going to take a five minute
16 break, so -- because we're -- because I want to
17 make sure I have enough time for our next
18 dynamic panel.

19 So we can return around 2:18 East
20 Coast time, for our virtual folks. We greatly
21 appreciate it. But thank you.

22 (Whereupon, the above-entitled

1 matter went off the record at 2:13 p.m. and
2 resumed at 2:18 p.m.)

3 DR. WEHRING: All right. Hi,
4 everyone. That was a really short five
5 minutes. I apologize. But I know that
6 everyone will be really interested in hearing
7 what our next round of speakers have to say.
8 So, as folks are filing back in, I'll just go
9 ahead and get us started, introduce myself, and
10 invite the panelists or respondents and our
11 speakers to come on up and take a hot seat up
12 here for Session 4.

13 So, I'm Heidi Wehring. I'm a
14 Clinical Reviewer in the Division of
15 Psychiatry. I'm a Clinical Reviewer here in
16 the Division of Psychiatry at the FDA. But
17 most of my pre-FDA career actually focused on
18 the treatment of schizophrenia. And clinical
19 research moving towards helping to improve the
20 lives of persons with schizophrenia. So, this
21 is a topic really near and dear to my heart.

22 And we have just a fantastic expert

1 panel of speakers and respondents that are
2 filing up on stage. A lot of these folks
3 actually -- most of these folks have already
4 been cited in the earlier topics today. So,
5 there are going to be some familiar themes that
6 are going to come in here. So, basically,
7 we're going to start with looking at the
8 clinical outcome assessments for measuring
9 negative symptoms of schizophrenia. And talk
10 about some of the non-clinical outcome
11 assessment measurements.

12 So, I'll start this session with Dr.
13 Jack Blanchard, and he'll be beginning our talk
14 with looking at the outcome assessments in
15 negative symptoms of schizophrenia. And I'll
16 let him give a little bit of his background
17 about why we chose him to give us discussion on
18 this topic. Thanks so much.

19 DR. BLANCHARD: Why did you?

20 (Laughter.)

21 DR. BLANCHARD: My career has been
22 dedicated to understanding negative symptoms.

1 From graduate school, looking at anhedonia to
2 assessing negative symptoms. And I'm going to
3 talk about that research during the course of
4 my presentation.

5 So, I'll be focusing on the clinical
6 assessment interview for negative symptoms, the
7 CAINS. Giving a little background which I
8 think I can move through quickly because of the
9 prior conversations.

10 But scale development in the 1980s
11 allowed us for the first time to quantify
12 negative symptoms and to begin to understand
13 their clinical significance. Critically
14 important. Allowed us to advance the field.
15 But over the years, a number of concerns were
16 raised about these instruments, despite the
17 advances that they brought.

18 I'm highlighting a few of these
19 here. Basically, what we're focusing on is the
20 inclusion of items, the inclusion of constructs
21 that don't seem to be central to the definition
22 of negative symptoms. And therefore, risks the

1 introduction of error variance in how we
2 measure and quantify negative symptoms.

3 So, some of these scales include
4 items that really, as I said, don't fit with
5 negative symptoms. One example here with the
6 NSA, is this idea of emotional range, where the
7 lack of anxiety, sadness, anger, is
8 pathologized as reflecting the presence of a
9 negative symptom.

10 Or other symptoms looking at
11 cognitive impairment. Cognitive impairment can
12 be associated with negative symptoms. It's not
13 part of the core definition of these symptoms.
14 So, to include things like attention or
15 abstract thinking, may be problematic.

16 The other concern is that when we
17 look at assessing negative symptoms, many of
18 them are defined by their experiential
19 component. How do you feel? Are you motivated
20 to do something? Are you interested in doing
21 something? Do you gain pleasure from doing
22 something?

1 But some of these scales don't ask
2 about experiential aspects. They don't ask the
3 participant how they feel. Instead, they look
4 at the heater. They look at performance and
5 infer deficits in motivation, infer deficits in
6 pleasure from those performance deficits.

7 The other concern is that in some
8 cases, we see poor reliability, either at the
9 scale level or item level. And then some of
10 these scales lack really detailed anchors,
11 interview of scales, and other concerns about
12 making sure that we can use these
13 collaboratively and consistently.

14 So, all of these concerns were noted
15 over 20 years ago. We're having similar
16 conversations. Twenty years ago, there was
17 this conference about how do we advance the
18 field in interventions for negative symptoms.
19 Out of the conference came acknowledgement
20 about these limitations. And the need to
21 develop next generation scales.

22 And so, out of this really were two

1 scales that were developed. Each taking a very
2 different approach to scale development. I'll
3 be focusing on the CAINS, and then Greg is
4 going to talk about the Brief Negative Symptom
5 Scale, the BNSS.

6 So, for our approach, what we
7 decided to do is we really felt like this
8 undertaking had to be significant and required
9 funding from NIMH. So, collaborators Ann Kring,
10 Bill Horan, Raquel Gur, we came together and we
11 had a multi-site, multi-PI study to address how
12 we could develop the next symptoms scale.

13 And the modifications that we
14 addressed in developing the CAINS, are listed
15 here. And basically, we were trying to fix
16 those things, that we'd come to learn about
17 limitations, with other scales.

18 So, we removed item content that was
19 unrelated to negative symptoms. We looked at
20 discussing experiential deficits. And the
21 approach that we took was to start with a large
22 pool of items, just like drug development. You

1 may have ideas about what's going to work. You
2 may have your best guess, clinically informed
3 research, informed about what's going to
4 perform.

5 But ultimately, we wanted data to
6 adjudicate the decision as to what items
7 survive. What items got trimmed, refined,
8 altered? And so, we started with that large
9 pool, understanding that we would end up going
10 shorter on it.

11 We then used advanced statistical
12 techniques like IRT to inform us. What items
13 are working? What range of scale do we have?
14 Is it a five-point scale? Is it a seven-point
15 scale? We could guess, but we wanted the data
16 to tell us what to do. Finally, we created a
17 manual. We have standardized interview probes.
18 We have training videos.

19 And so, the 23 items that we started
20 with, again, large pool, tapping those five
21 consensus domains that were talked about
22 earlier today. I'm not going to go through all

1 the different content but again, we're
2 spreading a wide net and trying to give
3 everything a chance to perform. And if it
4 doesn't perform, we're going to trim it out, as
5 you'll see.

6 And we did this in an iterative
7 fashion. We started with an early data
8 version, that had those full 23 items. And
9 that first study in 2010 was really just "what
10 can we learn about it? What can we do in terms
11 of developing our measures?" And then in the
12 2011/2013 studies, those were the grant funded
13 studies. Starting off with Horan, with 23
14 items, five-point scale, 281 patients across
15 our four sites. Looking at all those features
16 that I have listed there. Taking that down to
17 16 items, revising the scale based on
18 statistics data. And then taking that out
19 again, multi-site with Kring et al., with 16
20 items, ultimately trimmed down to three.

21 And the final scale, you see here,
22 you have nine items. Tapping that, motivation

1 and pleasure that you heard about earlier
2 today. And four items, tapping into
3 expressivity, blunted alpha et cetera. We
4 found that the scales were internally
5 consistent. We had good rater agreement. We
6 had convergent validity, discriminant validity
7 with depression, psychosis, cognitive
8 impairment, and short-term test-retest
9 reliability. And so, from this, we
10 disseminated that 13-item scale. And the idea
11 was, for purpose of that grant, was to develop
12 a scale that would be used, that would have an
13 impact on the field. One way to measure impact
14 is to look at our citation impact. Over 500
15 publications have cited that 2013 paper. The
16 vast majority, over 400, are in psychiatric
17 journals. Is that surprising? But we also
18 have neuroscience journals. We have circa from
19 pharmacology journals et cetera.

20 So, since 2013, in addition to these
21 citations, we can interrogate the validity to
22 the CAINS. What have we learned about it that

1 might give us confidence to consider it in a
2 drug trial? So, I'm going to walk you through
3 each of these, pretty quickly because of time
4 considerations.

5 But the first issue is about
6 replication. Can other individuals, not in our
7 hands, use this scale? And how does it
8 perform? And probably the best study that we
9 have is leveraging the MOSAIC that had over 500
10 participants, across 15 centers. This is not a
11 drug trial. It was not an imaging trial. It
12 was simply trying to understand the phenomenon
13 of negative symptoms at a representative
14 sample, and how it impacts these individual's
15 lives. And the battery was the CAINS along with
16 other negative symptoms scales. And replicated
17 exactly what we reported in 2013. Showed those
18 same two subscales, internal consistency,
19 discriminate validity, convergent validity, and
20 now an extended test-retest reliability with
21 over 400 participants, extending what we had
22 reported on previously. So, this is

1 reassuring.

2 The other thing that we can look at
3 is patient reported experiences. That's
4 something that we've come back to throughout
5 today. Great, we're getting these clinician
6 meetings, what does it mean from a patient's
7 perspective?

8 So, here what I've done is captured
9 results across a number of studies, just a
10 sampling. And on the two far-right columns,
11 you have clinician-rated CAINS for the MAP and
12 expressivity. And then on that left column,
13 these are patient reported questionnaires,
14 self-report questionnaires. They're reporting
15 on the constructs listed there.

16 And we can look at the relationship
17 between CAINS and these different dimensions.
18 And what you can see, is that clinician-rated
19 MAP is associated with many features of
20 patient reports. They're reporting worse
21 quality of life. They are reporting greater
22 social anhedonia, less social closeness.

1 Individuals who have more severe MAP also are
2 reporting more loneliness, less social-
3 emotional support, less feelings of affiliation
4 in direct encounters with individuals in the
5 lab. When we asked them to report on the size
6 of their social network, they're smaller, not
7 surprising. And their self-reported social
8 functioning was worse when they have higher
9 negative symptoms as rated by the clinician.

