FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

DRUG DEVELOPMENT FOR CHRONIC FATIGUE SYNDROME AND MYALGIC ENCEPHALOMYELITIS: PUBLIC WORKSHOP

DAY TWO

Scientific Drug Development Meeting

Friday, April 26, 2013

8:45 a.m.

Bethesda Marriott

5151 Pooks Hill Road

Bethesda, Maryland 20814

Reported by: Natalia Thomas
Capital Reporting Company

1 MEETING ROSTER

2 Lucinda Bateman, M.D.

3 Fatigue Consultation Clinic

4 Salt Lake City, Utah

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6 Badrul Chowdhury, M.D.

7 Director, Division of Pulmonary, Allergy, and

8 Rheumatology Products, ODE II, OND, CDER, FDA

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10 Lily Chu, M.D.

11 M.S.P.H.

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13 Lisa W. Corbin, M.D., FACP

14 Associate Professor, Division of Internal Medicine

15 University of Colorado Denver School of Medicine

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17 Dr. Edward Cox, MD, MPH, Director,

18 Office of Office of Antimicrobial Products,

19 (FDA, CDER, OND)

20

21 Jordan Dimitrakoff, M.D., Ph.D.

22 Assistant Professor, Tufts University, Boston, MA

1 MEETING ROSTER

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3 Nancy Klimas, M.D., FACP, FIDSA

4 Chair, Department of Clinical Immunology

5 Director, Institute for Neuro-Immune Medicine

6 Nova Southeastern University

7

8 RADM Sandra Kweder, M.D.

9 Deputy Director, Office of New Drugs, CDER, FDA

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11 Nancy Lee, M.D.

12 Deputy Assistant Secretary for Health

13 Director, Office of Women's Health

14 Department of Health and Human Services (HHS)

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16 Susan Maier, Ph.D.

17 Deputy Director, Office of Research of Women's Health

18 National Institutes of Health (NIH)

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20 Dennis Mangan, Ph.D.

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22

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Theresa Michele, M.D.
4
Clinical Team Leader Division of Pulmonary, Allergy,
5
and Rheumatology Products (DPARP), Office of Drug
6
Evaluation II (ODE II, OND, CDER, FDA)
7
8
Robert Miller, Patient
9
10
Jose. G. Montoya, M.D., FACP, FIDSA
11
Professor of Medicine
12
Division of Infectious Diseases and Geographic Medicine
13
Stanford University School of Medicine
14
15
Bernard Munos, MS, MBA
16
Founder, InnoThink Center for Research in Biomedical
17
Information
18
19
20
21
22

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2 (continued)

3 Melissa Robb

4 Associate Director for Regulatory Affairs

5 Office of Medical Policy Initiatives,

6 Office of Medical Policy, CDER, FDA

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8 Jody L. Roth, MS, RAC

9 Director Regulatory Affairs, Biomedicines

10 Eli Lilly and Company

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12 Peter C. Rowe, M.D.

13 Professor of Pediatrics

14 Johns Hopkins University School Medicine

15 Director, Chronic Fatigue Clinic

16 Johns Hopkins Children's Center

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18 Ashley F. Slagle, MS, Ph.D.

19 Oak Ridge Institute for Science and Education (ORISE)

20 Fellow

21 Study Endpoints and Labeling Development Staff

22 ONDIO, CDER, FDA (contractor)

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4 Christopher R. Snell, Ph.D.

5 Professor, Health, Exercise and Sports Sciences

6 University of the Pacific

7

8 Janine Spotila, JD

9 Patient

10

11 Elizabeth R. Unger, Ph.D., M.D.

12 Chief, Chronic Viral Diseases Branch

13 Division of High-Consequences Pathogens and Pathology

14 Centers for Disease Control and Prevention

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16 Suzanne D. Vernon, Ph.D.

17 Scientific Director

18 The CFIDS Association of America

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20 Christine Williams, MEd

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11 Medicine, Nova Southeastern University

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13 Therese Michele, M.D., Clinical Team

14 Leader, Division of Pulmonary, Allergy,

15 and Rheumatology Products (DPARP)

16 Office of Drug Evaluation II

17 (ODE II, OND, CDER, FDA)

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11 General Internal Medicine
12 University of Colorado Denver School
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15 Lily Chu, M.D., MSPH, International
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Professor of Medicine, Division of
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8 Nancy Lee, M.D., Deputy Assistant

9 Secretary for Health, Director, Office

10 Of Women's Health, Department of

11 Health and Human Services (HHS)

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13 Susan Maier, Ph.D., Deputy Director

14 Office of Research on Women's Health

15 National Institutes of Health (NIH)

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17 Theresa Michele, M.D.

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

2 DR. WOODCOCK: Morning, everyone. Good
3 morning, we're about ready to get started, so if we
4 could have our Panel 1 speakers come up to the front.
5 Yeah, come on up and have a seat.
6 So good morning, everyone. On behalf of the
7 FDA, it's my pleasure to welcome you to Day Two of the
8 Drug Development Workshop for Chronic Fatigue Syndrome
9 and Myalgic Encephalomyelitis.
10 Day One was certainly an amazing day. I have
11 to say I was just so incredibly impressed by how
12 articulate and topical all of the comments were from
13 the patient groups, and also how much I learned.
14 Despite sitting through many hours of CFSAC testimony,
15 this was just really amazing I think in bringing out
16 the symptoms and making everything so very clear.
17 So thank you, thank you, to all of the
18 patients who spoke yesterday; very incredibly helpful.
19 We have I think an excellent panel lined up
20 for Day One. I'll just do some brief introductions. We
21 have Dr. Bernard Munos, who is going to be speaking on
22 derisking drug discovery, and he is the -- get the

1 right title here -- the founder of Innothink Center for
2 Research in Biomedical Innovation.
3 Following that, we have a talk on drug
4 repurposing by Dr. Suzanne Vernon who's the Scientific
5 Director of the CFDIS Association of America. And
6 finally, we have someone from the Office of Medical
7 Policy at FDA who's the Associate Director for
8 Regulatory Affairs, Melissa Robb, who is going to tell
9 us all about FDA's expedited programs for serious
10 conditions, and hopefully explain a little of the
11 mystery behind some of the FDA rules and regulations
12 that pertain to this area.
13 Following that we'll have an audience
14 question and answer period and this is going to run a
15 bit differently from yesterday. So you've all gotten
16 these nifty little yellow sheets, if I can borrow one
17 here. They look like this. These are for your
18 questions. So please, as you think of a question just
19 jot it down on one of these sheets.
20 If you have more than one question, you can
21 do more than one sheet and someone will be walking
22 around about 15 minutes prior to the end of the talk

1 and will collect them, and then we'll bring them up to
2 the moderator, and we'll use that in order to get
3 through as many of the questions as we can. It'll also
4 allow us to group the questions.
5 Depending on how many there are, it's
6 possible that we may not get to all of them, but we'll
7 try to cover the ones that are most pertinent to the
8 topic at hand. So with no further ado, we're going to
9 go ahead. I'm winging this a little bit, because I'm
10 obviously not Admiral Kweder, but even though she has
11 pretty big shoes to fill, and I wear a very small size,
12 I think we'll get through it.
13 So the objectives, I think we covered the Day
14 One objectives yesterday very nicely, engaging
15 patients. And you heard this yesterday, but today we
16 hope to take what we learned yesterday and bring it
17 forward to truly examine the common issues in drug
18 development and hopefully consider some of the
19 scientific and regulatory tools that we might bring to
20 bear to move drug development forward in this area.
21 Chronic fatigue syndrome, as you all know, is
22 a serious and debilitating disease. We don't know what

1 causes it. And we heard yesterday so beautifully
2 articulated by the patients, many of the symptoms, and
3 we are going to build on that today. As you know,
4 there are no approved therapies and that's kind of why
5 we're here.
6 Just a couple of words about the
7 nomenclature. As we mentioned yesterday, chronic
8 fatigue syndrome and myalgic encephalomyelitis we
9 recognize that there's a lot of controversy about these
10 terms. Some people want to lump them together. Some
11 want to split them apart.
12 At FDA we've taken no particular stand on the
13 name. We're using this to be inclusive. You don't
14 have to have a name of a disease to have a drug to
15 treat it. So that's sort of our approach to it. And
16 again, we're using the term drug development to be very
17 inclusive and we're not looking just here at what FDA
18 can do, but what all of the stakeholders in this can do
19 to move the process forward.
20 As you know, FDA has a very narrow focus in
21 drug development. What we do is we do the regulatory
22 side of things. So we don't run clinical trials on

1 drugs. We don't tell drug developers what to develop.
2 We look at the data that they have developed and bring
3 in to determine if a product is safe and effective to
4 put on the market.
5 So CDER's mission is to promote and protect
6 the public health by assuring that safe and effective
7 drugs are available to all Americans. And because of
8 that, we have to apply careful judgment to scientific
9 assessment and the risk benefit balance, and that's
10 where the patients come in, in helping us determine
11 what that risk and benefit balance might best be
12 applied to a particular disease.
13 Marketed drugs have to be a blend of these.
14 No drug is risk free, but what we need to do is make
15 sure that we know what the risks are; that the risks
16 are managed; that quality in manufacturing and -- other
17 parts of the development process is assured; that we
18 know what the trials showed; that advertising is
19 appropriate; and information is available to the
20 patients on the drugs, both in the product label, in
21 the patient handouts.
22 We also have to ensure that the drug is

1 effective. That it's studied with proper endpoints and
2 standards and those standards have changed over the
3 years. Drugs that were approved 25 years ago might not
4 have the same approval now, should they go on the
5 market.
6 So how do we do this? Well, FDA regulations
7 began as interstate commerce. These were for companies
8 who were intending to market drugs and usually these
9 drugs development programs are funded by the
10 pharmaceutical companies.
11 They engage the academicians and the
12 community researchers to actually do the studies, but
13 the pharma funds them and designs the studies. We at
14 FDA oversee drug development, assuring the safety and
15 that appropriate regulations are being followed to
16 protect patients, and we work with their sponsors.
17 So the drug companies come to us with their
18 programs and we provide them advice on these programs
19 on how to best get their drugs approved. We also
20 review all the findings when they're submitted to FDA.
21 In order to do this review work we incorporate a
22 variety of different disciplines.

1 These include chemistry, that's that
2 manufacturing process; animal toxicology which is
3 required to even test a drug in humans; we employ
4 statisticians and FDA statisticians actually take the
5 raw data and rerun the analyses that the pharmaceutical
6 companies did in their NDA to show that the drug is
7 effective.
8 We employ physicians, such as myself, that
9 look at both the protocols to ensure that safety is
10 being maintained, as well as review things from a
11 clinical perspective to determine even if the
12 statistical number is reached, what does that mean
13 clinically to the patient?
14 And we employ a variety of inspectors, both
15 for the manufacturing plants and also for the clinical
16 sites. And we take all that and when a product is
17 ready to be approved, we'll often take it to public
18 advisory committee so that we can include the patient
19 perspective.
20 So what do we look at in between from when a
21 drug initially goes into humans with an investigational
22 new drug application or IND, to when it gets on the

1 market with a new drug application. We look at the
2 chemical composition to make sure that the drug is
3 manufactured in a safe way. We look at animal studies
4 to ensure that we have some data knowing what the
5 toxicities are, if that's appropriate to give to
6 humans.
7 For example, if you had a drug that you gave
8 to animals and every animal you gave it to died, that
9 probably wouldn't be a good drug to test in humans. And
10 then how you assure the safety, you have to look at the
11 range of possible doses so that you can choose the
12 appropriate dose.
13 And the plans for the clinical trials, you
14 need to again look at doses, look at how big the trial
15 should be, how you compare the drugs, what the
16 endpoints will be; you'll hear a lot of things as we go
17 through our talks today.
18 And there are multiple points of interface
19 between the FDA and the sponsors throughout this
20 process which can take a number of years.
21 So the gold standard -- this comes from the
22 Code of Federal Regulations, and this is what we

1 consider to be an adequate and well-controlled study as
2 laid out in the law. It has to be designed well enough
3 to be able to distinguish the effect of the drug from
4 other influences, such as a spontaneous change, a
5 placebo effect, or biased observations.
6 And an adequate and well-controlled study,
7 that's what we're talking about; that's the whole basis
8 of this conference today is to talk about adequate and
9 well-controlled studies and what they might look like
10 in this disease area. They permit a valid comparison
11 with a control, which is often a placebo, but could be
12 an active control, and they have a well-defined patient
13 population.
14 So we're going to talk about that a little
15 bit. There are also adequate measures to minimize
16 bias, such as randomization. You don't know which
17 patient gets the drug, which patient gets the placebo.
18 And methods of assessment of response are well-defined
19 and reliable.
20 So this means that you have your statistical
21 plans laid out along with your protocol before you
22 start your study. The analysis of the results is

1 adequate and assesses the effect of the drug itself.
2 In addition, you have to ensure that the
3 conduct of the study is appropriate, so that people are
4 recording what they say they're recording.
5 And it's straightforward when the disease is
6 defined, but it's not as easy in a disease such as
7 this, where you're not clear what the endpoint should
8 be. You're not quite clear what the patient population
9 should be. So that's the struggle.
10 And the clinical trials really matter. This
11 is what makes or breaks a drug. It's essential to
12 assess the safety and efficacy of a drug. The measures
13 that you use for endpoints matter a lot, because they
14 have to be objective, easy to quantify or signs, and
15 those you have to know how does that translate into how
16 a patient feels, functions, or survives, because that's
17 the end game of where we're all shooting for.
18 Subjective symptoms are fine, too. You just
19 have to have a way to measure them and that's actually
20 what we want, is we want something that's going to make
21 the patient feel better. Pain, fatigue, all of these
22 are -- could be appropriate endpoints.

1 And the patient also matters, because the
2 disease frames the whole scientific and regulatory
3 considerations. The serious nature of the disease
4 determines how much risk you would tolerate in a drug
5 versus the benefit. But what's absolutely critically
6 important is regardless of the disease, the standard of
7 evidence is the same.
8 So it doesn't matter if you are looking at an
9 orphan disease in a tiny little population, or a
10 disease like diabetes that affects everybody or a
11 disease such as a rapidly, progressive cancer that
12 kills people in six months, or a disease such as
13 chronic fatigue syndrome that's a serious disease
14 that's chronically debilitating.
15 All of these diseases have the same level of
16 evidence required. It's been mentioned some of the
17 guidances that are out there, for example for Alzheimer's,
18 they do not change the standard of evidence that's
19 required.
20 So our agenda, I think we've gone over. And
21 I know we're running a little bit behind today, so with
22 no further ado, I am going to turn the panel over to

1 Dr. Kweder and we'll go ahead and get started. Thank
2 you all. Panel 1: Drug Development: Innovation,
3 Expedited Pathways, Regulatory Considerations
4 Background and Meeting Goals
5 RADM KWEDER: Well first, I have to apologize
6 for being late. I don't have any grand story to tell.
7 I didn't do anything dramatic. I was sitting at home
8 drinking coffee making sure I got here for 9:00. And
9 so I do apologize.
10 How many of you have ever been to a Jesuit
11 school, or know about Jesuit schools? Okay. My son
12 goes to a Jesuit high school up the street, and this
13 morning I had to get up early because he had something
14 that the Jesuits call JUG; it's called Judgment Under
15 God.
16 And it's your punishment; it's like your
17 detention, your JUG. And he got JUG this week and his
18 punishment was he had to be at school at 6:30 in the
19 morning, yesterday and today and tomorrow morning on
20 Saturday for some infraction which shall go
21 unmentioned. He's a senior. And I thought, oh crap,
22 I'm going to get JUG. Yeah really, I'll be back

1 tomorrow.
2 But again, I want to thank you for being
3 here. And I know that Dr. Michele has already
4 introduced who the panelists are. But before we do
5 that, I think one of the things that's important even
6 though you know sort of their professional, a bit about
7 their professional background, I'd like to just ask
8 each panelist, when you get up to give your
9 presentation, if you would please just say a few words
10 about how you came to do what you do now.
11 You know, just a little bit, because we've
12 got to get a sense of who you are. We've kind of heard
13 your educational a little bit. You talked about your
14 educational background. Did Terri go into all the CV
15 stuff? Oh no, even better.
16 So even better. What I'd like them to do is
17 I'd like them to each -- you know I have their bios,
18 okay. But you know that's all stuff. I want to know -
19 - I want you to tell these people where you come from
20 and how you got to where you are, just in a snippet.
21 So as you're giving your presentation, they
22 have a sense of what you bring to this topic, and I

1 think it's far more than what I could say that you
2 printed out in advance for me.
3 So I'm going to get you -- and I will start
4 with myself as the moderator. I started my career at
5 FDA in the Antiviral Drugs Division. It was brand new.
6 And when I came to an Antiviral Division in 1988, it
7 was three months after the approval of AZT.
8 Now, unknown to many people, at that time,
9 there were multiple, multiple other drugs in the
10 pipeline, because an etiology for HIV had already been
11 identified as a virus. So Burroughs Wellcome was not
12 the only company working on this. There were a
13 multitude of companies working on this and the other
14 associated viral infections that patients with AIDS,
15 which we called it at the time, had.
16 We couldn't measure viral load. It wasn't
17 possible. We didn't have measures for it; we just knew
18 it was a virus. Today viral load is everything. And
19 we spent, in the Antivirals Division, a number of years
20 working with academicians and company experts, trying
21 to find a surrogate marker for AIDS, because the only
22 endpoint you could study in the clinical trials was

1 death.
2 There was no marker. Today, we don't look at
3 that. We look at immune function, CD4 cells. Well,
4 that was the first surrogate. Today we look at that a
5 little bit, but we look at viral load, because we can
6 measure the virus. And so we approve drugs early based
7 on that surrogate marker, and that's the Accelerated
8 Approval which you're going to hear about from Melissa.
9 But that was my introduction to the FDA.
10 I've been at the agency a number of years since then.
11 I have been in the post-marketing safety side. I spent
12 other years looking at other anti-infective drugs and
13 for the past 10 years, I've been where I am today,
14 which is in the Office of New Drugs.
15 In my office, I'm the Deputy Director of that
16 office and we oversee all of the clinical therapeutic
17 divisions for all drugs and therapeutic biologics. So
18 I am going to turn this over and we are going to begin
19 with Dr. Munos.
20 So Dr. Munos, why don't you come on up and
21 tell us a little bit about yourself and get started on
22 your talk. Drug Innovation and Derisking Drug Discovery

1 DR. MUNOS: Good morning everybody and thanks
2 to the organizer for inviting me to make this
3 presentation today. As you can already tell, I've got
4 an accent, so I am not a born and bred Hoosier even
5 though I spent most of my life in Indianapolis.
6 I came originally from Europe, from France,
7 where I got my first degree many years ago in animal
8 science. Then I came to this country on scholarship to
9 study first economics at the University of California,
10 Davis, and then business at Stanford.
11 Joined the industry in 1980 and I've seen it
12 fall from grace over the last 30 years when I was
13 active; I was with Eli Lilly for 30 years in
14 Indianapolis. Basically because I saw it going from
15 what I would call a culture innovation, which made
16 working in the industry back in the '80s absolutely
17 exhilarating.
18 I mean it was one of the best times in my
19 life. I couldn't wait to go work in the morning, it
20 was that good. And that culture changed in the '90s,
21 from what had been a culture of creativity and
22 innovation, to a culture of process.

1 And initially I felt uncomfortable about this
2 but I didn't really know why, and it took me about 10
3 years to figure out that it was the impact that this
4 change had on innovation that was worrying me. You
5 know this was an industry that spent tens of billions
6 of dollars on research every year, and yet no one had a
7 clue about where innovation comes from and how we're
8 going to get more of it, and I thought that was
9 mismanagement on a grand scale.
10 No one was even worried about it. So I
11 decided somebody needed to do something about it and I,
12 foolishly perhaps, decided that I would be that person.
13 I would start it. And did some research, published
14 some papers that got some attention, and the more it
15 went and the better we started to understand what
16 actually produces innovation.
17 So today, 10 years later, we're miles ahead
18 of where we were just 10 years ago and I will allude to
19 some of those findings in my presentation.
20 RADM KWEDER: Now, wasn't that more
21 interesting than what I would have said.
22 DR. MUNOS: So the problem that gets us here,

1 that gathers us here today is how do we get more
2 innovation in CFS, and why don't we have innovation
3 there in the first place, like we have in HIV, or like
4 we have in a number of other fields.
5 Well the first thing that you discussed today
6 that we know is that CFS, the problem of innovation in
7 CFS is compounded by the fact that this is a complex
8 disease that is often mistaken for other diseases. Its
9 borders are fuzzy.
10 We've got multiple etiologies. So it's not a
11 simple thing to deal with. And the traditional drug
12 R&D model is not really suited to tackle something like
13 CFS. Just for those who are not familiar with the
14 pharmaceutical industry, I will take two seconds and
15 describe how it works.
16 We have scientists in the industry. We call
17 them the drug hunters. They're very, very talented
18 people who basically look at what's happening at the
19 frontier of science. And when they see something that
20 is really interesting, really breaks through, that they
21 think they can turn into a commercial product that
22 patients can buy, then they will start a program of

1 translation, which is basically a whole series of
2 scientific activities aimed at turning that scientific
3 discovery into, as I said, a commercial product, a
4 physical product, and get it approved by FDA.
5 So that's -- the first problem is there. I
6 mean CFS not being an established discipline on its
7 own; it's not like cancer or like diabetes where
8 scientists can really follow what's happening in the
9 science in those areas.
10 There's not a science of CFS, or if there is
11 it's not a well-established one. So they may see
12 things that may relate to CFS, but do not relate them
13 as such. So there's a dearth of translatable research,
14 a dearth of discoveries that scientists can readily
15 identify that could be translated into novel drug for
16 CFS.
17 We've got a consequence of that also, lack of
18 infrastructure basically defined as data and tools.
19 Even though we've working in that field, you have been
20 involved in that field for many, many years, it's not
21 where it needs to be.
22 I talked about the fuzzy borders of the

1 disease and the fact that many of its symptoms are
2 often misdiagnosed for other things. That doesn't
3 help. It just introduces another dimension of
4 confusion. The treatments address the symptoms, not
5 the disease.
6 I mean if you go to patients like me, for
7 example, and look at the CFS community you'll find all
8 sorts of things; literally dozens and dozens of drugs
9 being used, all of them to treat the symptoms, not the
10 underlying cause of the disease.
11 And you know let's face it. If you are
12 dealing with such a situation where things are so
13 confused and ill-defined, it becomes very difficult for
14 regulators to really regulate the science in that
15 particular area. You know, what is the natural history
16 of the disease?
17 What are the causes of the disease? What are
18 the midpoints, the endpoints? Unless you have that
19 information, all the information to address this
20 question, it becomes very difficult for regulators to
21 do their job.
22 So the job remains in front of us. We've got

1 to do it, and I would propose in the next -- in the
2 rest of my talk, that what we need in CFS is what I
3 call the development of an innovation supply chain.
4 It's not all that complicated, really.
5 We need what you might expect intuitively.
6 Well, the goal is if we want scientists to work in CFS,
7 we've got to make it worth their while. We've got to
8 allow them to basically make it easier, cheaper, and
9 faster, as I put it here, to work on CFS.
10 Scientists tend to follow the path of least
11 resistance. I mean it's smart of them. And so if you
12 have the infrastructure, the tools, the data, that
13 makes it easier and cheaper and faster for them to work
14 on your disease, that's where they will flock.
15 They follow data for reason that we will talk
16 in a few minutes. So we need data. We already have
17 some, but it's not enough and it's not in the right
18 format and it's not good enough, so we need more and
19 better data.
20 We need tools to go along with that data. We
21 need partners. We need money. And lastly, we need
22 leadership and passion. And I should stress already

1 that we have quite a bit of that already, but we need
2 to maybe connect it a little bit better than it is
3 connected today.
4 So we need data that seems to be obvious.
5 There cannot be any science without data, but it
6 doesn't hurt to remind everybody. And there's another
7 quote there that I think it's worth bringing to the
8 attention to the attention of this group.
9 "If you think about the scientific revolution
10 in history, they've been driven by one thing, the
11 availability of data. From Copernicus to quantum
12 mechanics, it is data that drives innovation." So
13 let's keep that in mind.
14 And in the case of CFS, the data challenge is
15 magnified by the fact that it is, as we know, a disease
16 that is fairly heterogeneous. And therefore, to
17 understand what's going on there, we need more data
18 than we would if the disease was simpler.
19 We need lots of data. We need patient data.
20 We've got already patients, registries in this country.
21 Given the complexity of the disease, it would be even
22 better if those patient registries were international,

1 because if you add to the fray, patients with a
2 different genetic background, different environments,
3 different nutrition, different what everything, chances
4 are that their reaction to CFS, the course of the
5 disease, might be different and we might be able to
6 pick up some signals there that would lead us to a
7 better understanding of the disease.
8 The natural history of the disease is
9 something that we know to a certain extent, but we need
10 to get better there, and thankfully the technology
11 allows us to do that. We've had discussion already
12 with the CFIDS Foundation and you've got technology
13 today that allows CFS patients to track their mobility,
14 to track their efforts, with those data collected
15 effortlessly by biosensors.
16 Biosensors which could be location in a cell
17 phone. They could be FitBits like this thing, that
18 tracks how many stairs you climb per day and how many
19 miles and when you actually do those activities. So
20 not only can you track the extent of the physical
21 exercise, but also its intensity. And all that can be
22 collected effortlessly and wirelessly sent to a server