10 One pattern that you can see here,
11 is that the CAINS MAP is more consistently and
12 robustly related to these patient-reported
13 experiences, compared to expressivity. That
14 fits with a lot of other literature. Happy to
15 talk about that later if there's time to answer
16 any questions.

17 So, the other thing that we can look
18 at is real-world experiences. I know Greg is
19 going to talk about that some more in terms of
20 EMA [Ecological Momentary Experience]. For
21 those of you who are not familiar, we're
22 leveraging the fact that we're all carrying

1 around a smartphone. We can ping someone
2 multiple times today at random intervals, and
3 ask you in-the-moment, who are you with? What
4 are you doing? How are you feeling?

5 And so, we can look at these
6 clinician ratings on the CAINS, and does that
7 relate to those in-the-moment reports and
8 experience? And here are two studies recently
9 done. Both use the CAINS, focusing on
10 motivation and pleasure. In both studies, what
11 we're finding is that higher clinician-rated
12 motivation and pleasure deficits are associated
13 with in-the-moment decreases in anticipatory
14 pleasure for Merchant et al (2022), overall.

15 And then for Abel et al (2024), focusing
16 specifically on anticipated social pleasure.
17 So, clinician ratings have meaningful
18 relationships to in-the-moment experiences, out
19 in the real world, as these people are
20 experiencing and navigating their social world.

21 The next thing that we can look at
22 is -- we talked about clinician ratings, we've

1 talked about self-report, we've talked about
2 in-the-moment self-report -- but what about
3 behavior? This morning, we heard, I found a
4 very compelling example of an individual with
5 negative symptoms, struggling for employment
6 because of the interpersonal consequences of
7 negative symptoms and the behaviors that are
8 part of that.

9 And so, in this study we looked at
10 the association of negative symptoms and social
11 skills and how that may cascade into social
12 rejection. And so, on the far left you see our
13 predictors that we had. We assessed paranoid
14 ideation, because of its relevance to
15 interpersonal functioning, marked with positive
16 symptoms. We had CAINS. We also were assessing
17 sleep in this study because our lab and many
18 other labs, have now established that sleep
19 problems can contribute to functional
20 impairment as well as symptom severity. And
21 then in the middle column there, we had
22 objective-behavioral ratings from coders, video

1 tapes of the social interactions from our
2 participants. And they are rating social
3 skill. They're rating positive facial
4 displays.

5 And then finally, we had naive
6 raters watch those same video tapes, and
7 they're not coding on the skill. They're not
8 coding anything. They're simply reporting on
9 subjectively, "how do you react to this video
10 of this individual? Would you want to spend
11 time with that person?" And what we found was
12 that negative symptoms impacted ultimately
13 social rejection through social skills
14 deficits. So, CAINS clinician ratings are
15 manifesting in social behavioral deficits and
16 that ultimately is having an impact on social
17 rejection. Showing the meaningfulness of those
18 clinician ratings.

19 The other thing that we can talk
20 about is neural responding. That was something
21 that you heard about in great detail this
22 morning. I'm not going to go into all those

1 different models. But I'm just going to touch
2 on findings indicating that clinician-rated
3 CAINS are related to neural responding. And
4 so, what kind of neural responding might we
5 want to look at? This morning we heard about
6 reward. I'm going to tap on that. But there's
7 also another benefit of social affiliation that
8 we all experience. And that benefit is social
9 affiliation helps us cope with stress. It
10 reduces the challenges that we have when we are
11 encountering threats in our environment.

12 This is sometimes referred to as the
13 social regulation of emotion. And we can study
14 that in the scanner. And so, we can bring
15 people into a scanner, and while they're in the
16 scan, they are watching cues. And those cues
17 can be safety cues, "Nothing is going to
18 happen, relax." Or they can be cues of threat,
19 "In our study there is a chance of shock."

20 And what you see in that upper-left
21 brain scan is the green. It's showing that
22 activation as an individual responds to cues of

1 threat. Not surprisingly, you have widespread
2 neural activation.

3 We then used a paradigm from Jim
4 Coan at University of Virginia, and he studies
5 the social regulation of emotion in healthy
6 individuals. And we borrowed that here. So,
7 the hand-holding paradigm is simply, you're
8 watching these images, the cues alone. And
9 then we have another trial where a partner
10 comes in. An affiliate partner comes into the
11 scanning room, says nothing, and simply holds
12 the person's hand. And Jim had previously
13 demonstrated that if you look at couples,
14 friends, and they do that, you see attenuation
15 of neural activation in the face of threat.
16 So, affiliative contact is attenuating neural
17 response to threat. And we asked the question,
18 "do motivation and pleasure deficits, are they
19 related to not experiencing that benefit of
20 social affiliation?" And that's exactly what we
21 found. Those individuals who have higher
22 motivation and pleasure deficits, have less

1 benefit from that affiliative contact. They
2 continue to show that neural activation.

3 The other thing that we looked at
4 was reward. And we looked at two forms of
5 reward, monetary incentive delayed tasks that
6 you see there. And those blue triangles are
7 pointing to the ventral striatum reactivity,
8 replicating prior studies. In a scanner, doing
9 a task, interesting video of a monetary reward.
10 Money is falling into a glass jar. You see
11 that neural network becoming activated in
12 anticipation of that reward.

13 Well, we're really interested in
14 social reward. Everything we've been talking
15 about with negative symptoms, really focuses on
16 social pleasure, social motivation. So, we
17 took that same individual who held the hand in
18 the prior protocol, videotaped them with
19 positive social responses, smiling, thumbs up,
20 great job. And instead of money, now they're
21 seeing that brief video. And again, those blue
22 triangles you can see the ventral striatum

1 being activated to social reward. We looked at
2 the association between reward responses and
3 motivation and pleasure deficits. And what we
4 found was that MAP symptoms are related to
5 blunted ventral striatum reactivity, to social
6 reward, not monetary reward. And those
7 associations held when we controlled for
8 positive symptoms, depression. So, finding
9 support for CAINS clinician-rated symptoms
10 being related to neural activity to social
11 reward.

12 The final thing I want to touch on
13 has to do with sensitivity to treatments.
14 That's obviously something of interest here.
15 So, I just did a quick review. This is
16 probably not comprehensive of the literature,
17 and we have six studies here. I want to point
18 out that five of these are psychosocial
19 interventions. Some of these are RCTs, but if
20 you look at the far right, I've indicated those
21 negative symptoms where they're using CAINS.
22 And where they're finding significant

1 differences between the active treatment and
2 the comparator. And in these cases, the CAINS
3 is detecting a significant difference.

4 There are a few studies, not many,
5 and we have to be cautious about interpreting
6 them, but there are a few studies that found
7 CAINS detecting a signal, but other negative
8 symptom instruments not detecting a signal.
9 You want to be cautious about interpreting it,
10 but it does lend credence to the sensitivity of
11 the CAINS. And shows that it may be promising
12 for future drug trials.

13 In terms of use in other settings,
14 this is an unofficial list of CAINS
15 translations. I've put an asterisk next to
16 those that indicate that there's a published
17 validation study. Other languages that you
18 have there, those are investigators letting us
19 know that they've translated it, but I don't
20 think there's a publication on that yet. But
21 the point is, is that it's been used in a
22 number of countries.

1 So, just in brief, I've tried to
2 overview some of the positive attributes of the
3 CAINS and the research that we have so far,
4 across multiple dimensions. Showing that it
5 may have promise for use in intervention
6 trials.

7 And I'm going to close by just
8 acknowledging my collaborators, my students,
9 current and former. And the grant funding from
10 NIMH, that's supported this research. And I'll
11 stop there, and I have time, actually.

12 DR. WEHRING: Thanks so much, Dr.
13 Blanchard. So, we're going to go ahead and
14 continue our session. I'll let Dr. Greg
15 Strauss speak for himself. We are really lucky
16 to have perspectives from different clinical
17 outcomes assessments, as well as digital health
18 and other techniques to be discussed next.
19 Thank you.

20 DR. STRAUSS: Thank you, Heidi. So,
21 I'll be talking to you about two things today.
22 One will be the brief negative symptoms scale,

1 which we call the BNSS for short. And also
2 digital phenotyping measures. So, I'm going to
3 try to do double duty here and march you
4 through both.

5 The BNSS is a 13-item clinical
6 interview-based assessment scale that was
7 developed in response to the NIMH consensus
8 conference that Jack mentioned. And it was
9 designed to measure the five core consensus
10 domains. It also has one additional domain
11 that is measured, the lack of normal distress.

12 It's rated after a brief 10 to 15-
13 minute interview. And it has a very concise
14 manual and workbook, which has been helpful for
15 training raters to become reliable, especially,
16 for clinical trials. And in conjunction with
17 WCG, we also have professionally-developed
18 training videos and gold standard ratings, that
19 have now been used in over a dozen clinical
20 trials, plus additional experimental psychology
21 studies.

22 It's been translated into over 20

1 languages now. And the psychometric validation
2 studies are strong. We have data supporting
3 reliability in terms of inter-rater, internal
4 consistency and test-retest reliability. And
5 also, validity in terms of convergent and
6 discriminant validity. And importantly, these
7 good psychometric properties are replicated
8 across the numerous translated versions of the
9 scale.

10 Today I'm not going to spend much
11 time reviewing those psychometric properties.
12 What I'm going to do that I thought would be
13 most helpful, is walk you through how the BNSS
14 meets criteria for the FDA's eight COA
15 criteria, A through H.