1 every day.
2 And if you get thousands of patients who are
3 doing that at the same time, pretty soon you will have
4 some serious data for scientists to work on, and all
5 that hardly cost a thing. So I think it's one thing
6 for the patient community to think about it, band
7 together, and avail themselves of this technology in
8 order to provide the scientists with this natural --
9 that's where it starts -- the natural history of the
10 data.
11 And it's even more powerful if that natural
12 history can be connected with genomic data. Up until
13 now, really, that was a dream. That dream is becoming
14 true. It takes right now about $5,000 to genotype
15 someone and that cost is expected -- basically it drops
16 down by about 65 percent every year.
17 So that cost is expected to reach a thousand
18 dollars before we know it. And at that time, it may be
19 worth considering or at least offering the CFS patient,
20 the systematic free genotyping of their genome, so that
21 the scientists have even more data to work with.
22 That's all that data collection effort is and

1 likely to be done by anyone but the CFS patients. You
2 know the industry will not do it, because again the
3 disease is ill-defined. We don't really have
4 specialists of CFS. So it's just not, it's not one of
5 their preoccupation. They worry on big things like
6 diabetes or cancer or Alzheimer's.
7 So the patient community really has to take
8 that in its hands, but as I said, it is becoming
9 possible to do that on a shoestring and therefore
10 should be considered. Technology, as I put it here,
11 makes it possible to collect high quality data cheaply;
12 data that FDA will love, because it's collected in
13 real-time.
14 It's sent wirelessly to some computer. There
15 is no possibility for intervention for editing the
16 data. It is high quality data. So that's the first
17 point. We need data, better data, and it's in the
18 hands of the patients.
19 The good news is that if you build it, they
20 will come, and we know that, because -- by they, I mean
21 the scientists, and we know that because they do every
22 time. An example of a disease that shares some

1 similarities with CFS is the multiple myeloma, which is
2 also -- it's a rare cancer, but it's a complex cancer
3 with multiple etiologies.
4 And in 1998 a woman came down with multiple
5 myeloma and created a foundation, The Multiple Myeloma
6 Research Foundation. At the time, there was not a
7 single drug approved for that disease, and she decided
8 to do something about it. And what she accomplished
9 tells you, gives you an idea of what's possible.
10 Since 1998, she raised $225 million dollars.
11 Sequenced the myeloma genome. Started 45 trials with
12 23 new drug candidates. Got six approved which have
13 provided enormous relief to the patients affected. And
14 interestingly enough, the incidence of myeloma in the
15 population, you know the size of the patient community,
16 is smaller than the size of the CFS patient community.
17 Four per thousand and you can see here, for
18 CFS, seven to three thousand per -- per hundred
19 thousand. I'm sorry. Just the breadth of that bracket
20 tells you how fuzzy the border of that disease is. So
21 if you build it, they will come. So it's worth doing.
22 We need not only data, but we need tools,

1 because let's face it, there can't be much research
2 without tools, and data without tools doesn't get you
3 very far. Tools leverage the value of data. And the
4 combination of the two is the basic infrastructure that
5 you need.
6 The tools that we need are the basic tools of
7 drug discovery. There's nothing new there. They're
8 what scientists need in order to do their job. You're
9 talking about tissue banks. You're talking about
10 animal models, biomarkers, assays, and interestingly
11 enough, today you also need networking tools so that a
12 scientist working on CFS can better connect with each
13 other.
14 This is, as we have found from research, it's
15 an essential ingredient in innovation, is the ability
16 for scientists to cross-pollinate, not just with the
17 scientists that surround them, but with people half a
18 world away that work in the same field and have
19 completely different ideas that need to be shared.
20 So we need working tools, networking tools.
21 And just like for data, that tool development effort
22 isn't likely to be funded by industry, because frankly

1 for industry, CFS hardly exists. So it has to be done
2 by the patient community.
3 But again, the good news is that technology
4 makes it possible today, even for small disease
5 foundation, much smaller than the CFS community, to
6 fund such efforts. A good example there is the
7 Chordoma Foundation which was started a few years ago
8 by one single patient who was affected.
9 It was a kid. He was in college, and there
10 was nothing for chordoma at the time, and he decided on
11 his own to fund a foundation and start a program that
12 would lead to a drug, and he was successful. So if one
13 kid, college kid, can do it, the CFS patient community
14 can also do that for itself.
15 And most data and tools in order to be
16 helpful needs to be in open free access to everybody
17 who wants to work on that field. I know you'll get a
18 lot of pushback there. It's my data and so forth. No,
19 data is not competitive. Data is pre-competitive and
20 should be shared.
21 Everything upstream of drug candidate is non-
22 competitive and should be shared. I mean that's -- we

1 should collaborate on the science so we can better
2 compete on the drugs that incorporates the finding from
3 that science. The good news there is that if you
4 create the tools, the scientist will come and we know
5 that, because they do every time.
6 And the example there is an initiative called
7 the open source drug discovery platform, a project that
8 was started in India, of all places, in 2008 when the
9 Indians realized that tuberculosis is a big problem and
10 we haven't -- done really have a lot of cutting edge
11 science in that field or effective drugs for that
12 matter.
13 And in a space of barely four years, over
14 6,000 scientists around the world have joined hands in
15 order to collaborate virtually on a computer platform
16 in developing new treatment for tuberculosis. Today,
17 that effort generates two-thirds of the paper published
18 in the field of tuberculosis, and the whole effort runs
19 on less than $2 million a year.
20 So how -- I mean it's hard to do cutting edge
21 research cheaper than that. If it can be done in
22 India, it can be done here.

1 We need partners, scientists obviously. If
2 you've got the research infrastructure, now you need to
3 offer it to scientists and those scientists that should
4 be targeted are both established scientific leaders, as
5 well as young investigators. We've got a sad situation
6 in this country today where it takes a young, promising
7 investigator to reach age 42 before they can expect, on
8 average, their first grant.
9 This is not really acceptable evidence of a
10 badly broken system, but until we fix it, we've got to
11 -- you've got an opportunity to basically offer your
12 research infrastructure to people who are hungry to
13 discover stuff. CFS is a virgin field; one that has
14 not been worked as extensively as cancer.
15 There is discovery, major discoveries waiting
16 to happen in that field. If you offer the tools, if
17 you offer the data, some young scientist, who are by
18 definition, smart, will flock to what you've created
19 and started to work it and find the discoveries that
20 will bring innovation to CFS.
21 We also should include in the scientist that
22 we're trying to involve in that effort, the physicians

1 who treat patients. They are one front line; they are
2 the one who have the knowledge of the disease. And
3 there has been some very interesting research at MIT
4 done, to suggest that actually physicians working with
5 patients for whom no treatments are available, have
6 been historically a very powerful source of innovation.
7 Possibly the most powerful source of
8 innovation in the pharmaceutical industry over the
9 decades, because they know the disease, they know the
10 patients, they know a little bit about pharmacology,
11 and they will try to customize treatment for those
12 patients using drugs that have been approved for
13 something else.
14 It's kind of a Darwinian experimentation that
15 is repeated millions of times, every day across the
16 land. And when you have that sort of thing going on,
17 by luck or by design some of that thing is going to
18 work, and we see it in every disease.
19 So if you have patients (sic) that are alert
20 and if you network them, if you allow them to share the
21 clinical insight, especially the clinical observation
22 that are unexpected, I don't think it would be long

1 before someone will notice that, gee, you know, I had
2 this patient and she had disease XYZ and I gave her
3 that drug and her CFS go better or disappeared, and
4 there has been instances of that happening already.
5 So we need to harvest that sort of
6 creativity. Finally, when you get all that, you are to
7 the point where you can generate intellectual property
8 and you can see a drug at the end of the tunnel or at
9 least a pathway to get to a drug at the end of the
10 tunnel. And this is what you need to get the industry
11 interested.
12 So from that point on, I think you can start
13 looking for partners, corporate partners, big companies
14 but also small companies that can take the tools that
15 you've got, or the data, the discoveries that you've
16 made, and start helping you out in coming up with new
17 drugs.
18 The regulators, they are keen to help and you
19 can help them a great deal, especially in the area of
20 risk assessment and trade-off. Every drug approval
21 process involves risk assessment and trade-offs and the
22 patients are the best people to make those assessments

1 and those trade-offs.
2 The patients are the people who can help the
3 regulators design better trial protocol, as we've seen,
4 for example, with HIV. Because they know what sort of
5 risk they're willing to take and they're the only
6 qualified ones, in my view, to speak about this.
7 All those people, the scientists, the
8 companies, the regulators, if you ask them, they will
9 respond. They will respond because if, as far as
10 scientists are concerned for example, a good rule of
11 thumb is that 80 percent of the time and cost involved
12 in a research project is the cost of generating and
13 curating the data, which is a work that is necessary,
14 but frankly not very rewarding.
15 If you offer the scientists clean, curated
16 data, high quality data, they will come, because it's a
17 way for them to leapfrog that unrewarding stage and
18 basically multiply their productivity by five-fold. So
19 the scientists will come because you make it easier for
20 them to do high quality work than their other options.
21 We also know that passion shortens timelines,
22 lowers cost, and raises the probability of success.

1 It's sound perhaps unexpected, but if you want proof of
2 that, look at those disease foundations that are being
3 created by parents who have a child that may die, and
4 they are determined to save that child. They know
5 nothing about the pharmaceutical industry.
6 They're not even scientists. They don't have
7 any money, but they're going to save that child and
8 they create foundation and they agitates (ph) and they
9 become specialists of their disease and they go talk to
10 the most eminent specialist in the world that they can
11 find, and those specialists oftentimes find it
12 irresistible to -- or hard to resist, hard to say no to
13 those parents that are driven by that level of passion.
14 And before you know it, those parents who
15 started with nothing have research program. They have
16 scientific advisory boards. They have tools and data
17 out there. They've got compounds in development and
18 drugs on their way to the market. It happens all the
19 time.
20 It happens with diseases that are much
21 smaller than CFS, so it can happen here too. And
22 lastly, we all know that it's more exciting to work

1 with people who are passionate and for whom failure is
2 not an option. It just keeps life more interesting.
3 So they will respond.
4 Money? Yes, you need money but the good news
5 is that it gets in cheaper and in fact it is getting a
6 lot cheaper. We have all kinds of new research model
7 right now. I mean you probably all have heard about
8 the billions of dollars that it takes to come up with a
9 drug, not because -- well, it is very hard, but also I
10 think this is an industry unfortunately where waste is
11 very prevalent, but there's all kinds of new research
12 models that make it possible to run a very audacious
13 research program on a shoestring.
14 You may have heard about the open source
15 model, the crowd (ph) sourcing, the virtual pharma, we
16 don't have time to get into all these public
17 partnerships. The price is drug purposing and so
18 forth. So you've got a variety of models to choose
19 from and each one of them has a potential to deliver
20 new drugs.
21 The CFS community is larger than many rare
22 disease communities that have been successful at it

1 already. So it can be done. You need leadership and
2 passion and it's already there. The CFIDS Foundation
3 was created in 1987, so it's got 25 years under its
4 belt, during which it has raised over $30 million which
5 is not a trivial amount of money, and that effort can
6 be continued and expanded, especially with support of
7 the patients.
8 There's already existing networks and some of
9 the infrastructure required, so you're not starting
10 from zero, like those patients who all of a sudden find
11 that they have a problematic child. You're well on
12 your way and it can be done. Good luck and thank you.
13 RADM KWEDER: Well, that was just a perfect
14 start, a perfect start. We're going to do most of our
15 discussion after the three speakers, but let me just
16 ask if anyone in the audience has any clarifying
17 questions. Not a comment or a long question, but do
18 you have any clarifying questions, anything that
19 Bernard said that you didn't quite -- you want it
20 clarified. Yes. Right here, over here. Yes?
21 UNIDENTIFIED SPEAKER: (Off mic) MIT, was
22 that intellectual (off mic)?

1 DR. MUNOS: Yes, I'm sorry. Yeah, I tend to
2 use industry jargon. Yeah, IP stands for intellectual
3 property, patents, and secrets and all that stuff.
4 RADM KWEDER: The secret stuff. Okay. Dr.
5 Michele, did you have a question?
6 DR. MICHELE: Just to clarify (off mic) and
7 we'll bring them up as well so --
8 RADM KWEDER: Yes, yeah. So you should have
9 the yellow papers. Okay. Thank you, Bernard.
10 DR. MUNOS: You're welcome.
11 RADM KWEDER: Okay. Knowledge and Intuition
12 to Reposition Drugs ME/CFS
13 DR. VERNON: Good morning, everyone. My name
14 is Suzanne Vernon. I'm the Scientific Director of the
15 CFIDS Association of America. I got there by way of
16 the federal government actually started at the CDC
17 after finishing my graduate work at the University of
18 Wisconsin in Madison where I was -- in Madison, you go
19 and you drink beer by the lake every Friday. That's
20 our TGIF.
21 And one day we were all kind of hunkered down
22 at a table by the lake and there is this really bizarre

1 looking guy that walked up to the lake and was kind of
2 hanging around. He had this funky hat on. He had a
3 tie-dyed jacket on. I think the hat was even tie-dyed.
4 And he was smoking like a smokestack and he looked like
5 a hippie.
6 Anyway, the next day he was actually giving
7 us a lecture about discovering the association between
8 human papilloma virus and cervical cancer in Panama.
9 And many of you know, that was Bill Reeves. And the
10 story fascinated me, because here he was in a
11 developing country conducting field work, using
12 technology that was really cutting edge technology and
13 applying that cutting edge technology to populations,
14 and making a very important discovery that in many ways
15 changed the landscape for women with cervical cancer.
16 That, for me, solidified the idea of really
17 wanting to work at the CDC where you could put powerful
18 technology to play in populations and really tackle
19 public health problems like no other place could, and
20 we did so.
21 In 1998, we had the opportunity to start a
22 laboratory program to really identify some of the

1 underlying biological underpinnings of CFS. We worked
2 together with a large team of people for about 10 years
3 and that program is still going on. But I think the
4 thing that was really interesting and important to me
5 was again this idea of being able to study large
6 populations with powerful tools and generate a lot, a
7 lot of data.
8 The problem was, back 10 years ago or so, is
9 we really didn't have the kind of techniques,
10 technology, to really wrap our minds around this data.
11 And so over the course of a couple of years, we started
12 putting data out there and engaging people with ways to
13 really try to interrogate information, analyze the
14 data, and pull things out of it that maybe we wouldn't
15 see with just the naked eye.
16 And in 2007, the opportunity to really bring
17 some of this, I think incredible approach to bridging
18 basic research, basic epidemiology, to having an impact
19 in the patients happened with the opportunity to work
20 with the CFIDS Association as a translational research
21 leader in CFS, and I jumped at that opportunity,
22 because I think we're at a very, very important time

1 then and now, even more so now, where we can really
2 take this incredible knowledge that we have accumulated
3 over the years in the basic research arena and use that
4 to really make remarkable advances in CFS.
5 So that's how I got here. That's my road.
6 It was a very interesting one.
7 So I'm going to talk to you today about
8 knowledge and intuition to reposition drugs for CFS. So
9 as I said, we have over the past five years, been very
10 strategic in positioning ourselves as a translational
11 research leader, essentially creating a bridge between
12 the basic research, the laboratory, the epidemiology,
13 and the bedside, helping to provide the infrastructure
14 for basic researchers to bring their discoveries to
15 impact patient communities.
16 This is really what's known as derisking
17 science; making it attractive to industry, in order for
18 them to pick up the ball, and again, impact our patient
19 community. This has been our innovation pathway over
20 the past five years, to really provide an
21 infrastructure which allows that information flow,
22 those discoveries that occur at the bedside, to come

1 across the way and be attractive investments for
2 pharma.
3 Once piece of our infrastructures are
4 SolveCFS BioBank. That includes a sample repository
5 and a registry. To date, we have about 800 ME/CFS
6 patients in healthy controls. We've already partnered
7 with pharma and we have a number of funded
8 investigators, both our fund (ph) investigators and
9 investigators interested in using this resource already
10 using it, and this has happened in three short years.
11 So it's a remarkable demonstration that this
12 was a really, truly needed aspect of CFS research to
13 really get people interested. As Bernard said, if you
14 build it, in fact they do come, but you have to put it
15 out there and make sure that people understand what the
16 resource is.
17 We've also built a knowledge base and data
18 analysis and data sharing platform which you'll be
19 hearing more about in the coming months and this will
20 be open and available, so it'll provide a tool source
21 that's very much needed in our community, again to help
22 with the aggregation and the analysis and sharing of

1 data that we generate.
2 And as Bernard mentioned, the CFIDS
3 Association has been around since 1987. We are an
4 incredible resource of knowledge with chronicles, with
5 every other publication that has been printed over the
6 years, and this is also going to be made publicly
7 available on line at the push of a button, indexed and
8 everything, very soon.
9 And importantly, we've really sought out new
10 research avenues with drug repurchasing being one of
11 those. Even though drug repurposing isn't necessarily
12 new, it's become very attractive again, because of some
13 of the technology that we now have available to us as
14 far as knowledge and databases to query.
15 This is just a little summary of CFS. We
16 know we call it a number of different things, and to
17 date there's about 6,000 publications in PubMed
18 describing every aspect of CFS, from the basic
19 pathophysiology shown in the picture to the
20 epidemiology which describes one million people in U.S.
21 with CFS or 17 million worldwide.
22 We have identified many of the CFS risk

1 factors. We do understand the pathophysiology. We do
2 understand that there's a tremendous economic impact of
3 CFS. And we now know, as evidenced by this gathering
4 that FDA considers CFS a serious condition. Still,
5 there's some limitations. Over the past 25 years,
6 there's been about a $150 million spent by the federal
7 agencies on CFS to basically provide, gather all of
8 that data shown above.
9 Still a cause or causes have been elusive.
10 We still lack validated, replicated markers for
11 diagnosis and treatment. For that, we haven't figured
12 out or we do not have a regulatory framework for CFS
13 yet, and because of that, we still don't have an FDA
14 approved treatment and we have no standardized, widely
15 accepted clinical guidelines.
16 And because of that, we still have our
17 physicians, our wonderful physicians grappling with CFS
18 and managing their patient populations really with
19 symptom based treatments. But still, the good news is
20 we have a foundation of which we can build on. We have
21 an incredible knowledge base and knowledge expertise in
22 this area of which we can build on.

1 This is why drug repurposing is perfectly
2 suited for CFS. Drug repurposing is great for diseases
3 that have clear unmet medical need, that are
4 multifactorial in their disease pathophysiology,
5 because as you see in this picture, as you saw in that
6 picture -- so this doesn't have a pointer does it?
7 UNIDENTIFIED SPEAKER: No, I don't think so.
8 DR. VERNON: Okay. Oh, now I'm all
9 flustered. Darth Vader (sighing). Help me, Bernard.
10 DR. MUNOS: Drug repurposing.
11 RADM KWEDER: Yeah, why this is such a
12 disease well-suited to it.
13 DR. VERNON: Drug repurposing is a disease --
14 is not a disease -- is well suited --
15 UNIDENTIFIED SPEAKER: Suzanne, welcome to
16 our world.
17 DR. VERNON: Thank you for that welcome, Bob.
18 Okay. So a couple years ago when there was a lot being
19 written about drug repurposing, we had -- in reading
20 about it, we decided that CFS was a perfect candidate
21 for using a drug repurposing approach and it's because
22 it's multifactorial. It's defined by symptoms that in

1 many ways, and in many instances, overlap with many
2 other diseases that have drugs to treat it.
3 So it seemed like, again, the perfect
4 candidate to do that. So we sought partners to do some
5 drug repurposing work with us, and we partnered with a
6 small biotech company called Biovista. Actually, we
7 reached out to a number of different companies that
8 were working on drug repurposing and Biovista was one
9 of the companies interested in partnering with us.
10 Their platform is called a Clinical Outcomes
11 Search Space, or COSS and its trademark. And basically
12 what COSS does is it taps into existing knowledge. So
13 they use all of PubMed; so the 20 million abstracts or
14 20 million full text papers in PubMed Central and in
15 PubMed combined with databases that include a whole
16 bunch of information about clinical outcomes, 29,000
17 different data points, combined with molecular entities
18 in human targets, combined with all of these things up
19 here to make a very massive, big dataset, which they
20 then query with specific search terms.
21 And in our case, there's CFS specific search
22 terms, and then they extract that information to create

1 a unique or sets of unique profiles or little
2 fingerprints, bar codes. This is how this particular
3 search engine works.
4 Now this can be used not only to identify
5 drugs, let's say drugs that have known mechanisms of
6 action that work in a specific area or pathophysiology,
7 but it can also be used to identify biomarkers. The
8 work that I'm going to talk to you -- present today is
9 their drug discovery work and that's just the flow that
10 they use.
11 An important thing about this flow is that
12 even though there's a bunch of computer stuff at the
13 top end, you know searching, trolling, crawling the
14 literature, making all these correlations, the output
15 of that is a very comprehensive list that requires
16 extensive manual curation; people actually sitting down
17 looking at the things that the computer fit together,
18 and seeing whether or not it makes sense, to ultimately
19 hone it down to a list of very plausible sets of
20 information and associations.
21 Here's an example of the output. And Nancy,
22 I see you sitting there squinting. It's very hard to

1 see. Along this outside are symptoms and some of the
2 markers that have been identified in the literature. So
3 right over here, for example, there's some immune
4 dysfunction markers. Again, lumped together; genetic
5 polymorphisms. Symptoms around -- and around is
6 outside. Anything, any blue or colored line that comes
7 out, indicates a finding or a strong correlation.
8 And the most prominent correlations in their
9 bibliographic assessment of symptoms and mechanisms and
10 information in the literature, was one with serotonin.
11 Serotonin was repeatedly highly correlated with a
12 number of symptoms and markers in CFS.
13 Next, highly correlated was dopamine,
14 acetylcholine next, and then histamine. But serotonin
15 was really -- so there was this really strong
16 association with monoamine neurotransmitters with very
17 many aspects in CFS.
18 The next thing they did, another part of the
19 process, is to use other types of data, and adverse
20 events also gives some information about the mechanisms
21 that a drug -- how a drug works; its safety profile and
22 its mechanisms of action.

1 This is a relatively complicated graph, so
2 let me walk you through it. The orange line is an
3 adverse event that's reported as exhaustion. The blue
4 line is an adverse event of chronic fatigue. On the X-
5 axis are a number of different drugs in the database,
6 and this is the eHealthMe adverse events database.
7 So drugs on the bottom, and then on each Y-
8 axis is the frequency of the adverse event. This Y-
9 axis is the frequency of chronic fatigue. That Y-axis
10 is the frequency of exhaustion. And what they found
11 was that the frequency of exhaustion and chronic
12 fatigue was very high with certain serotonergic and
13 noradrenergic drugs on this side, over here.
14 And this was a surprise finding to them,
15 because as we know and as we heard yesterday, there are
16 a lot of these types of drugs used in CFS populations.
17 So it was an interesting counterintuitive finding, the
18 fact that perhaps some of the medications being used in
19 this population may in fact be contributing to some of
20 the symptom constellation.
21 This was further validated in another
22 database and this is AERS database, which is the FDA's

1 adverse events database. On the right you see the
2 eHealthMe drugs that are all associated with increased
3 levels of exhaustion or chronic fatigue. On the right
4 is the AERS database and those lines show that the same
5 report was found in both of those database.
6 The drugs in red were also drugs that were
7 reported to have an increased level of fatigue or low
8 efficacy from our SolveCFS Biobank. So three different
9 datasets which validated the same finding. So the
10 summary of these results using COSS is that CFS
11 symptoms and pathophysiology correlate with known
12 mechanisms of neurotransmitters.
13 And this again was described in the
14 literature, so a bibliographic correlation and
15 association that was a counterintuitive finding that
16 this particular mechanism could in fact be associated
17 with fatigue, but now it's actually fitting quite
18 nicely with a mechanism that's being extensively
19 described in the literature called the central fatigue
20 hypothesis.
21 Drug repositioning using COSS platform has
22 identified two drugs and that I didn't show you, but

1 two of the drugs can be used in combination to address
2 two to three CFS symptoms. The knowledge base
3 identification of these drugs was validated both by the
4 adverse events databases and by data in our SolveCFS
5 BioBank.
6 And we're currently in the process of
7 designing a proof of concept clinical trial to test
8 these drugs as a combination therapy. So a very
9 exciting result from a partnership that literally
10 started one year ago.
11 Another aspect of repositioning is to tap
12 into the clinical population. Like Bernard said and
13 like Dr. Kweder said, we need to tap into our physician
14 knowledge base. And we designed a tool to capture
15 clinical intuition and this is based on a meeting that
16 we had at Cold Spring Harbor last year in October and
17 Beth Unger said, we need to figure out how to capture
18 clinical intuition.
19 And we went away; we partnered with Biovista
20 again to develop a web-based tool and this is shown
21 here. It was a web-based tool that listed all of the
22 medications that are used to address the symptoms. And

1 again, a lot of that came from the literature. Nice
2 little pull-down menu approach. All of the symptoms
3 that had drugs associated with them are listed there.
4 So this would go out to the physicians and then they
5 would review it.
6 They'd mark it. They would indicate whether
7 or and not the drug had -- the efficacy level of the
8 drug, and then we basically analyzed the results. I
9 want to read this quote up at the top from Dr. Kweder.
10 "The key is that a lot of the research in
11 this to date have been out on their own -- researchers.
12 They're clinicians who are following a series of
13 patients for decades and no one has been able to tap
14 into that kind of information that they have."
15 This was a clear effort attempt to do just
16 that. We put it out there to about 30 physicians; we
17 got about a 50 percent response rate. It took a lot of
18 time for them to do this, so that 50 percent response
19 rate was great, and it was very valuable.
20 Here's another complicated graph. On the
21 left, on the Y-axis is the efficacy level from not
22 effective on the bottom, to very effective on the top.