16 Criterion A, why should negative
17 symptoms be assessed with clinical-interview-
18 based rating scales? Jack already answered a
19 lot of this, but I'll give you a couple of
20 additional items. One is that the absence of
21 an experience or behavior is harder to
22 conceptualize than the presence of one. In

1 other words, you don't know what you don't have
2 always. So sometimes it is helpful to have
3 clinician judgment against what is normative.
4 And this can be useful particularly in cases
5 where people have less insight or awareness,
6 perhaps due to cognitive impairment. [Second],
7 traditionally, negative symptoms have not been
8 measured through non-clinician collateral
9 reports from relatives or caretakers, for
10 example. Potentially, because these concepts
11 are hard to understand, and also, people may
12 not have complete access to all the information
13 necessary, since several of the domains are not
14 just based on behavior and observation, but
15 also on experiential processes.

16 [Third], self-report questionnaires
17 have been slow to be developed. I know of at
18 least three that have been developed for
19 negative symptoms. And they may not reliably
20 assess or validly assess all five domains. For
21 example, alogia and blunted affect which are
22 based on observation, are very hard for people

1 to self-report on.

2 [Fourth], more recently, there's
3 been a movement toward developing objective
4 computerized behavioral tasks. For example,
5 measures of reinforcement learning or effort-
6 cost computation. And in my opinion, these are
7 more intermediate phenotypes. They are things
8 that are closer to mechanism than they are to
9 clinical outcome.

10 So, clinical interviews hold a
11 strong place in the literature still, and these
12 are some of the reasons why.

13 So, does the BNSS assess all of the
14 aspects of negative symptoms that are
15 important? In relation to what clinicians and
16 researchers have deemed core, from the 2005
17 NIMH consensus conference, clearly, yes. The
18 scale was designed to assess the five domains
19 according to modern conceptualizations.

20 But we've also, very recently,
21 discovered through a qualitative study that
22 we've done in my lab, that the BNSS also

1 captures on important aspects from the consumer
2 and the relative/caretaker perspective.

3 I'll be showing you several slides
4 from this study. And I'm going to focus on the
5 patient data, but I'm glad to answer questions
6 about the relative/caretaker data afterwards,
7 if people have them.

8 What you can see here is we asked
9 people a few things. We asked them, "do you
10 agree with the definition we've provided?" And
11 "should any of these not be a negative
12 symptom?" And you can see with pretty high
13 agreement, people considered the six domains
14 assessed by the BNSS to meet their definition
15 of negative symptoms, the way that we defined
16 them. And they were defined in a more,
17 slightly more colloquial way than what would be
18 in the BNSS manual.

19 There was also little evidence that
20 items or domains should be removed. You can
21 see 27 percent for lack of normal distress, and
22 23 percent for alogia, which I think a lot of

1 clinicians, if they were to pick negative
2 symptoms domains to alter, those would probably
3 be the ones.

4 And we asked them, "well, how would
5 you define these constructs, if they did define
6 it differently than we do?" And the
7 qualitative responses were interesting. For
8 example, for alogia, people said things like,
9 quiet, reserved, confused. For blunted
10 affects: stiff, holding back. For avolition:
11 dull, unfocused, not having it together. For
12 asociality: shy. For lack of distress: tough,
13 experienced, not caring, holding your own. For
14 anhedonia: boredom, uninterested..

15 So many times, these are synonyms
16 worded in a different way, in a more colloquial
17 way than what Clinicians would use to describe
18 the components of them. But there were some
19 interesting additional facets that we gleaned
20 from this.

21 We also asked them, "are there any
22 additional negative symptoms that you think

1 exist in addition to the six we defined?" And
2 the responses received were minimal, but the
3 ones that came up multiple times were things
4 like, apathy -- which by the way, I consider to
5 be synonymous with the five domains. It's just
6 developed in a different literature, mostly in
7 neurology -- numbness, lack of energy,
8 confusion or foggy thinking, and catatonia.

9 Well, we also asked people a number
10 of questions and had them rate on an ordinal
11 rating scale, going from zero, if not at all, 1
12 is slightly, two is moderately, and three is
13 extremely, in relation to how important they
14 thought the five domains were. So, their own
15 subjective impression of the importance in
16 several areas.

17 So, for example, "how important is
18 it to you, to be doing well in each of these
19 areas, or improve? How much does it bother it
20 to have each of these negative symptoms?" And
21 things related to functioning, "how much does
22 having each of these make it difficult for you

1 to have a job, or go to school, or to
2 socialize?" "How much does it keep you from
3 having a good life?"

4 And the data -- I know these figures
5 are small but forgive that -- the key take-home
6 message is all of the domains except for, lack
7 of normal distress, were rated as slightly to
8 moderately important in these various ratings,
9 related to functioning, quality of life, from
10 the patient perspective. Lack of normal
11 distress fell a little bit below that bar.

12 The higher domains were anhedonia,
13 avolition and asociality. And blunted affect
14 and alogia being a little bit lower,
15 consistently. This raises a question in
16 conjunction with the psychometric data we've
17 seen on the lack of normal distress item on the
18 BNSS, that have made us start to consider
19 whether it's time to remove it, or at least,
20 make it optional.

21 The intent was to create a proxy for
22 the deficit syndrome because this has been the

1 primary means by which the deficit syndrome, or
2 primary and enduring negative symptoms, have
3 been studied in our field. And we've not been
4 successful in doing so with that item, yet.
5 So, maybe time to consider removing it.

6 Criterion C, do respondents
7 understand the questions as intended by the
8 measure developers? We basically asked people,
9 "are these questions clear?" We gave them each
10 of the questions and we asked them if they were
11 clear. And if they said, no, we asked them to
12 describe what they thought the question meant,
13 in their own words. What were we trying to
14 ask?

15 And you can see the percentage of
16 agreement was very high. So, people with
17 schizophrenia very clearly understood the
18 probes on the BNSS.

19 They also gave us very useful
20 feedback on what the sources of confusion were.
21 So, we might be able to go back and refine some
22 of the probes if we wanted to. And they even

1 gave us suggested changes to make.

2 Criterion D is, are scores
3 influenced by processes that are not part of
4 the negative symptom construct? Here there's a
5 little bit more work to do. But in general,
6 the answer is, no. Discriminant-validity
7 correlations are low, in terms of secondary-
8 negative-symptoms processes, such as positive
9 symptoms, suppression, anxiety, et cetera.
10 Item interpretation does not differ according
11 to demographics. For example, we show
12 measurement invariance across cultures and sex,
13 in collaboration with Tony Ahmed.

14 And we have found support for the
15 recall period use. There's an extensively
16 reviewed and validated model in the basis
17 affective science world, by Robinson and Clore
18 that specifies why a one-week period for
19 retrospective report, would be beneficial in
20 this type of interview.

21 You essentially, get people to
22 report on episodic memory or their actual

1 emotional experiences instead of semantic
2 memory, or their beliefs about how they
3 generally feel.

4 So, if you keep people within the
5 bounds of their episodic memory, you're more
6 likely to get accurate reports. And this is
7 one of the reasons why the BNSS, and also, the
8 CAINS uses that one-week timeframe.

9 Do fatigue or burden influence the
10 assessment? Here we don't know. We've not
11 done a formal tower ability study in relation
12 to the trial. But given that the interview is
13 brief, 10 to 15 minutes, we don't think so.

14 Does the motive assessment influence
15 results? We've seen similar psychometrics
16 between in-person and Zoom interviews. We did
17 have higher ratings at the start of the
18 pandemic. Those ended up normalizing, probably
19 because the environment normalized again. But
20 psychometric characteristics seemed pretty
21 similar across modes of assessment.

22 And then expectation bias, this is a

1 future direction. We've not been able to
2 formally deduce this yet.

3 Criterion E, is about scoring.
4 Initially, we recommended a 2 Factor solution
5 for the BNSS, based on the results of our
6 initial exploratory factor analysis. But a few
7 years later, we went ahead and we ran
8 confirmatory-factor analysis and lo and behold
9 one factor in our accepted two-factor solution
10 offered a poor fit for the data.

11 And a five-factor hierarchical model
12 was excellent. And interestingly, we found
13 this not just for the BNSS, but also for other
14 contemporary measures. Here you can see what
15 the factors look like. Here on the left, you
16 have the five domains. And on the right, you
17 have the two-superordinate dimensions, the MAP
18 (motivation and pleasure), and expressivity.
19 Beneath which, you have the five lower-level
20 domains.

21 And of course, we didn't believe it.
22 So, we tried to replicate it. Here on Ahmed et

1 al, we found it across multiple studies and
2 cultures. Six different cultures, multiple
3 datasets, measurement invariance in thousands
4 of people with schizophrenia in this study. We
5 found it in both clinical high-risk and first
6 episode patients. The same factor structure
7 with five factors in the hierarchical model,
8 with data from Hong Kong and America.

9 And then we also replicated it into
10 our samples from America and Italy, using a
11 different mathematical approach of network
12 analysis in community detection. So, we've
13 started to believe that this is probably the
14 best structure for the BNSS, if not, for all
15 negative symptom measures.

16 But there's a key question that
17 Laura Swett brought up of, are all domains
18 created equal? And here there's emerging
19 evidence suggesting that they in fact, may not
20 be. And here we find some evidence from our
21 qualitative study that avolition may be deemed
22 by consumers, to be more important than the

1 other domains. Here you can see an average
2 across all of the different questions.

3 Here you can see avolition receives
4 the highest rating, indicating that's the most
5 important. And when you directly ask about
6 importance itself, avolition is significantly
7 higher than the others.

8 Now, interestingly, we've seen this
9 more objectively too. We've run network
10 analysis on the BNSS and we found that in
11 people with schizophrenia, the domain that is
12 most central is avolition and also, alogia.