1 On the X-axis are all the symptoms that they were
2 queried about, and then each dot represents a drug that
3 they indicated had some level of efficacy. The only
4 ones I'm showing are those that had somewhat to very
5 effective levels of efficacy.
6 So the interesting thing is that most of the
7 symptoms that describe CFS have a drug that has some
8 level, a relatively good level, of efficacy to treat
9 it. There are -- to the right-hand side, about five
10 symptoms that do not have any drugs that affect
11 efficacy.
12 So the idea is then if you have some ability
13 to impact CFS at the symptom level management from --
14 at a very effective level, that this information was
15 also very valuable to gather; incredibly valuable to
16 gather.
17 And the other interesting thing is that the
18 drugs that were identified using the Biovista COSS
19 platform, were validated in this survey. So they're
20 not listed here, obviously, because we're not giving
21 any of the drug names. But this effort also validated
22 the Biovista finding.

1 So drugs identified as moderate to very
2 effective for treating specific symptoms -- sleep,
3 pain, and fatigue -- were those identified using the
4 Biovista COSS platform. And again, this is based on
5 correlations of symptoms and the drug's mechanism of
6 action.
7 One of the other things that the clinicians
8 noted in that survey was that Vitamin B12 injections
9 were reported as having moderate to very effective
10 levels for treating brain fog, although this effect is
11 transient. And we heard this yesterday, that a number
12 of patients use Vitamin B12.
13
14 And the reason that I put this up there is
15 because you'll be hearing next week in a webinar that
16 we're giving on the gut microbiome that we have
17 identified differences in the gut microbiome between
18 CFS and healthy people. And we know that the gut is
19 very, very important in Vitamin B12 fermentation and
20 availability, bioavailability.
21 So again, demonstration of really aggregating
22 a bunch of different knowledge to make these

1 connections that would otherwise have gone undetected.
2 Biovista COSS platform and clinicians
3 identified two predominant phenotypes in the CFS
4 population. So again, two very separate approaches
5 identifying two same subtypes, if you will, of CFS: an
6 immune phenotype, and a autonomic phenotype.
7 One of the other phenotypes or subtypes of
8 CFS that clinicians wanted to make a point that
9 everybody understood was out there, is the difference
10 between younger CFS patients and old. So age can
11 clearly delineate CFS subtypes.
12 And finally, we conducted a drug development
13 survey. You heard a little bit about the disease
14 impact from this drug development survey yesterday from
15 Kim. There were 20 open-ended questions or 20
16 questions posed by the FDA and we provided these in an
17 open-ended text format so as not to bias any of the
18 responses.
19 We divided these up into disease impact,
20 symptom, and treatment, and we analyzed it using some
21 technology, some pretty sophisticated part of speech
22 parsing using a natural language processing algorithm.

1 And the important thing about that is we tried to
2 standardize this very colloquial response by matching
3 it with unified and medical language system.
4 Now there it is. This is the ant screen. So
5 there is 500 million words -- no, is that right? Half
6 a million.
7 UNIDENTIFIED SPEAKER: Five hundred thousand.
8 DR. VERNON: That's it. Five hundred
9 thousand words in the 1,200 responses and those are
10 those half a million words up there. Now, this shows
11 you that there's a lot of challenges to dealing with
12 colloquial survey responses, but if you look on that
13 diagonal, you begin to see some very obvious clusters,
14 despite the fact that there's a lot of noise in the
15 system.
16 There's a few interesting clusters that are
17 popping out and we're in the process of now kind of
18 zooming in and each one of those clusters contains
19 about a thousand people and their corresponding bits of
20 information about treatment or about symptom or about
21 impact. So that's that diagonal right there.
22 Let me just share with you a little bit of

1 the very general high level responses. So from a
2 symptom perspective, we came up with three predominant
3 clusters of symptom responses from patients. One being
4 described as muscle pain, exhaustion, sickness,
5 headache, joint pain, post-exertion malaise, fatigue,
6 sore throat, brain fog.
7 Another was very much a pain subtype
8 described by pain in all parts of the body. Very
9 distinct group from the rest of the groups. And then
10 another one was described as exhaustion, arthralgia,
11 malaise, weakness, spasms, food sensitivities and sore
12 throat.
13 So the message from this is that clearly the
14 patient population is providing information, has
15 information that can allow us to begin to subtype,
16 identify phenotypes that we might not have found
17 otherwise.
18 There was not as much information from the
19 treatment realm. The biggest group of responses in the
20 treatment domain of the survey responses said that
21 there was a big use of non-drug therapies, nutritional
22 therapies, diet modification and anti-inflammatory

1 drugs.
2 The next was a pain using prednisone, which
3 really was used to manage again mostly pain symptoms
4 and then the third group was really an activity
5 modification group. So using a lot of pacing to really
6 manage their disease well.
7 So our next steps in drug repurposing is
8 again to get underway with submitting our pre-IND
9 documentation for the proof of concept clinical trial
10 and to expand our SolveCFS BioBank, because that will
11 be a main part for the participation in the trial and
12 other trials resulting from this work.
13 Optimize our clinical information platform.
14 So that clinical intuition platform, so that we can get
15 more input from physicians and that will help us really
16 understand patient phenotype and comorbid conditions
17 which are very common in this population.
18 And then operationalize patient-centered
19 passive and active data collection using some of the
20 devices that Bernard had mentioned, as well as
21 providing data sharing platforms that are user friendly
22 and engaging, and sticky.

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1 So thank you for your attention. I'd like to
2 thank Biovista. I would like to thank the physicians
3 and providers who provided the clinical intuition data,
4 and I would like to show my thanks and appreciation to
5 the ME/CFS patient population, families, and friends
6 for really jumping in with us and giving us data to
7 make this happen.
8 RADM KWEDER: Thank you so much, Suzanne.
9 Our next speaker is Melissa Robb, and I want to state
10 the obvious that we are a little bit over on time. We
11 will allow this session to go over. We will still take
12 a 15-minute break, but we may end up shortening the
13 lunch by just a few minutes to make up that time.
14 I think these basic topics are really, really
15 important and I want to make sure that we lay a sound
16 foundation for the discussion and the rest of the day.
17 Regulatory Pathways for Expediting Drug Development
18 MS. ROBB: Okay, thank you, Sandy. My name
19 is Melissa Robb. I work in FDA's Office of Medical
20 Policy Initiatives and I'm the Associate Director for
21 Regulatory Affairs there. I've been with FDA for about
22 a little over 10 years and I started in one of the

1 review divisions as a project manager.
2 About five years ago, in 2007, when the Food
3 and Drug Administration Amendments Act was enacted, I
4 started working closely in developing different types
5 of programs that spanned lots of drug classes, and was
6 working mostly on post-marketing initiatives that were
7 new to the agency by some new authorities given to us
8 by Congress with that legislation in 2007.
9 In 2012, the Food and Drug Administration
10 Safety and Innovations Act was passed, and there was a
11 lot new authorities around innovative and expedited
12 programs for drug development focusing on serious
13 conditions and also on areas on unmet medical need.
14 So that's really what I'm talking about here
15 today is the focus that the agency is really putting on
16 innovating and bringing new products to market, and
17 bringing them to market quickly. I don't have any
18 disclosures. I work at FDA.
19 So I'm going to give you a little background
20 to set the stage. I mentioned FDASIA, the Safety and
21 Innovations Act from 2012. And thinking back from that
22 Act, that's not something new for FDA to want to

1 facilitate and expedite drug development.
2 It's something that we've been doing for
3 quite a long time, and we have a lot of regulations in
4 that area. Specifically I think the first time we
5 articulated our thinking on speeding the availability
6 of new drugs, was with our Sub Part E regulations that
7 we put out in 1988.
8 And what that did is really talk about the
9 idea or a general philosophy that FDA had towards
10 assisting development of new therapies for serious
11 conditions, especially where there exists unmet need.
12 And I think you've heard from Sandy and some of the
13 other speakers, that while we want to facilitate and
14 expedite drug development, that doesn't alter the
15 requirements for safety and effectiveness.
16 And we're not lowering the standard; we're
17 looking at other ways to provide the needed evidence so
18 that we can be assured that drugs that are approved are
19 both safe and effective and have appropriate risk
20 benefit assessment for the diseases that they're
21 intended to treat.
22 So following the Sub Part E regulations, the

1 Accelerated Approval regulations were put out in 1992,
2 and I'm going to talk about these a little bit more, so
3 I'm just -- this is a quick overview timeline thing.
4 Also in 1997, the Fast Track provisions were put in
5 place and also the Priority Review came about in 1992
6 and I'll get into all those in a little more detail.
7 So like I mentioned FDASIA was a new law in
8 2012. Title 9 of that law specifically addressed
9 expedited drug development and reinforced the
10 commitment of FDA to expedite drug development. It
11 clarified some of the requirements for Accelerated
12 Approval which had been place through our, FDA's
13 regulations and had been initially put in place through
14 earlier Congressional laws.
15 It created a new type of program called
16 Breakthrough therapy which I'll discuss in a bit more -
17 - and it also required FDA to issue draft guidance on
18 Accelerated Approval by July of this year, and on
19 Breakthrough, we had 18 months, so that's not until
20 January of 2014 is the due date.
21 So there are four existing programs now:
22 Fast Track designation, Breakthrough therapy -- the new

1 one, Accelerated Approval, and Priority Review. I'm
2 going to talk about each of them. But before we talk
3 about them, I want to kind of get some ideas or set the
4 stage for some common terms that are present in all of
5 those programs.
6 So serious conditions are conditions that are
7 associated with morbidity, that has impact on day-to-
8 day functioning. We, at FDA view serious to be broader
9 than life-threatening, but life-threatening diseases
10 would be considered serious also, but it does not need
11 to be life-threatening to be considered serious.
12 In addition, many of these programs include
13 the concept that they have to address an unmet medical
14 need and there's an obvious unmet medical need if
15 there's no approved therapies. However, some
16 conditions even with approved therapies can have an
17 unmet medical need and still be eligible for some of
18 those programs.
19 So I'm going to start out talking about Fast
20 Track. And the first -- the way that I've organized
21 them, they kind of are organized by how these programs
22 would be used by a sponsor to facilitate their drug

1 development. So this is a program that's used during
2 the development stage, and it's really intended to
3 expedite the development of the molecule for FDA review
4 in the clinical development time.
5 So Fast Track is intended for serious
6 conditions that have an unmet need and you would be
7 eligible to get a Fast Track designation if you had
8 data to demonstrate that there is potential to address
9 this need. Now, the data for Fast Track can be
10 clinical or non-clinical and that's going to be an
11 important distinction when I talk about the new
12 program, Breakthrough, next.
13 So in essence, Fast Track is much broader,
14 the eligibility. You don't have to have so much. But
15 what FDA tries to do is expedite the development, meet
16 with sponsors and discuss study designs and ways to
17 make their drug development program more efficient.
18 And this is a program that we've had for almost 20
19 years now.
20 So it's not something new that we've been
21 doing. It does have a component that affects the
22 review time in that it allows sponsors to submit

1 complete portions of an application through what's
2 called rolling review.
3 So typically sponsors have to submit, get all
4 their data, analyze it and have a complete package
5 before they submit a new drug application or a
6 biological license in application NDAs or BLAs. But if
7 a sponsor has received Fast Track designation, they're
8 eligible to submit parts of their application as they
9 become available. And the goal there really is to
10 expedite the review process and get the drug to market
11 quicker.
12 So Breakthrough therapy kind of builds off
13 Fast Track. It's another one of those programs that
14 are intended for the development part -- the clinical
15 development part and not the review phase where it's at
16 FDA, but where the sponsor is trying to develop the
17 evidence to submit.
18 And the criteria here is that it's a serious
19 condition and that there's preliminary clinical
20 evidence that indicates the drug may demonstrate a
21 substantial improvement over existing therapies. And
22 so this is intentionally a higher bar than Fast Track,

1 but what it gets you is all the Fast Track benefits but
2 more intensive guidance on an (inaudible) drug
3 development.
4 There's definitely a commitment on behalf of
5 all of the agency, especially those within the centers,
6 CDER and CBER, who are implementing these provisions to
7 work closely with senior managers and experienced
8 review staff to look at opportunities to shorten the
9 development timeline.
10 There's cross-disciplinary review and looking
11 at impacts that will affect approval outside of just
12 the clinical development. Looking at issues like
13 manufacturing and inspections, and different ways to
14 make sure that the whole package is ready to be to
15 market as soon as possible.
16 So Breakthrough is new. We don't have tons
17 of experience with it. We have designated a handful of
18 products already. It came with the 2012 legislation,
19 so it's already being adopted. And I think we see it
20 being used in the rare disease community, but also in
21 other types of indications.
22 So Accelerated Approval is a little bit

1 different than the Breakthrough and the Fast Track. So
2 if you think of them, Breakthrough and Fast Track are
3 really useful tools for sponsors of products who are
4 trying to facilitate their drug development.
5 When we're thinking about Accelerated
6 Approval we're thinking how -- the endpoints that we're
7 using to approve a drug. So we still have that same
8 requirements for safety and effectiveness, but we're
9 using different endpoints to establish that. So the
10 regulations, there's regulations in the Code of Federal
11 Regulations, Part 314 is for drugs, and Part 601 is for
12 biologics.
13 But FDASIA had some important clarifications
14 that they put in, and that was the legislation from
15 last year, that allowed additional flexibility and
16 clarity to how the FDA implemented the Accelerated
17 Approval program. It allowed the FDA to take into
18 account the availability or lack of alternative
19 treatments in making a decision if there were drug
20 development programs that should be considered for
21 Accelerated Approval.
22 In addition, it clarified the type of