13 Now, what does that mean? It
14 basically, means that avolition, motivational
15 deficits are driving the other symptom domains.
16 They may have a causal connection and lead to a
17 cascading effect of changes when motivational
18 deficits are present.

19 We extended this in data from the
20 phase IIb roluperidone trial, that you can see
21 here, published in Schizophrenia Bulletin. And
22 what we found is that compared to placebo, the

1 drug roluperidone was able to increase the
2 centrality of avolition. And the extent to
3 which it did so, dictated the magnitude of
4 change in all the other domains. So,
5 successfully treating avolition was key to the
6 improvement of the entire negative symptom
7 constellation.

8 And of course when their phase III
9 trial was completed, we wanted to see if we
10 could replicate this. So, here we saw there
11 was a significant overall effect on negative
12 symptoms this time, using the PANSS. And we
13 used a different network analytic approach,
14 called Network Intervention Analysis. And what
15 this allows you to do, is basically isolate the
16 treatment related effect, compared to placebo.
17 And see which symptom is driving the overall
18 improvement in the negative symptom
19 constellation. And is that a direct or
20 indirect effect?

21 What we found is that it was the
22 PANSS item for emotional withdrawal, which is

1 the closest thing on there to avolition, rated
2 on the newer negative symptom scales. So, we
3 took this as being a nice replication of the
4 earlier study. Interestingly, we ran follow-up
5 analyses. Thank you, if any reviewers are in
6 the room. That are in supplemental materials,
7 where we basically, tried to see, are these
8 roluperidone effects driven by secondary
9 negative symptoms?

10 And they were not. They were not
11 driven by depression, or positive symptoms.
12 Interestingly, the drug did have a direct
13 effect. You can see that redline there, from T
14 to POS, on positive symptoms itself. Using
15 this mathematical approach, it was able to
16 reduce positive symptoms, even though it's, you
17 know, not touted as an antipsychotic for that
18 purpose.

19 Criterion F, do the scores
20 correspond with specific health experiences
21 that people with the illness have with regard
22 to negative symptoms? Just like Jack

1 mentioned, same thing, correlations with EMA-
2 based negative symptoms we found pretty
3 consistently with measures in daily life.

4 Here again, do the scores correspond
5 with individual experiences that the patients
6 have? The answer is, yes. You can see that
7 they indicated that all the domains are related
8 to these important aspects of quality of life
9 and functioning. And we've also demonstrated
10 sensitivity to change. The BNSS has been shown
11 to be sensitive to change in at least ten
12 clinical trials. The majority of which were
13 psychosocial, with only a few null findings.

14 And here you can see this busy table
15 is from the roluperidone phase IIb trial. This
16 is an anchor-based table, indicating the
17 magnitude of change from baseline that's
18 required to produce a CGI effect of a 1-point
19 or a 2-point change in improvement. And the
20 thing that I want you to pay attention to, is
21 in the far-right column. What you see is
22 effect size.

1 These are Cohen's d values and you
2 can see they're in the medium to large range.
3 So, a 1-point improvement on the CGI is
4 producing a medium to large effect-size change
5 across these various negative symptom domains.
6 So, the BNSS is sensitive to change.

7 But as Dr. Swett mentioned, a
8 critical question is, so what? Is that
9 magnitude of change meaningful to people with
10 the illness? Here the answer seems to be, yes,
11 when I looked at this data I had available to
12 me from the Risperidone Trial. What you see
13 in this table is data from our qualitative
14 study. We essentially, asked people, we showed
15 them the BNSS anchors, and we walked them
16 through it and asked them, "where do you think
17 you would rate yourself right now?" "Where
18 would you want to be for your life to
19 meaningfully improve?" And left that open to
20 their interpretation of what meaningful meant.

21 What you see in this table is that
22 the magnitude of improvement, difference

1 between the clinician rating on the BNSS, and
2 the person's ideal rating for themselves was
3 about the same magnitude of difference as what
4 roluperidone produced on a 1-CGI-point change.
5 So, 1-CGI-point change on this drug was
6 equivalent to what people with the illness were
7 saying, would be ideal for them to change as
8 well.

9 In other words, roluperidone does
10 seem to be improving negative symptoms to a
11 level that's meaningful not just to clinicians,
12 but to people with the illness.

13 So, as a quick summary, here you can
14 see the eight COA fit-for purpose criteria.
15 There is still some work to do on the BNSS.
16 But there is some evidence for at least each of
17 the criteria supporting that it meets the
18 recommendations.

19 Now, in Part 2, I'm going to talk to
20 you about digital phenotyping. And this
21 involves the use of technology to measure
22 symptoms in the real world, or from clinical

1 interviews. It's, typically, divided into
2 active and passive approaches. Active, simply
3 refers to something that people with the
4 illness must initiate. Such as an ecological
5 momentary survey on the phone, or an ambulatory
6 video, or a cognitive test performed on the
7 phone.

8 Passive methods in comparison are
9 basically unobtrusive. They're collective in
10 the background, usually through sensors of a
11 smart band, or a smartphone, while people are
12 going about their daily lives.

13 To start off, I'll show you here,
14 the conclusion. We're probably about halfway
15 there, in my opinion, in terms of what's needed
16 for the assessments to meet the FDA COA
17 criteria. But we've made a lot of rapid
18 progress in a short period of time.

19 So, Criterion A, why should negative
20 symptoms be assessed with digital phenotyping?
21 As wonderful as the clinical rating instruments
22 are, and I do of course think that they have a

1 very important purpose in the field, there are
2 some limitations. One is subjectivity. There
3 are social desirability effects. Cognitive
4 impairments can influence the retrospective and
5 prospective reports. Halo effects, cultural
6 biases, there is also imprecision, right.
7 These are made on a, usually it's zero to five,
8 zero to six ordinal rating scale. So, the
9 level of precision can be limited by that.

10 They also have lower resolution in
11 terms of time and context, right. With digital
12 phenotyping, you can get hundreds, if not
13 thousands of data points per day. And you can
14 drill down into the exact context in daily life
15 that may matter the most to an individual
16 symptom profile.

17 They may also be less sensitive to
18 treatment effects. And often require very
19 large n's for studies to be completed. Digital
20 phenotyping offers you much more power and it's
21 yet to be determined how much more cost
22 effective it is, but it does have that

1 potential.

2 Here you can see an overview graphic
3 of what some of the measures are. These are
4 just a few examples from what we've been using.
5 We've used smartphones and bands to measure
6 things like accelerometry, which is the measure
7 of movement. It's how much variability and
8 magnitude of movement is there.

9 Geolocation, which is a measure
10 developed from GPS coordinates. So, you nearly
11 continuously monitor someone or get data each
12 time they move a certain amount in space. And
13 you can use that to map different variables of
14 interest. Like percentage of time at home, or
15 distance traveled from one time point to the
16 next or number of location clusters.

17 We've also had measures of speech
18 that are collected from the internal sensors of
19 the phone. So, rather than directly recording
20 people's speech and samples from the ambient
21 noise, what we've done is we have a program
22 that can basically, on the fly, calculate a

1 value.

2 So, it's not recording a sample
3 that's stored. On the fly, it's calculating
4 whether human speech is present in the
5 background and the level of intimation of the
6 voice of that speech, and spitting out the
7 variable that gets saved automatically into a
8 dataset.

9 We've also paired that with EMA
10 surveys, where we ask about location, activity
11 context, social context, interest, pleasure et
12 cetera. And have people perform an ambulatory
13 video at the end of the survey. So, for
14 example, holding the phone up in front of them,
15 and responding to a probe, such as "tell me
16 what you did over the last hour" or "How you
17 felt, and about your symptoms."

18 We can then decode that later for
19 various measures of interest, like facial
20 affect intensity and frequency and variability.
21 Acoustic measures related to intonation in the
22 voice, and pitch. And all sorts of other

1 acoustic properties.

2 You can also interestingly, take
3 data from your old video recorded interviews,
4 and plug it into software that has automated
5 algorithms for things like facial and vocal
6 affect and acoustic properties.

7 Here's an example of one measure
8 that we think is really promising from a
9 collaborator, Alex Cohen of LSU, called speech
10 latency. This is essentially, a measure of
11 verbal response time, as an objective marker of
12 a number of elements of psychopathology. This
13 might be like a g-factor for cognition, if you
14 will, that relates to negative symptoms more
15 broadly.

16 So, here for example, this is a fake
17 video of me with one of my grad students. But
18 you ask them a question on the BNSS, something
19 like who did you spend time with this week?
20 And you look at the pause after the interviewer
21 stops their question, and the time it takes the
22 participant to start their response. "I saw my

1 uncle and two cousins this week." "Oh, how
2 often did you see them?" Pause, "Only on
3 Monday." "What did you do when you got
4 together?" "We watched Georgia beat LSU in
5 football," right. So, the term latency we know
6 is a critical predictor of negative symptom
7 response. And as I'll show you later, is a
8 critical predictor of sensitivity to change.

9 Criterion B, do these assessments
10 capture all important aspects of the negative
11 symptom construct? They have an inherent face
12 validity. So, these are measures of movement
13 collected in daily life, behavior collected in
14 daily life, social activity, emotional
15 expressivity, all collected in a more
16 ecologically valid way. So, they do have an
17 inherent face validity and a ground truthiness,
18 if you will to them.

19 But the digital phenotyping measures
20 are, generally, modestly correlated with
21 clinical rating scales. And you can see an
22 example from data from our lab here, that our

1 values tend to be about .3/.4 between BNSS,
2 anhedonia and avolition and asociality with
3 their corresponding EMA survey measures.