1 endpoint that can be used. Traditionally, FDA has used
2 often surrogate endpoints for the use of Accelerated
3 Approvals. In FDASIA, it clearly talks about the use
4 of a clinical endpoint, which we've kind of adopted
5 this term, intermediate clinical endpoint, that can be
6 measured earlier than an irreversible morbidity or
7 mortality, but is likely to predict that or another
8 clinical benefit.
9 So the key to Accelerated Approval is the use
10 of endpoints that are different than we see with
11 traditional approvals. So accelerated approval still
12 has many criteria that are similar to the other
13 programs. It is only for serious conditions. You need
14 to show or establish a meaningful therapeutic benefit
15 over available therapies, and you also have to show
16 that it's reasonably likely that the endpoint that
17 you're using will predict the ultimate clinical benefit
18 that you're seeking to impact in that disease state.
19 So you have to show two things with
20 Accelerated Approval: that the endpoint that
21 you've shown is reasonably likely to predict the
22 benefit, and that there's safety and efficacy with that

1 endpoint. But the very big advantage is it can shorten
2 the time to approval, because often these surrogate
3 endpoints or clinical endpoints don't take as long to
4 measure.
5 So when you're looking at measuring a chronic
6 disease state and you can find a measure that predicts
7 your ultimate goal at an earlier time, that can save a
8 lot of time. So Accelerated Approval is often useful
9 in diseases that have a long -- say chronic diseases,
10 and where you would have to study the drug for an
11 extended period of time to get the ultimate outcome
12 that you're interested in knowing about.
13 And the surrogate or intermediate clinical
14 endpoint may occur rapidly or sooner, and then that
15 informs the approval. It's been used extensively in
16 cancer and in HIV, especially Sandy alluded to the use
17 of viral load which was very common in the early days
18 of HIV.
19 But it does have certain requirements that
20 are associated with the approval. One is the
21 restriction on promotional materials, that they have to
22 be reviewed by FDA prior to being disseminated. But

1 also it requires post-marketing confirmatory trials to
2 show that the evidence that you proved, that it's
3 reasonably likely to predict the benefit is -- you have
4 to validate that.
5 And so those two requirements come with all
6 accelerated approvals or most. And there's also
7 expedited withdrawal procedures that can be used, if it
8 turns out that the accelerated approval was not borne
9 out in these confirmatory trials.
10 So the final program that I'm going to talk
11 about is the Priority Review Designation and this is a
12 program that's intended to shorten the review time. So
13 the Fast Track and Breakthrough help developers. The
14 goal is to shorten the development time. Priority
15 Review is something that shortens the time FDA has to
16 review an application.
17 So typically applications are reviewed within
18 10 months. That's a goal date that was established
19 with PDUFA, the Prescription Drug User Fee Act, in
20 1992. And what that did is acknowledged that there was
21 a gap in FDA's review of certain -- of all
22 applications, and tried to find additional funding and

1 resources to support certain expectations of the FDA.
2 And so with that came the priority and the
3 standard review. And so standard review is 10 months.
4 And for drugs that are deemed to be priority review,
5 the goal is to have those reviewed within six months.
6 For CDER the criteria is that you need to demonstrate a
7 potential to be a significant improvement in either
8 safety or effectiveness, and then the goal would be
9 that you get a shorter review time.
10 So all of these programs, especially the
11 development programs, the ones that have had the
12 development stays (ph), focus on the importance of
13 early communication between the sponsor and the FDA,
14 and the goal is really to facilitate drug development
15 to help look at study designs that optimize the way
16 patients are enrolled, optimize the collection of data,
17 in order to make studies and drug development more
18 efficient, and have smaller, shorter, trials.
19 An emphasis on the new, on regulatory science
20 and the evolving understanding of the mechanisms of
21 diseases are very important in order to implement these
22 approaches. So looking forward, we're currently

1 working towards getting the draft guidance, that's
2 required by the legislation, out by July of this year.
3 There will likely be a comment period where
4 we'll be asking for any thoughts on the guidance. And
5 our intention is to be putting out one guidance that
6 discusses all of these programs, in order to make it
7 easy to understand where they're most appropriate and
8 how they can be useful. And then following that, we'll
9 be issuing final guidance also.
10 And on this slide I just put a couple
11 resources that might be useful. There's currently some
12 information sheets around Accelerated Approval and
13 Priority Review and Fast Track that you can reference
14 on the FDA website, and a fact sheet on Breakthrough.
15 And in addition, the 2012 Drug Approval Report that
16 CDER put out, discusses some of the different types of
17 development programs that were approved during 2012
18 that took advantage of some of these programs.
19 But I guess it's important to note that these
20 programs aren't mutually exclusive. We do see many
21 drug development programs that take advantage of more
22 than one of these and that's great. That's what

1 they're intended to do.
2 They all have different contributions they
3 can make to drug development and getting patients
4 access to these important life changing medications
5 sooner. So that's my talk.
6 RADM KWEDER: That's great. Thank you very
7 much. Before you sit down though, could you just kind
8 of stand up there, Melissa? Just stand right where
9 you're standing. I want to point out that Melissa is
10 wearing a uniform. She wears this every day.
11 I don't wear this one every day. I have one
12 just like hers that I wear most of the time. If you
13 look around the room, you'll see several people in
14 uniforms. You can sit down, Melissa.
15 And there other folks here, and a couple
16 people asked me about it yesterday, so I encourage you
17 to ask them about what they do at FDA, but we are all
18 commissioned officers in the U.S. Public Health
19 Service. That is not the navy. It's not an airline.
20 But if you think about the Surgeon General, that's the
21 Surgeon General of the U.S. Public Health Service.
22 We are an all officer corps; we're one of the

1 seven uniformed services in the United States. We do
2 not have guns. That would be a real mistake to give
3 healthcare providers weapons. But the Public Health
4 Service is about 8,000 officers today. We are
5 stationed in places like FDA, NIH, provide medical care
6 in the Indian Health Service, and a number other
7 places.
8 We even have -- we have people all over the
9 world. And we do the same jobs that our non-
10 commissioned officer colleagues do in the agency, but
11 in addition, we have other requirements. We have
12 fitness requirements. We have -- called readiness
13 requirements, understanding disaster relief. And we're
14 called upon in times of disaster to deploy.
15 So, for example, last week a team of mental
16 health professionals from the commissioned core were
17 sent to Boston. A team of mental health professionals
18 were sent to New Town, Connecticut in December. We
19 have, we basically ran the immediate disaster
20 activities at Hurricane Katrina.
21 So that's who we are and so be sure --
22 you can examine their uniforms. They'll tell you what

1 a gig line is if you're not familiar. So we have a
2 number of questions here and I really do want to thank
3 the panelists. This is one of the most interesting
4 sets of presentations that I've had the pleasure of
5 listening to and particularly moderating Audience
6 Question and Answer Period
7 RADM KWEDER: We've got a couple of questions
8 about where can we find the material presented by the
9 panelists? I believe the slides are going to be
10 available on the FDA website where you'll be able to
11 link to this meeting, so that you can see them up
12 close.
13 I know I had a small version of the slides
14 and I was kind of squinting. So yes, people will have
15 those available so that you can look at them more
16 closely. And I have a number of questions here, but I
17 first want to ask the panelists what questions you
18 have, if you have any questions for each other, or
19 comments for each other?
20 DR. VERNON: I have a question for Bernard.
21 So I think you alluded in your presentation to the fact
22 that CFS appears to be on the right track as far as

1 being able to be innovative and expedited and
2 innovative in a disruptive way. What kind of time
3 frame would you put on us being the Chordoma or MMRF or
4 one of those organizations that clearly is innovative
5 and doing good things?
6 DR. MUNOS: I can give you a couple of rule
7 of thumbs there. If you go and try to develop a drug
8 the traditional way, you're talking about a 10 to 15
9 year timeline, which is probably more than the patients
10 in this room would like to see. If you go the drug
11 repurposing routes, the hope there is that you can
12 bring innovation to patients within five years.
13 So I would -- now, this can be sped up if
14 patients do join hands and collaborate and work
15 together to help make it happen. You've got
16 physicians, scientists out there waiting to help,
17 literally, they just don't have the tools, they don't
18 have the data.
19 I was thinking last night, for any disease,
20 natural study involving a thousand patients would be a
21 Godsend, would be something that is hard to fathom, but
22 needless to say, enormously helpful to scientists. The

1 technology that's available today would probably allow
2 thousands of CFS patients to enroll and collect the
3 data within the next few months and make it available
4 to the scientists.
5 So I really think that the -- whatever
6 timeline I can talk about, it's too long, but those can
7 be shortened dramatically by getting serious about it.
8 And I know you're serious about it, but I think you
9 need to connect maybe better than you are right now.
10 Go to patients like me, look at the CFS
11 community out there. I think last time I checked there
12 were hundreds of people. Well, we've got a million
13 people I heard, CFS patients in this country. So
14 there's many that could contribute who are not
15 contributing for various reasons. Maybe, most likely I
16 would think because they're not aware of the
17 possibilities. That's what we need to get better at.
18 But I think if we do, we'll see those timelines shrink.
19 RADM KWEDER: Dr. Munos, this is a question
20 for you as well, and you -- the question is do you have
21 any suggestions about network, the networking part to
22 bring down the -- to cut across silos and work

1 collectively?

2 DR. MUNOS: Well, I think you can have

3 networking at two levels; at the level of the

4 scientist, the physicians, and also at the level of the

5 patients. And to be effective, I think those two

6 levels need to cross-pollinate with each other. There

7 is some interesting research, unfortunately it's only

8 one study, but interesting research that was done a

9 couple of years ago to look at rare diseases and try to

10 find out what causes innovation to happen where it

11 hasn't been seen before.

12 And the conclusion there is that it takes a

13 critical mass of physicians who are networked together

14 and start exchanging all kinds of ideas about the

15 diseases, but it also takes a network of ideas, a

16 network of hypotheses about the particular diseases,

17 that is rich enough to allow those physicians to draw

18 from.

19 So when you have enough physicians, when you

20 have enough ideas, then it starts to emerge as if by

21 magic. And that's a dynamic that we need to put in

22 motion. I think we have physicians that are involved

1 clearly in CFS, maybe they're not as networked as they
2 should be. I'm not sure. Maybe they don't know each
3 other; they don't cross-pollinate enough.
4 And we've clearly patients who are activists
5 who are agitating out there, but again, we've got a
6 million people in this country who have, who are
7 affected by CFS, just to mention patients, and we need
8 to draw far more into this effort than seem to be
9 currently involved.
10 RADM KWEDER: Okay, I have a number of
11 questions here for you, Suzanne. This question is, you
12 searched only for fatigue and exhaustion in adverse
13 event database, so it's not surprising that you came up
14 with neurotransmitters. Have you looked at orthostatic
15 intolerance, multiple infections, or abnormal immune
16 functions? It seems to me you are biasing your results
17 by your choice of search terms.
18 DR. VERNON: I'm actually not as familiar
19 with what the adverse events databases information has
20 in theirs or is the types of adverse events listed.
21 Can you guys help me out on that?
22 RADM KWEDER: There are thousands.