4 The magnitude of correlations with
5 passive measures is pretty similar, usually
6 about .3 to .6. But this is really quite a bit
7 lower than what you would expect. For example,
8 if you had two clinical rating scales that you
9 were looking at correlations with, you'd expect
10 something like .8 or higher.

11 And there are a number of reasons
12 for this. One is methods variance. You would
13 not expect the correlations to be as high as
14 they would with the clinical rating scale, due
15 to methods experience. But also, temporal
16 resolution and context, right. How far do you
17 zoom in for these passive measures? Do you go
18 into every hour? Do you average every minute,
19 every second? Do you average across one week
20 to make them comparable to clinical ratings
21 scales? These are issues that the field is
22 still grappling with.

1 In our self-perceptions qualitative
2 study, we also asked people about digital
3 phenotyping measures. We asked them for
4 example, "do you think that these measures are
5 relevant for measuring negative symptoms?"
6 "Can you measure negative symptoms through
7 smartphones and smart bands?" And the
8 responses on average were, either around
9 moderately, or in between slightly and
10 moderately.

11 And we asked them about things like
12 geolocation, accelerometry, ambient speech, the
13 ambulatory videos, turn latency, and the EMA
14 surveys. So, we had a decent, but not
15 overwhelming, list for them to evaluate. And
16 we gave them descriptions of what each one was,
17 so that they knew what we were actually talking
18 about.

19 We also asked them, "How do you
20 think your life would change if you were to
21 improve on these types of measures?" And use
22 the same rating scales before. And what you

1 see is that they did consider these things to
2 be important. They thought that if they did
3 show changes on these digital phenotyping
4 measures, that their functioning would improve;
5 that their quality of life would improve, at
6 least slightly or moderately so.

7 Now, one thing that people often
8 wonder about these digital phenotyping
9 measures, is "what concerns do people have when
10 using them? What concerns particularly do
11 people with schizophrenia have about them?"
12 And what we did, is we asked them, "Do you have
13 concerns about using any of the technology
14 described, to measure your negative symptoms?"
15 And you can see for each of the measures, the
16 responses were below, slightly. So, there was
17 minimal concern. But when they did have a
18 concern, we had them "Tell us about them." And
19 most consistently what they asked about, what
20 they said was, being audio recorded. They were
21 afraid that they would be recorded all the
22 time. They thought it should only be when

1 asked. That it could be invasive if frequent.
2 Not being recorded, not recording others
3 unknowingly.

4 And, essentially, we found through
5 this and other studies, when you explain to
6 people that it doesn't do that, they're much
7 more comfortable with the technology. But
8 there are apps out there that people are using,
9 that do record actual samples. So, that's
10 something to consider.

11 They also, worried about whether the
12 data obtained would be natural or forced. Had
13 questions about the privacy and security of the
14 data. People didn't like the idea of being
15 dependent on using a phone or device throughout
16 their lives, if their clinicians wanted to
17 measure their symptoms.

18 They worried that the smart bands
19 might be glitchy or uncomfortable. Whether
20 they would be reminded of having the illness by
21 completing the EMA surveys and whether that
22 would make them more ill. And some people

1 worried about being tracked continuously by
2 GPS. They wanted to be able to turn on and
3 off, which some apps do allow that.

4 We also, asked them whether the
5 questions we were providing in the EMA surveys
6 were clear or not. And here the response, 94
7 percent of the time, was that they were clear.
8 And we had them describe to us what they
9 thought we were asking about. How to make it
10 better in instances where they thought it was
11 not clear and did receive some helpful
12 feedback.

13 Now, are the scores of digital
14 phenotyping influenced by processes that are
15 not part of the negative symptom construct?
16 Here discriminant validity tends to be good.
17 The correlations are generally low with
18 measures not part of the negative symptom
19 construct, either in terms of clinical ratings
20 scales, or concurrently collected EMA. For
21 example, measures of depression, anxiety, or
22 positive symptoms. But I will say that they're

1 not quite as good as the clinical ratings
2 scales. So, the correlations are a little bit
3 higher than what you typically see there.

4 Does item interpretation differ
5 according to demographics? We don't know.
6 There's not been a lot of work done on this.
7 And we need to do some work on measurement and
8 variance. But one of the advantages of digital
9 phenotyping is that you don't need to
10 necessarily make a retrospective report.

11 So, you can completely eliminate the
12 need for recall by asking people how they feel
13 in the moment. You know, their activities in
14 the moment. Are the scores influenced by
15 processes, not per the construct? Well, what
16 about fatigue or burden?

17 We studied this systematically, and
18 throughout it all we did study on adherence and
19 tolerability for EMA and paths of digital
20 phenotyping. What we found is that people with
21 schizophrenia and healthy controls, found it
22 highly tolerable. They rated the experiences

1 highly positive and not very negative.

2 But we did find that adherence
3 dropped during one week, not just for EMA
4 surveys, but even for some of the passive
5 measures, and wearing the band. And so, this
6 is something where we do need longer term
7 studies. We've only done this for a week, but
8 we need more methodological studies to track it
9 long-term.

10 But importantly, negative symptoms
11 were not the predictors of lack of adherence.
12 It was things like age, being busy, like
13 whether people had children or not, right.
14 These were some of the things. Life being
15 disruptive rather than not having motivation.

16 If anything, the patients with
17 higher negative symptoms we found were more
18 likely to be compliant, because they were
19 sitting at home and life was not as disruptive
20 to performing the activities on the phone.

21 Does motive assessment influence
22 results? Here there's a lot of work to be

1 done. We know that incentives probably matter.
2 How much money you give people in the EMA
3 survey for example. Do you pay them for doing
4 the passive data collection? It might
5 influence whether they wear the band or keep
6 the phone on them. Are you providing a phone
7 or having them use their own phone, right. We
8 don't know how much that matters yet.

9 How much do different operating
10 systems matter, right? We know that Android
11 versus Apple, collected different parameters.
12 They allow you to collect some things on
13 Android, that cannot be collected with Apple,
14 right. Methods variance may also matter.
15 Here's an example of this. We did an
16 accelerometry study where we had people wear a
17 band and also, collected accelerometry through
18 their phones.

19 They were supposed to have both of
20 them on, concurrently. And we could tell when
21 they weren't wearing the band. What we found
22 was that the phone was able to differentiate

1 people with schizophrenia and controls. They
2 were group differences, but the band could not.

3 In contrast, the band had
4 correlations with negative symptoms, measured
5 through the BNSS, whereas, the phone did not.
6 So, there are discrepancies, both in terms of
7 the magnitude of group impairment and the
8 connection with negative symptoms. So,
9 modality or mode of measurement may matter
10 here.

11 We don't know yet about expectation
12 bias, and I think this is critical to study.
13 So, we need long-term studies to be done. And
14 we need to do a lot of work on scoring, right.
15 So, what is the right level of temporal and
16 spatial resolution? How far do you zoom out or
17 zoom in? How do you combine EMA and passive
18 measures to drill down into the situations of
19 greatest interest?

20 So, for example, do you only get VOX
21 or speech measure during instances where they
22 report having been in a social interaction?

1 Also, do we need normative data on healthy
2 controls in people with schizophrenia to
3 facilitate the interpretation of this type of
4 data by consumers and clinicians alike?

5 Would you know what a change in
6 three meters, from one time point to the next,
7 meant? Of course not. Or a certain change in
8 accelerometry? We need norms to put these into
9 more interpretable value sets, similar to
10 neuropsychological tests.

11 We have interestingly, Tony Ahmed
12 and I have been playing around with some of the
13 digital phenotyping data we've collected. And
14 we have over 100 people at this point, and we
15 wanted to see, could we include measures we
16 thought should be relevant to each of the five
17 domains, and find either a two-factor or five-
18 factor solution?

19 Here, what we found is again, one
20 and two-factor solutions were not a great fit.
21 And the five-factor was not quite as good as
22 the clinical rating scales, but it was the most

1 optimal. I suspect that there will be the more
2 measures you put in, there will be more and
3 more factors that will emerge.

4 We also, again, asked, you know, do
5 these scores correspond to specific health
6 experiences? And remember, patients thought
7 they related to quality of life and
8 functioning, so they do think that digital
9 phenotyping is relevant to their health
10 experiences. And there has been some evidence
11 for sensitivity to change already.

12 One way to measure this is through
13 context effects. So, here you can see EMA data
14 on anhedonia. That is what's on the Y-axis.
15 You can see that in some activity types, in
16 some locations, people with schizophrenia do
17 and don't have anhedonia.

18 For example, when at a family
19 member's home, they do not have anhedonia.
20 When in public, they do not. But when they're
21 at their own home, they do. When they're out
22 running errands, they don't have anhedonia, but

1 when they're engaged in a recreational activity
2 or eating, they do.

3 So, context, this is one way of
4 measuring sensitivity to change across various
5 activities and locations. You can do the same
6 thing, pairing the active and passive data.

7 Here we show that both people with
8 schizophrenia and healthy controls have more
9 social activity identified through the speakers
10 of the cellphone with our VOX measure, when
11 they self-report being in a social interaction.
12 So, that's helping to validate that particular
13 ambulatory measure.

14 This is data from Bill Horan, Phil
15 Harvey and colleagues at Karuna. You saw a
16 little bit of this earlier in their open-label
17 12-month study of KarXT. Here they show
18 sensitivity to change in terms of improvements,
19 in terms of decreases in unproductive
20 activities, increases in productive activities,
21 spending less time at home. So, their drug,
22 KarXT was able to cause these changes. And EMA

1 was sensitive to be able to pick them up, using
2 these survey-based measures.

3 This is data from Alex Cohen, from
4 the phase III trial of brilaroxazine. And what
5 they did, is they took over 2,000 audio clips,
6 audio recordings from clinical interviews and
7 Alex processed them for certain acoustic and
8 speech variables. One was turn latency, that I
9 mentioned to you earlier.

10 He was, essentially, able to segment
11 out participants who had a certain magnitude of
12 turn latency deficit, which they termed "vocal
13 biomarker positive," and compared that to
14 people who did not have this vocal biomarker.
15 And what they found is that the originally
16 negative results of the trial, null results,
17 became positive when you identified, when you
18 stratified patients based on this digital-
19 phenotyping-based biomarker.

20 So one, an alternate way to use
21 these methods is as an enrichment tool to
22 identify your biomarker of interest that you

1 think should separate people on negative
2 symptoms.

3 And I will stop here on this slide
4 and just conclude by saying, again, a bit more
5 work needs to be done, but it is a very
6 promising measure. And I think the field has a
7 lot of excitement on using these digital
8 phenotyping measures, especially in conjunction
9 with clinical rating scales and other measures.

10 Thank you, and I'd like to
11 acknowledge NIH and my team and collaborators
12 who helped conduct this work. Thank you.

13 DR. WEHRING: All right. Thank you
14 so much, Dr. Strauss and Dr. Blanchard. With
15 our time remaining, I'm really excited to turn
16 it over to our respondents. Let Dr. Blanchard
17 and Dr. Strauss rest for a moment. And I'd
18 like to just kind of go down the line, maybe
19 starting with you, Dr. Horan, and get your
20 reflections, response based on your area of
21 expertise, about the discussion they started.

22 And also, if anything stuck out to

1 you as something that was really a poignant
2 point, or something that was missing in our
3 discussion, to kind of help move us forward.
4 Oh, and please introduce yourself. I think I
5 forgot to say that. Thanks.

6 DR. HORAN: Thanks, Bill Horan with
7 the EMS in UCLA. I'll mention two things.
8 Number one, I had never seen all that
9 qualitative data before, that Greg Strauss
10 collected. And that's, it's really impressive
11 and really encouraging. Particularly for
12 things like perceived participant importance of
13 avolition, and how that relates to functioning
14 and daily life. Also, acceptance of things,
15 like EMA measures.

16 My second point is, I continue to be
17 impressed by the rapidly-growing data on EMA,
18 particularly as a measure of avolition
19 symptoms. It's really those avolition symptoms
20 that seem to be most strongly related to
21 functioning in daily life. Participants
22 perceive them as very important.

1 And with EMA, in the moment, you can
2 just ask people, "What are you doing?" "Is it
3 a productive activity, or is it passive?"
4 "Where are you? Are you at home or are you out
5 of the home?" "Who are you with? Are you with
6 other people, or are you alone?" And you can
7 also ask about their emotion. "Are you feeling
8 happy? Are you feeling sad? Are you feeling
9 content?" You can collect all that information
10 in the moment. And those are all direct
11 behavioral outputs, correlates of avolition.
12 We're getting to the point where these are not
13 just things that are being done in sort of
14 small academic studies, but some of those
15 studies are involving hundreds of patients, in
16 large clinical trials.

17 And finding reasonable associations,
18 correspondents with things like the NSA, or the
19 personal and social performance scale. And
20 then even sometimes seeing them converge with
21 measures like, steps taken, or activity levels.
22 So, I think it's getting closer and closer to

1 the time where maybe we can start working with
2 regulators to understand what it will take to
3 validate these measures for use in clinical
4 trials, as endpoints. What should be the gold
5 standards? Is it going to be the PANSS'
6 negative symptom factor that we need to find
7 correlations with, or do we need to think of
8 other things? If it is something like the BNSS
9 or the PANSS' negative symptom factor, what
10 does the correlation need to be? It's, you
11 know, as Greg was showing, it may not be
12 exactly what we're used to, using correlations
13 between clinical rating scales. So, we seem to
14 be getting to that point, where maybe we can
15 start working toward using these as endpoints.
16 Thanks.

17 DR. KIRKPATRICK: Greg, forgive me,
18 the brilaroxazine was significant for positive
19 and negative symptoms. The data you showed was
20 correct about what happens with vocal. You may
21 be thinking about another study, where turn
22 latency made something significant that was not

1 previously significant.

2 We have, you know, those of us
3 interested in digital phenotyping, have kind of
4 a story, we have a pitch, which is, "Oh, my
5 gosh, these clinical rating scales are subject
6 to all kinds of weaknesses, recall, rater bias,
7 patient's willingness to tell you what's really
8 going on." We say about the digital
9 phenotyping, "This is great. I mean look at
10 all these wonderful ways that they're so much
11 bigger than the scales." They say, yes.
12 You'll say yes, but how they valid? "Well, they
13 predict clinical rating scales." That's it?
14 That's embarrassing. And what's interesting is
15 the correlations, as you pointed it out, tend
16 to be 0.33, maybe 0.5. So, they're clearly not
17 redundant. So, then the question becomes, is
18 one of them better than the other?

19 Well, maybe one kind of scale --
20 well, it's not necessarily the case the digital
21 phenotyping measures are better. There may be
22 something very complicated that human beings

1 are doing that we can't articulate and can't
2 teach a machine to do, possibly. Maybe one
3 kind of approach is better for certain things.
4 And the other one is better for other things.
5 We simply don't know.

6 So, we need to get out of this
7 circular reasoning of, "This is bad, this is
8 better because it is as good as what's bad."
9 And a way to do that, I think, is to go to
10 other sources of information. And, preferably,
11 a basket, because every other source of
12 information about assessing someone's function
13 is going to be flawed as well.

14 So, I think it would be things like,
15 patient report, informant report, families or
16 people who know someone very well. I took it
17 that you were not big on functional capacity,
18 but I think as part of the basket that's a
19 reasonable contributor. And then another one
20 is sensitivity to change, including sensitivity
21 to treatment effect, of things that we know
22 already work.

1 So, another piece of that basket
2 might be independent verification of key
3 things. So, for instance, a clinical trial or
4 some other research, a staff member could call
5 and say, and ask if this person, in fact, lives
6 independently. To what extent does he or she
7 take care of all activities of daily living,
8 including going to the grocery store? Or do
9 they, in fact, have an intimate relationship
10 with someone? Things like that. So, and then
11 maybe we can get out of this circle -- kind of
12 embarrassing circular reasoning.

13 Another thing about the latency
14 measure, it's interesting because of the
15 background of it. There is fairly extensive
16 literature in the psychological literature. a
17 lot of research on that, outside of the context
18 of clinical trials, suggesting that, you know,
19 we already know a fair amount about what turn
20 latency may mean.

21 So, you had kind of an a priori
22 reason to go in and look at it. And that

1 includes looking at the effect of cognitive
2 load in normals, compared to people with a
3 broad range of serious mental illnesses. The
4 other thing that's nice about it is that it's
5 clinically interpretable. It is a kind of
6 psychomotor retardation. And that makes good
7 clinical sense. And so, to quote Mark Opler,
8 who I think just left, so I can claim he said
9 whatever I want to say, he claimed. But he has
10 frequently said these numbers are arbitrary.
11 But his point is really excellent. There are a
12 thousand digital phenotyping measures. There
13 are 12 that matter.

14 If you go in and you do machine
15 learning, and it's unguided in any way, with
16 any kind of a priori thought, you're going to
17 get wonderful predictions. And they're not
18 going to replicate, because they're not part of
19 the 12. And I think to get to the 12, as soon
20 as possible, we need to have some a priori
21 basis for doing so.

22 Last, but not least, can we have a

1 moment of silence for Item 4, lack of normal
2 distress?

3 (Laughter.)

4 DR. KIRKPATRICK: Not a moment of
5 laughter, I was asking for silence and respect.
6 All right. You know, I think there is a
7 phenomenon there

8 DR. WEHRING: Thanks so much, Dr.
9 Kirkpatrick. Dr. Marder.

10 DR. MARDER: Yes. Steve Marder from
11 UCLA. You know as I look at this session,
12 which is really outstanding, there are two
13 themes. One is, we've made real progress in
14 developing two very good clinical assessment
15 instruments that are based on clinician
16 ratings, the BNSS and the CAINS. Both of them
17 are substantial advances.

18 The problem is, as somebody who does
19 a lot of these ratings, particularly with the
20 CAINS, one can see that there are limitations
21 to clinical ratings that really need to be
22 addressed. And Brian and others, and Greg,

1 referred to them. It's, people can recall the
2 severity of their hallucinations, at least I
3 believe they can do it relatively well.

4 I don't have great confidence having
5 done these ratings, that they could really
6 recall with adequate precision, how motivated
7 they were to work during the past week. I'm
8 not - that motivation varies. The time of day
9 that you do a clinical assessment, may not be
10 the time of day that they can get the best
11 information about that person's motivation.

12 And things like social interest,
13 really depends upon context that the person is
14 in. And then when you put them in this
15 situation, of a clinical interview, everything
16 gets changed. So, what I would like to do is
17 to sort of reframe the question of what are the
18 limitations of our clinic-based assessment
19 instruments that could be addressed with new
20 technology. The problem is there's chaos out
21 there, with multiple different measures. And I
22 don't think we should talk so much about what

1 we can measure, because we could measure a lot
2 of things. But -- how can we take the
3 limitations of our current instruments, and
4 improve precision using digital instruments?

5 And how can we reach as a field, and
6 sort of help FDA decide what the best kind of
7 multimodal instrument is? And I think that's a
8 problem that I don't think we have a plan to
9 resolve. But I can say how to resolve -- I
10 mean, I think we would know how to do it. It
11 would require sort of groups of people
12 evaluating the current instruments, developing
13 clinical trials, perhaps using industry
14 settings in order to compare them in real
15 clinical trials.