1 DR. VERNON: Thousands?
2 RADM KWEDER: Thousands of terms. There's a
3 whole dictionary of terms. So you can go in and search
4 for others.
5 DR. VERNON: Yeah. So that's a very good
6 point, and yes there probably is some bias to that
7 search, but the result was pretty clear that fatigue
8 and exhaustion was associated with the mechanism of
9 action of these types of drugs. And I think that's a
10 really good point to go back into the data and do the
11 same type of searching for adverse events associated
12 with other symptoms. Yeah, very good point.
13 RADM KWEDER: Okay. And also, Suzanne, I got
14 a bunch here. But are your drug development survey
15 results available online?
16 DR. VERNON: Oh. Yes. Well not yet.
17 RADM KWEDER: But they will be?
18 DR. VERNON: Yeah, the responses -- they're
19 still, we're still collecting data and then we're going
20 to be analyzing them and write them up and we'll put
21 them out there.
22 RADM KWEDER: Okay. And along the same lines

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1 there's -- this is the same thing -- it's known that
2 the "CFS" literature includes studies based on overly
3 broad and non-specific definitions. As a result, these
4 studies include patients who don't have the disease
5 that patients described yesterday. Did you eliminate
6 those studies from the Biovista analysis, and if not,
7 how has that influenced your results?
8 DR. VERNON: It used all information. It's
9 20 million abstracts and 250,000 full text articles.
10 And so it wasn't -- again, the search was based on
11 terms that are used to describe CFS, and a number of
12 biomarkers and kind of the physiologic parameters that
13 have been used to describe CFS.
14 So it's really a very agnostic approach to
15 trying to find associations tapping in to all kinds of
16 knowledge that describe the possible mechanisms that
17 could help us explain the physiology of CFS. So it
18 wasn't -- we didn't use a --
19 RADM KWEDER: So you didn't try and call out
20 the articles in first place. What you did, as I see
21 it, is you cast a very, very wide net.
22 DR. VERNON: It's all knowledge. It's all

1 knowledge.
2 RADM KWEDER: And in that process, you're
3 going to get -- you're going to start to see conditions
4 or symptoms, signs and symptoms coalesce into
5 groupings, and that is ultimately what you found.
6 DR. VERNON: Right.
7 RADM KWEDER: And you found that actually
8 there's probably more than one condition, or there's
9 more than one subtype of the condition, which is what
10 we heard yesterday, particularly from some of the
11 clinicians, that they're -- so there's probably -- this
12 is a heterogeneous, this is a probably heterogeneous
13 group of subsets.
14 DR. VERNON: So I think maybe the way, the
15 symptoms and the signs that we use to set up the
16 original search terms are inclusive of those that are
17 outlined in the Canadian criteria and in the
18 international criteria. So it's very, we tried to be
19 as inclusive as possible.
20 RADM KWEDER: Okay. So Melissa, I've got a
21 couple here for you, and I'm not -- you can decide if
22 you're comfortable answering to this level of

1 specificity. But do you -- is low grade fever a
2 surrogate marker?
3 MS. ROBB: I mean, yeah, I don't feel
4 comfortable commenting on specifics, and I think you
5 have to consider the disease also when you're looking
6 at certain outcomes and if there are appropriate
7 measures for that, but not being a clinical expert in
8 this area, I probably shouldn't --
9 RADM KWEDER: And let me see if I can take
10 this on a little bit. So is low grade fever a
11 surrogate marker? And the question is, a surrogate
12 marker for what? Okay? For what? And when you're
13 talking about surrogate markers, you have -- you're
14 looking at things that predict something else, and so
15 it depends. What is the something else that it
16 predicts?
17 So I use the example in HIV of viral load;
18 the amount of virus that can be measured in the blood.
19 We know that the amount of virus over time, in the
20 blood, actually predicts other kinds of illness and
21 prolong mortality. Prolongs -- the longer you can keep
22 the blood, the virus level low in the HIV patient, the

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1 longer the patient will live. Dr. Cox, is that a fair
2 description? Thank you. That's our expert.
3 So it's a surrogate marker for mortality.
4 That has been well established. Okay? That has been
5 shown. So it is used -- so when we first started these
6 studies of HIV, allowing the use of viral load, we
7 expected it probably would predict mortality down the
8 road, something else down the road. But the companies
9 under accelerated approval, were required to show that
10 it actually predicted that in subsequent -- by
11 continuing their clinical trial after the approval.
12 Another example. Orthostatic hypotension.
13 Midodrine is a drug that's used to treat orthostatic
14 hypotension. And the theory was that if you could show
15 an initial effect in the clinical studies of midodrine
16 on blood pressure, that it improved, it raised blood
17 pressure, that you could show over time, as a marker,
18 that patients clinically had fewer symptoms and just
19 did better and there were other measures that use that.
20 Trial after trial has been done since
21 midodrine was approved under accelerated approval, that
22 have failed to demonstrate that that is true. Nobody

1 can show this. It seemed so simple. And so there has
2 been a lot of controversy about whether that drug
3 should stay on the market or come off the market under
4 accelerated withdrawal, which is part of the approval.
5 So whether something's a surrogate marker
6 depends on what the disease is, what you're trying to
7 have show it as a surrogate marker of. And a great
8 example is cholesterol. Well established that lowering
9 cholesterol prevents heart attacks and strokes. We now
10 approve drugs on the basis of elevated cholesterol. We
11 don't make companies test those to demonstrate that
12 lowering cholesterol really does do that. We just
13 accept it. But that is -- it's a classic surrogate
14 marker.
15 So it depends and it's complicated but I
16 think -- but that's what we're talking about when we're
17 talking about Accelerated Approval is a marker that is
18 predictive of something else, but the key is, you've
19 got to show after the approval that that is, in fact,
20 the case. We have just dozens of these in many fields
21 that are involved. Is that -- anything you want to
22 add, Melissa?

1 MS. ROBB: Yeah, I mean I think I was going
2 to add that Sandy touched on was that at some point
3 surrogates are considered reasonably likely --
4 RADM KWEDER: That's right.
5 MS. ROBB: -- and are the basis for
6 accelerated approval. When we have that confirmatory
7 evidence, we can often use surrogates that were once
8 used for Accelerated Approval, for traditional
9 approvals.
10 RADM KWEDER: Absolutely. Absolutely. And
11 you know I am -- we are way over time. Way over time,
12 and we have a lot of other questions, but I'm just
13 going to say, we can't get to them. What I would like
14 you to do is I would like you to find the presenters
15 during lunch and ask them your questions.
16 We are going to have just about 30 minutes
17 for lunch, I'm sorry to say. So you may want to bring
18 your lunch back in here in the afternoon, back for the
19 next panel, for the third panel. So thank you very
20 much to all the panelists.
21 We'll take a very brief break. So mosey back
22 quickly.

1 (Break) Panel 2: Symptoms and Treatments: A
2 View from Clinicians and Patients
3 DR. MICHELE: So we are running quite a bit
4 behind, but we do want to take the full time for this
5 panel, because we feel that it's very important, so
6 unfortunately that means we'll be eating an abbreviated
7 lunch, but we have 50 minutes so we're going to finish
8 at -- just a little before 11:30 and then we'll have a
9 question and answer period for 15 minutes after that.
10 So I'm just going to start off and introduce
11 myself and then we'll go down the table. You all know
12 me, I think by now. I'm Terri Michele. I am a
13 physician by training, a pulmonologist. I am currently
14 a clinical team leader in the Division of Pulmonary,
15 Allergy, and Rheumatology Products at FDA.
16 Prior to that, I spent 10 years in industry
17 designing clinical trials. So the Division of
18 Pulmonary, Allergy, and Rheumatology Products is
19 currently the host division for all of the chronic
20 fatigue syndrome applications that come into the
21 agency, and I am also the agency representative on the
22 CFSAC.

1 So I'll turn it over to my co-moderator, Dr.
2 Nancy Klimas.
3 DR. KLIMAS: I'm Nancy Klimas. Many of you
4 know me; I'm a clinical immunologist from South
5 Florida. I recently left the University of Miami after
6 28 years and started a new institute called The
7 Institute for Neuro-Immune Medicine at Nova
8 Southeastern University in Fort Lauderdale. So I
9 didn't have to move. It was good.
10 It's been great and exciting and we're doing
11 really, really cool things, but I won't take the time
12 of this panel to describe all of that. But I have been
13 taking care of patients with ME/CFS for more than 28
14 years now, and I also split my time between chronic
15 fatigue syndrome related research and Gulf War illness
16 related research, and direct clinics in both of those
17 areas. So I'm very -- I'm veteran centric in much of
18 my research.
19 This new institute that we have is
20 establishing both clinics and the research world and
21 what's very cool about it is that that research world
22 is right on top of the clinic that architecturally we

1 put the clinic in with the lab and the research
2 scientists and the scientists have to walk through the
3 waiting area of the clinic, which is probably some sort
4 of HIPAA violation, but we won't talk about that.
5 But anyway, the patients, they get to see the
6 suffering of the patients and it's very, very
7 motivational for them to actually know you and see you
8 and share your stories. I think it really keeps their
9 eye on the target. So I'm very excited to be a part of
10 all of that. I'll pass the microphone to Cindy.
11 DR. BATEMAN: I'm Lucinda Bateman. I'm a
12 traditionally trained general internal medicine
13 specialist in Salt Lake City. I initially practiced
14 primary care for about 10 years, but since 2000 have
15 had a clinic called the Fatigue Consultation Clinic,
16 where we assess and treat patients with unexplained
17 chronic fatigue mostly within the spectrum of chronic
18 fatigue syndrome, ME, and fibromyalgia.
19 Oh, and I should add, too, that we also serve
20 as a center for clinical trials and research and that
21 arm of our clinic has increased in the last probably
22 five or six years.

1 DR. CORBIN: I'm Lisa Corbin. I'm the new
2 kid on the block. I'm from University of Colorado
3 Denver, and I got interested in taking care of patients
4 with CFS when I think naturally gravitated to our
5 nearly formed Center for Integrative Medicine 12 years
6 ago. So my background is internal medicine. I got
7 interested in integrative medicine because my patients
8 were asking me questions I couldn't answer about
9 alternative therapies and I thought, hey, there's a lot
10 of good stuff out there.
11 There's a lot of harmful stuff. We're not
12 training our residents and future doctors. We need to
13 do that. So that's how I got interested in the field.
14 And I think it was a pretty natural thing for patients
15 with CFS to gravitate towards alternative medicine,
16 because 12 years ago and still today, we don't have any
17 approved drugs to treat CFS.
18 So people are out there looking for anything
19 that might help. And so that, for a lot of people
20 involves exploring alternative medicine. So the last
21 12 years has been a journey for me, trying to learn
22 more and more about CFS and trying to help patients

1 have much better lives, and I've got all my comments
2 that I'll continue on with that, when we get back
3 around to it.
4 DR. CHU: I'm Lily Chu. I'm a patient. I
5 also have a background in internal medicine, geriatric
6 medicine, and health services research, and finally I'm
7 a board member for the International Association for
8 CFS/ME, which is a non-profit, scientific organization
9 that many of the clinicians and researchers attending
10 this meeting today are members of.
11 DR. MONTOYA: I'm Jose Montoya, Professor of
12 Medicine and Infectious Diseases at Stanford University
13 School of Medicine. My background is internal medicine
14 and infectious disease. I got into CFS after, in 2004
15 I had an encounter with one of my patients sent to me
16 for an infectious disease possibility and I got really
17 surprised and dismayed by the suffering that this
18 patient had gone through and I thought that there was a
19 possibility of an infectious agent behind the illness
20 or at least in the perpetuation of the illness.
21 And since then I have built a whole clinical
22 and research program at Stanford that is aimed at

1 hopefully one day be able to contribute in one or the
2 other to see what is the central process, the central
3 pathogenesis in CFS, what are the possible infectious
4 triggers that could lead eventually to treatments.
5 MS. WILLIAMS: I'm Chris Williams and I am a
6 patient. I became ill in 2008. I spent 30 years in
7 the federal government; about half that time on Capitol
8 Hill as a Health Policy Adviser for the Senate majority
9 leader, George Mitchell. And about the second half of
10 my career at the Agency for Healthcare Research and
11 Quality which is part of HHS.
12 When I became ill, I was still working and I
13 was able to work for about two and a half years with
14 accommodations from my boss. During that time I became
15 the representative for my agency to the CFSAC Chronic
16 Fatigue Syndrome Advisory Committee to the Secretary. I
17 now sit on the board of the CFIDS Association, so I am
18 both a patient and a patient advocate.
19 MS. SPOTILA: And I am Jenny (sic) Spotila.
20 I'm an attorney by training. I used that training for
21 just over a year before I got sick in 1994, and I've
22 been disabled since then. I got into advocacy in the

1 late '90s and have stayed in it. I served on the board
2 of the CFIDS Association for six years; was Chairman
3 for two.
4 After serving that term out, I started the
5 blog, Occupy CFS. Hopefully, you're familiar with it.
6 And cover the medicine, the research, the politics, and
7 the experience of being ill.
8 DR. MICHELE: All right. Well, thank you all
9 for your introductions. As you can see, we have a
10 rather illustrious panel here, and I'm very excited
11 about continuing the conversation that we had
12 yesterday. So what we're hoping to do today is kind of
13 build on that conversation and bring in the clinician
14 viewpoint.
15 But we've also, as you see, integrated
16 patients on the panel as well, because we want to make
17 sure that we're staying on track and seeing things from
18 a patient viewpoint. So this panel runs a little bit
19 differently than the other panels that you've heard
20 both yesterday and today. Panel 4 will run similarly
21 this afternoon. Panel Discussion
22 DR. MICHELE: The idea here is that we're

1 going to have some facilitated discussion. And so
2 we're going to go to -- they have not put all of my
3 slides in here. Okay. Well, with that, I will read
4 the questions to you. So question one is what were
5 your key takeaway messages from the discussion
6 yesterday on the most significant symptoms experienced
7 by patients with CFS and ME? So please also describe
8 any significant differences in your experiences as
9 clinicians or as patients compared to yesterday's
10 discussion.
11 DR. KLIMAS: And if I could add, for the sake
12 of time, if it's already been said by another panelist,
13 you don't have to repeat it, you can't just concur. So
14 we're going to try to answer a lot of questions in a
15 relatively short time. So we're going to roll down the
16 panel, let's starting with Cindy.
17 DR. BATEMAN: I made a priority list on the
18 plane of how I'd answer that question, and then I
19 tucked it in my binder and listened yesterday, and I
20 would say that the presentation of the patients matched
21 my list exactly. And that would be -- I don't think I
22 need to go through it, but this illness is dramatically

1 limiting in terms of physical and mental stamina.
2 It's characterized by post-exertional
3 malaise, which is flare of those severe illness
4 symptoms that involve cognitive impairment, flu-like
5 symptoms, disturbed sleep, a whole spectrum of pain,
6 autonomic symptoms, endocrine symptoms, and central
7 sensitivity. And I would add at the bottom of my list
8 that an important aspect is the psychological suffering
9 these patients go through because of their illness and
10 this came out; the fear and the despair that comes
11 along with this illness.
12 The takeaway point I came away with from the
13 meeting was the cognition and maybe the fear, were the
14 top on list was the horrible suffering from illness,
15 and the very severe limitations from the cognitive
16 limitations being high priority.
17 DR. CORBIN: I concur.
18 DR. CHU: Well, yesterday my experience was
19 very much like what many of the other patients
20 discussed here, and to prepare for this, Dr. Lenny
21 Jason (ph) and his team help me design and analyze an
22 online survey to answer some of the FDA's questions.