16 And I think there are methods for
17 moving the field forward from what's now, the
18 methods chosen are too often dependent upon the
19 salesmanship of the person who developed the
20 measure, then the actual quality of the
21 measure. And its ability to measure what it
22 says, with precision. So, I think we have a

1 problem about how to make our assessments of
2 negative symptoms more precise. But I think
3 there are probably strategies for addressing
4 it, if we move in that direction. I'll stop
5 there.

6 DR. WEHRING: Thanks so much, Dr.
7 Marder. Dr. Ahmed. Thanks.

8 DR. AHMED: Yes. Hi. Anthony
9 Ahmed, Weill Cornell Medicine. It's a real
10 honor to be part of this session with a lot of
11 people like Bill and Steve and Greg and
12 everybody else, and Jack, who was my honors
13 graduate school professor. So, it's a real
14 honor to be having this discussion with you.

15 I'm also an inpatient psychologist.
16 I work with patients with schizophrenia in an
17 inpatient psychiatric rehabilitation facility.
18 In that context, I want to make one clinical
19 point, and then I'm going to circle back to the
20 psychometric issues that we're struggling with.

21 In this program, this is a
22 psychiatric program where we provide a lot of

1 evidence-based psychosocial rehabilitative
2 interventions, skills training interventions,
3 like cognitive remediation and social skills
4 training and everything.

5 But programs like this are sort of
6 going out of the market, primarily because
7 there's a lot of pressure in terms of the
8 length of stay of such programs. This is
9 probably one of maybe two or three tertiary
10 psych rehab facilities.

11 Who are the patients that we see in
12 this program? Well, these are patients who
13 struggle with the most functional deficits,
14 with the most skills deficits. Others are
15 patients that struggle with engaging in the
16 community and staying in the community and
17 maintaining community tenure, because, well,
18 they don't have the skills. Most of these
19 patients are relatively symptomatically stable
20 when you think about processing those negative
21 symptoms and emotional distress. But they are
22 struggling with engaging in their community and

1 being part of the community.

2 A lot of the data that was shown
3 earlier today about the prevalence of patients
4 with permanent negative symptoms, like, yeah,
5 you'll getting rates of about maybe 20 percent,
6 maybe just under 20 percent. But in settings
7 like ours, those rates are even higher. And
8 those are the patients that we struggle with
9 the most. Other patients, like, do relatively
10 well, for the most part, when we discharge them
11 or we put them through our rehabilitative
12 interventions.

13 But the problem is we don't have
14 enough time for those patients who struggle
15 with these persistent negative symptoms and
16 permanent negative symptoms, to really gain
17 within that length of stay period.

18 Now, programs like ours are
19 continually under pressure to continue to
20 reduce our length of stays. And what that
21 means is that, you know, like, well, our rehab
22 -- and I really appreciate Jack's slide about,

1 you know, all of the behavioral health
2 psychosocial interventions that show
3 improvement, or contribute to improvements in
4 negative symptoms. But if you look at the
5 length of those interventions, the length is
6 quite long. We're talking about 8 weeks, 12
7 weeks, 10 weeks, 20 weeks. We don't have that
8 kind of time, you know, in rehab programs,
9 okay?

10 If we don't come up with something
11 that can support the work that we're doing in
12 behavioral rehabilitation, we will see the last
13 of the programs like the program called the
14 Second Chance Program. So we need -- there is
15 a little bit of urgency here.

16 Now, to the psychometric points.
17 You know, I think the information is clearly a
18 theme. But I do want to make the point that --
19 and certainly in the context of some of the
20 data that we published on the two-factor and
21 the five-factor models -- you know, the
22 hierarchical model that we really settled on,

1 that we think has a lot of, you know, like,
2 validity for predicting cognition, for
3 predicting function, for predicting everything,
4 you know, like, you know, we really think -- I
5 think the conclusion that we're drawing from it
6 is that the two-factors are important, okay?
7 And we think that that's a good place to start
8 . And we also think that the five-factors are
9 important, but we don't think that you need to
10 pick one against the other, necessarily.

11 Now, there are domain-specific
12 effects that were seen, especially given the
13 impact of avolition. You know, but I think you
14 still need to collect, you know, administer the
15 comprehensive scales. You know, I think, you
16 know, the BNSS and the CAINS certainly, you
17 know, ideal if you have those. But we can still
18 capture the motivation and pleasure and
19 emotional experience factors even with the
20 PANSS. You know, we have data that we're
21 analyzing. And, in fact, a few have actually
22 published the two-factor approach to the

1 matter, the seven items in the PANSS, and even
2 in clinical trials data was seen that, you
3 know, those still capture, you know, to a
4 certain degree, the scope of those two factors.

5 And, as you can see in Greg's data,
6 looking at the impact of avolition is very
7 central, that there is enough there to show
8 some process in terms of how this network of
9 symptoms change in the context of our treatment
10 studies.

11 So, the individual domains, like,
12 important those granular domains, but we don't
13 also want to forget about the forest itself,
14 the forest of the scope of symptoms. And so we
15 should continue to collect that data whenever
16 possible.

17 One final point has to do with,
18 like, how the scope of work that Jack Blanchard
19 and Greg and Brian Kirkpatrick have done with
20 getting translations of the CAINS and the BNSS.
21 And one thing that's clearly missing, and I
22 think it's pretty obvious to everyone, is that

1 there are no translations in languages from the
2 African continent. I think that goes to
3 collaborations that we need to establish with
4 researchers in South Africa and Nigeria and
5 some of those countries where their academic
6 institutions are well-established.

7 And, yeah, and I'm going to stop
8 there. Pass it on to David.

9 DR. WEHRING: Thanks so much, Dr.
10 Ahmed. And, Dr. Reasner, we let you anchor
11 this. We thought it would be nice to kind of
12 come full circle to address some of this from
13 the regulatory perspective. So, you know, no
14 pressure. Thanks.

15 DR. REASNER: Okay. Then I'll start
16 with my disclaimer. No, actually, I wanted to
17 say that these comments are really from the
18 measurement lens, because that's my role in the
19 Division of Clinical Outcome Assessment. And
20 regulatory decisions are a multi-disciplinary
21 process.

22 Also, I think some of these comments

1 are really about the really exciting ideas that
2 I heard today. That these are about research
3 hypotheses, research designs, and I have to
4 think a little bit more about the implications
5 for us sponsoring late phase. And how this
6 might change, because we sort of have the
7 short-term.

8 We have the tools we have today. We
9 have important ongoing programs. And then we
10 have sort of our aspirations about where we
11 might go, in terms of the tools. And what
12 sorts of differentiated profiles we might be
13 able to recognize in the future. So, those are
14 not in the same timeframe. Although Mark
15 warned us this all could change very quickly.

16 So, one thing I wanted to just
17 mention in terms of the validity-evidence
18 table, which you very kindly used in your
19 presentation. In Item B, which is about
20 capturing all important aspects of the
21 construct, in this case, the NSS construct. I
22 just want to say at least from my perspective

1 as an individual reviewer, it doesn't all have
2 to be in one assessment, in one tool.

3 I think sometimes we do need a
4 primary endpoint, in order to declare a
5 positive trial and move forward past the
6 inferential gate, to talk about the secondary
7 endpoints, and even exploratory endpoints. But
8 I think that if the measurement strategy is
9 comprehensive, that's really, I think, the
10 primary interest. Because there may be an older
11 tool that omits certain concepts that are now
12 recognized. It doesn't mean it's not useful.
13 But maybe you back fill those, supplemental
14 concepts in a secondary or exploratory
15 assessment, or endpoint.

16 So, I think, think about assessing a
17 patient completely, but build your endpoint
18 hierarchy in a way that's practical with
19 statistical power, right. Maybe putting
20 reliable endpoints higher in your hierarchy.

21 And on a few points, and I want to
22 blend a few different questions, we had some

1 questions from folks online, and of course some
2 questions came up earlier, and some questions
3 have been posed in this session, regarding the
4 digital health technology, I will say that in
5 this context, it seems to have sort of great
6 potential. And so, what I would point out, and
7 some of this work is already ongoing, I'm not
8 conversed in that health literature. But I
9 would say things such as the concepts
10 underlying blunted affect, seem really amenable
11 to a digital health technology.

12 And some of that, I think, would
13 enable a comprehensive assessment of the
14 patient by combining different recorders. You
15 have your digital recorder, maybe for blunted
16 affect. You have your observer who can observe
17 behaviors that the observers can observe. And
18 you have an, you know, your learned clinicians
19 and that context. But that can move your
20 assessment into different places.

21 And, you know, some of the digital
22 health technology can be applied in clinic, and

1 some can be out, you know, free ranging. And
2 this idea of that, you can also probe, either
3 through EMA, so it could be random phone calls,
4 or activity triggered phone calls, or something
5 like geo-mapping, you know. I think that's
6 very powerful and don't usually use the example
7 of dyspnea.

8 So, your phone can tell you when
9 you've just walked up the stairs. And if you
10 got a phone call, and someone called you to
11 rate your breathlessness, that would be a very
12 powerful way of looking at patient symptoms.
13 So, similarly in our context in schizophrenia,
14 I think that could be very powerful.

15 So, yes, it's complicated to apply
16 the regulations and guidance to digital health
17 technology, but much of the work that you all
18 are familiar with about, like reliability, you
19 know, will apply to these digital technology
20 endpoints as well. So, you can apply your
21 experience. And I think that that has great
22 potential.

1 Oh, and I wanted to say that in
2 terms of the multicultural aspect, they may
3 also remove some of the cultural and
4 demographic variables from the room. And that
5 could be very interesting. I'd love to see
6 those data. That would be, I think, helpful.

7 There was a little discussion
8 earlier about, you know, is it worth looking at
9 individual items and whatnot. And I think the
10 answer from a research perspective, again, I
11 don't how to bring it up to an endpoint that
12 has alpha control that you present to a
13 regulator. Now, that might take some thought.
14 But I think, the individual items will be of
15 some interest.

16 And an example that I thought of,
17 was within anhedonia. So, we know that the
18 profile on anhedonia differs between different
19 indications. And so, you might have patients
20 with comorbid conditions, like depression or
21 undiagnosed comorbid conditions, or prodromal
22 syndromes, right.

1 Then you could use individual items
2 like a few items like anticipatory anhedonia
3 and a few items of consummatory anhedonia. You
4 can profile those patients and you could either
5 exclude them from your trial, or you can
6 recruit them. But maybe they're not in your
7 primary analysis or maybe they're in a stratum.

8 But anyhow, understanding that that
9 profile is different at the individual item
10 level, not necessarily the main domains that
11 the developers anticipated, but maybe informed
12 by today's research. I think that would be,
13 you know, something that's worth doing. And,
14 you know, you should continue to look at those
15 things.

16 Just one thing about, I guess
17 there's just a natural tension that came up a
18 couple of times, I would mention. You know, we
19 want to reduce variability. We want to
20 maintain generalized ability, and it matters
21 what phase of development you're in, right.

22 So, asking a question in phase II,

1 and which I think was discussed in an earlier
2 session, I think is, "is the ideal place?" And
3 there's not a lot of room to provide advice on
4 what assessments to use, or how to score them,
5 or how to construct endpoints. If the first
6 conversation is, you know, shortly before your
7 investigative meeting, and you're planning
8 those things.

9 So, I think building that
10 conversation -- I'll say it, right -- early and
11 often, you know, is really helpful. And the
12 Division of Clinical Outcome Assessment
13 actually do a lot of consultation at pre-IND
14 stage. And I think that's very helpful.
15 Because there's a lot of investment in the
16 program, and the patients are waiting.

17 And then along that line, in terms
18 of sources of variability, so much changes when
19 the patient enters the trial, right. You have
20 sort of physician/patient alliance. You have
21 the beliefs about treatment. You have
22 apparently different rates of rescue, used by

1 site. A lot is going on. So, I think that
2 it's, you know, important to recognize that
3 you're going to see those shifts.

4 And if you can account for those
5 variables, maybe to put on my statistician's
6 hat for a minute, you know, stratification, a
7 lot gets put into the site effect. So, maybe
8 rescue methods end up in the site effects, not
9 explored.

10 Also, in terms of this idea of
11 providing sort of a psycho-behavioral package
12 for every patient. Consider how patients are
13 treated across sites and whether those are
14 equivalent.

15 I know if you can standardize, maybe
16 that's a little too aspirational. But I've
17 often thought that we're neglecting a little
18 bit, making sure the patient experience is
19 consistent across sites. So, that's a few
20 preliminary thoughts. And thank you for your
21 time and the invitation.

22 DR. WEHRING: Thanks so much, Dr.

1 Reasner. Do we have time for a question,
2 before closing remarks? Great.

3 Dr. Campbell, do you have some
4 online participants?

5 DR. CAMPBELL: Yes, we have some, a
6 couple online questions. So, I want to ask two
7 questions. I think they're kind of important.
8 The first one is "Given that the PANSS
9 recognize the importance of informant data, why
10 was informant data not included in the CAINS?"

11 "Are there problems with the CAINS
12 ability to identify negative symptoms in
13 clinical trials as a result of the lack of
14 informant data?"

15 DR. BLANCHARD: So that decision I
16 think was just driven about something that was
17 raised earlier, is the availability of
18 collateral informants is challenging. And the
19 data that we've collected from direct report
20 from a participant, the accumulated validity
21 data would indicate that, it's not a problem.

22 Could you enhance certain aspects of

1 the assessment, if you included those other
2 assessments? Possibly. But the evidence that
3 we have now, with a clinician rating based on
4 just the participant, is pretty compelling.

5 So, I don't see it as a problem for
6 including it in clinical trials.

7 DR. CAMPBELL: And one other
8 question that I think is important when we
9 think about leveraging prior data and wanting
10 to pool data to help us better inform trial
11 development going forward.

12 And the question is, "How shall we
13 interpret previous clinical trial results,
14 where generalized, a more general schizophrenia
15 patient population was recruited but not
16 predominant negative symptoms. And they used
17 the PANSS negative symptom scales, was used in
18 a short trial, and they claimed the drug
19 benefits while they may not have been a more
20 predominately negative symptom group. So, how
21 can we leverage that prior data to help inform,
22 going forward?"

1 DR. STRAUSS: I can make one
2 response here. I think we should try re-
3 analyzing data, using cut point criteria.
4 Similar to what some of the more recent trials
5 have done. So, separating out patients,
6 identify the subgroup that meet the unique
7 predominate or persistent subtypes. And then
8 just analyze it that way and see if the results
9 hold.

10 DR. WEHRING: All right. Any
11 questions from the audience? We're almost out
12 of time, so last chance.

13 Well, you guys were so clear that we
14 don't have any more questions. Thank you all
15 so much for your participation and for the
16 outstanding discussion. Really appreciate it.

17 DR. FISCHER: All right. So, I did
18 budget some time in the schedule for a wrap-up,
19 and the wrap-up is also a cushion, because I
20 knew we were going to go over. So, I had
21 initially planned on taking some notes and
22 PowerPoint, and then having some slides. Kind

1 of summarizing the day and all of talks. But
2 there's way too many slides. There's way too
3 much and I don't know if my notes would make
4 sense. So, I'm just going to wing here.

5 But I really want to first of all
6 thank all of the participants, all of the
7 panelists, all of the speakers for today.
8 Everybody who joined us virtually, people who
9 submitted questions, I think this day was very
10 successful. I'm not judging the day by whether
11 we have all the answers we need, because of
12 course, we still don't have all the answers we
13 need.

14 But I think we've identified a lot
15 of the questions that we need to answer, which
16 is a very important part of this day. In the
17 past, there have been a number of academic
18 communities and collaborations taking a look at
19 negative symptoms, and how best to define the
20 group? How best to do clinical trials?

21 But I think even though the FDA had
22 been participants in some of those past

1 activities, this is the first time the FDA is
2 actually initiating a statement about this,
3 about negative symptoms, and treatment
4 development. And looking forward to answering
5 some of these questions from a regulatory
6 perspective.

7 So, I think that this was really
8 important. Some of the take-home points that I
9 want to emphasize are that it's great to hear
10 about the lived experience from people who have
11 schizophrenia. And of course, with what
12 Michelle had said earlier, with our patients'
13 listening sessions, and with some of the things
14 that we're trying to do to figure out if a drug
15 has a clinical, meaningfulness to people. We
16 want to hear from, directly from patients, from
17 caregivers. We want to know what makes a
18 difference in people's lives.

19 I think it was great to hear about
20 the neurobiology and how we're starting to see
21 the interaction. That we can't look at
22 negative symptoms really in isolation, that

1 they're really part of a constellation of
2 symptoms. And we want to look at them in
3 conjunction with things, like cognitive
4 impairment in schizophrenia.

5 We definitely have some problems
6 that we need to address with study design. But
7 I think there are also some things with study
8 design that we've figured out. We really need
9 to think about who to enroll in studies, how to
10 design the studies, things like, active
11 comparators, placebo controls, some things to
12 think about there. But how to best design a
13 program to show an effect?

14 When it comes to scales, some of the
15 important cultural considerations, you know,
16 not just back translating a scale, but actually
17 in addition to having a scale that is
18 culturally sensitive, having a rater that's
19 culturally sensitive as well.

20 So, they can kind of interpret
21 things and rate things with that in the back of
22 their mind, to figure out whether the things

1 that they're seeing should be considered
2 negative symptoms or should be considered part
3 of the culture of the person that they're
4 interviewing.

5 I think it's also important to
6 figure out where we have the interface, between
7 clinical ratings, and digital phenotypes. So,
8 we had some great presentations today to hear
9 about some of these new exciting scales that
10 were developed because of the, I guess, the
11 things we noticed with some of the older
12 scales, that could be improved upon.

13 But now, we're kind of in this brave
14 new world of digital phenotyping and machine
15 learning and EMA. And I think that it's not
16 going to be an either-or question. It's going
17 to be how do we integrate these two concepts
18 together, to come up with the best way to
19 measure negative symptoms. So, I think these
20 are exciting times to figure out how these
21 digital phenotypes are going to inform our
22 clinical ratings.

1 So, finally, I just wanted to
2 mention that for all the people who asked
3 questions virtually, that we didn't get to
4 today, those questions are very important to
5 us. Because it also shows what people are
6 interested in, who have attended this session.
7 And so, those are going to factor in to our
8 thoughts, moving the meeting forward, thinking
9 about things.

10 As far as a product from the
11 meeting, we are going to post the slides on the
12 website. And we are going to have some kind of
13 summary. We haven't decided yet whether this
14 is going to be a journal article or a white
15 paper.

16 Maybe even a guidance for industry
17 from FDA. So, we're still in internal talks
18 about what the work product will be from this.
19 But there will be a product that will summarize
20 the meeting for people.

21 So, I just want to thank everybody
22 again, for their attendance. And just remind

1 everybody who has luggage in the back to just
2 make sure that it's your suitcase, because many
3 of them look similar. So, again, thanks for
4 coming and safe travels home.

5 (Whereupon, the above-entitled
6 matter went off the record at 3:54 p.m.)
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C E R T I F I C A T E

This is to certify that the foregoing transcript

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was duly recorded and accurately transcribed under
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Neal R. Guss

Court Reporter