1 We had over a thousand people responding
2 nationally and internationally. And the responses I'm
3 going to talk about today come 360 to 470 responses
4 from U.S. residents with a confirmed diagnosis of ME or
5 CFS. And 50 percent of the population were people who
6 did not participate in the CFIDS survey, or will (ph)
7 be submitting responses to the FDA. So this is a
8 slightly different population.
9 But the five most significant symptoms we
10 identified from patients were fatigue, post-exertional
11 malaise, pain, sleep, and cognitive problems. And
12 symptoms that were brought up that haven't been
13 discussed as much in the past, but as patients
14 mentioned yesterday, were also mentioned in our survey
15 and these included multiple chemical or other
16 sensitivities, gastrointestinal symptoms and
17 orthostatic intolerance.
18 These symptoms were deemed to be significant
19 by over 50 percent of our subjects. We didn't really
20 talk about impact yesterday specifically, but people
21 did mention it in the discussion. What I'd like to say
22 is that we used the standardized measure of physical

1 functioning. We found our respondents to be more
2 disabled than 95 percent of the general U.S.
3 population.
4 And only 13 percent were employed, with most
5 people saying they could not work because of ME or CFS.
6 Even for a basic activity of daily living such as
7 personal care, 89 percent of our respondents needed
8 assistance or had to change their pre-illness routine.
9 On their worst days, 60 percent of our respondents were
10 bedridden, and on their best days, 75 percent were
11 mostly home bound and could only do some light
12 housework at most.
13 There are some other things I want to
14 mention, but I will mention that later.
15 DR. MONTOYA: Concur with the previous
16 panelists observations that the painful stories that I
17 heard yesterday, it certainly reflect the suffering
18 that the patients that I see at Stanford go through.
19 The two most salient clinical features include the
20 cognitive dysfunction for what I have observed and what
21 I heard yesterday, and the fact that the crashes are
22 unpredictable.

1 There are three observations that I didn't
2 hear yesterday or maybe I missed them, but one of them
3 that is common for our patients when we ask them, their
4 ability to drive, to drive their cars, gets
5 significantly impaired. And it's not a surprise,
6 because driving requires a lot of tasks simultaneous
7 while we call the perfect example of multitasking and
8 this gets impaired.
9 And you can see when the patient is doing
10 really bad, that it is always with someone with them,
11 accompany, because they're driving them. And when/if
12 they get better, significantly better, then you start
13 to see them coming to their visits alone.
14 The second issue is that we have observed
15 that there is a cohort of patients where herpes simplex
16 virus -- I'm talking about the common oral herpes or
17 even the genital herpes appears to have either
18 triggered their CFS; they say my illness started right
19 there, or becomes the perpetrator (ph), the trigger for
20 the ongoing CFS illness.
21 And I'm not saying that that could be the
22 only trigger for that patient, for those patients, or

1 it could be the only trigger for the whole illness.
2 But it appears that herpes simplex alone could be a
3 trigger or a facilitator of the illness in this cohort
4 of patients that we have, that have revealed that to us
5 and we have paid attention to that, and it seems to
6 work for that group.
7 And the third is that it has become clear to
8 us that in a given patient there are several triggers,
9 not just one event, that either starts the disease or
10 perpetuates the disease. You can't imagine when you
11 want to test the efficacy of a drug, how the effect of
12 the drug could be undermined or could be diluted if you
13 have several triggers happening in that patient
14 population.
15 So this is a fact to keep in mind when
16 designing trials, because we have noticed that lack of
17 sleep, cognitive, emotional, or physical overload can
18 trigger an exacerbation of CFS. And if the patient is
19 doing well on the drug because it's effective, but does
20 not have all these other factors controlled, including
21 a reactivation of a simple virus like herpes, you can
22 see how the data could become confusing in terms of

1 drug efficacy.
2 MS. WILLIAMS: I would say I would concur
3 with most of what was said yesterday. I think as I
4 tried to say in a couple of informal comments, I am
5 considered on the mild end of the spectrum. However,
6 the mild end isn't good either. You still have a lot
7 of significant impacts. And I think one of the things
8 about me that is a little different, is I became sick
9 at the age of 56, which I think is well along the end
10 of the bell curve in terms of the age of onset, and I
11 do wonder how that has affected, and how it will affect
12 me as I age.
13 I'm now 61 and I did not think I was going to
14 be spending my golden years on the couch. And so I
15 wonder how much the research may look into sort of the
16 double whammy of aging, this population aging, and what
17 affect that that's going to have.
18 The other issue, in terms of the kinds of
19 symptoms of concern -- my biggest problem or the thing
20 that bothers me the most is the flu-like symptoms that
21 come back if I have done anything and sometimes I don't
22 know what I've done. But the flu symptoms to me are

1 the worst thing that I have to deal with because it
2 makes me feel really sick, and I don't feel well enough
3 to do anything.
4 And I think the other thing that came up
5 yesterday, someone talked about fear versus anxiety.
6 Fear is sort of knowing something bad is going to
7 happen, and anxiety is anticipating it might happen. I
8 think for me from the time I got sick to now, one of my
9 greatest anxieties was that I would get worse.
10 And for the first couple of years, I was
11 pretty stable, and then after I retired, surprisingly
12 enough, I did get worse. And that to me is like a big
13 question mark. How could I have gotten worse when I
14 stopped working and I had all this off my plate and now
15 I was just going to focus on my personal life and --
16 but it was at that point I got worse.
17 So now I am anxious that I won't get better
18 or I will get even worse than I am now. So I think
19 that the fear, the anxiety of getting worse is
20 something I'm sure that all patients live with,
21 regardless of what level of severity they become ill.
22 MS. SPOTILA: I thought the comments

1 yesterday were outstanding and I just want to applaud
2 every patient who spoke, because I know it takes a lot
3 of courage to talk about something so personal in a
4 roomful of people when who knows how many are watching
5 on the web. So you should be applauded for that. You
6 should feel really good about your presentations. And
7 I think one of things that struck me from the first
8 panel was Dr. Kaiser talking about the working ill and
9 as advocates we focus so much on the severely ill,
10 making sure they have a voice, making sure they can be
11 seen.
12 But I know so many people who struggle to
13 work and function or raise their children with this
14 illness and they look okay, but they go home from work
15 at the end of the week and they collapse and we can't
16 lose sight of these people as well, because they are
17 part of the patient community.
18 We talked at length yesterday about the post-
19 activity collapse, trying to describe the different
20 kinds of crashes, not being predictable, but one word
21 that none of us used was fatigue or tired. Those are
22 placeholders to me. Those are code words. We say

1 we're tired. We say my fatigue is bad, but that's not
2 actually what we're saying.
3 What we're saying is the five minute
4 description of what a crash is and what I did the day
5 before and how I'm going to pay for it for two weeks.
6 Cognitive issues, people spoke very compellingly about
7 that and all of the different domains of cognitive
8 function that are affected; not just concentration and
9 memory, but executive function, decision-making,
10 processing time, and I think that's relevant for
11 designing trials.
12 If you want to measure whether someone is
13 improving in cognitive function, you better measure
14 multiple dimensions in order to capture where they
15 started and where they finish to see if there was
16 improvement. And then also cognitive endurance is very
17 much like physical endurance.
18 Someone spoke about having social time for an
19 hour and 45 minutes and if you go half an hour over
20 that, you're in really big trouble. I think Dr. Kaiser
21 talked about going to his wife and saying, we have to
22 leave the party right now. And I know I have a look on

1 my face that my husband can look at me and say, we need
2 to go right now.
3 Someone spoke about the domains or the
4 dimensions of the illness being so intertwined. So a
5 bad nights' sleep is going to make everything worse the
6 next day. If your IBS and your gut issues kick up,
7 it's everything else is going to be worse. It's all
8 intertwined and that creates more challenges I think
9 for designing clinical trials.
10 And then differences, we didn't talk about
11 gut disturbances yesterday very much. Orthostatic
12 intolerance and I think we didn't talk about how those
13 issues can be masked. So I never tested positive for
14 any actual orthostatic intolerance issue, but when I
15 started wearing a heart rate monitor for pacing
16 purposes, I found I was having episodes of tachycardia
17 that I could tie to physical symptoms of episodes that
18 I experience, and so tried some beta-blockers and they
19 improved.
20 So there are probably lots of symptoms we
21 have that could be measured, that could be identified.
22 We're just not necessarily looking at them the right

1 way. And then in terms of pain, I talked about that a
2 little bit yesterday; others did as well. Again, code
3 words.
4 Muscle pain, there's 15 different kinds of
5 muscle pain, where it is, what it feels like, how
6 intense it is, does it come and go, and that's a very
7 big issue. For me, it's been a big part of the
8 struggle with the illness, and not just muscle pain.
9 Joint pain, we talked about that. Lily mentioned
10 stomach pain and nerve pain. I have times where it
11 feels like my spine is on fire, literally, on fire, and
12 I'm this close to going to an emergency room.
13 And what stops me is the diagnosis. Because
14 I know I won't get treated. So there's again, a lot of
15 suffering that is going under the radar. We're not
16 going to providers because we don't think we're going
17 to get the care that we need in that moment.
18 DR. KLIMAS: Thank you. That was very
19 helpful. And I'm just going to make one comment about
20 fear and anxiety. It just struck me that I spent the
21 first -- I've been a HIV provider forever, since before
22 the dizzies began, and I remember spending the first

1 half of our HIV time with patients talking about fear
2 and anxiety. Half the appointment was about instilling
3 hope and getting people to hang on.
4 And I think that that's -- I just feel like
5 I'm -- that's exactly what I do in my chronic fatigue
6 practice. I spend half of my appointment trying to
7 instill hope and getting people to hang on, because I
8 think that we are progressing in science and that there
9 is hope to be had. But it's hard when you live in this
10 illness to see it when you're suffering. And it's just
11 like coming all around again, but we've all been there.
12 Our next discussion point is what kind of
13 clinical variables do you, the panelist, think the most
14 relevant for clinical trials? What might be valid,
15 quantifiable, reliable outcome measures or endpoints
16 for clinical trials when we evaluate future therapies?
17 And anyone can jump in. It doesn't have to
18 be Cindy every time.
19 DR. CHU: Well on our survey, first I wanted
20 to say that I think any symptom of CFS and ME could be
21 used as a valid quantifiable or reliable outcome
22 measure. It just depends on which scales you want to

1 use or which tests you want to use, depending on the
2 drug you want to test.
3 We did ask in our survey about five objective
4 tests that have been commonly researched or talked
5 about, and 66 percent of our respondents had at least
6 one abnormal result. So for example, for natural
7 killer cell activity, which Dr. Klimas is an expert on,
8 70 percent of the people in our survey noted an
9 abnormal result.
10 And our thought is tests like these could be
11 used as study inclusion criteria, as outcome measures,
12 and as a way to select subgroups for analysis. We
13 believe that studying subgroups may yield more
14 effective treatments given the heterogeneous nature of
15 CFS, rather than CFS as just an overall disease.
16 The second comment I want to make is that
17 it's very important to come up with a good outcome
18 measure for post-exertional malaise. And later today,
19 Dr. Chris Snell is going to talk about one way to do
20 that with cardiopulmonary exercise testing. My thought
21 is that even though post-exertional malaise has been
22 mentioned as a symptom of CFS since 1994, it wasn't

1 until the last few years that it's really been defined
2 within the CDC, and then also within the Canadian and
3 international consensus criteria.
4 I think when physicians think of post-
5 exertional malaise, they think of post-exertional
6 fatigue, which is not the same thing. Post-exertional
7 fatigue is very common in a lot of other illnesses;
8 chronic lung disease, chronic heart disease. Post-
9 exertional malaise is more than fatigue. Yesterday you
10 heard people describing how they have sore throats as
11 part of it or as a precursor to it.
12 You have the collapse. You have the
13 confusion. This is a symptom that needs to be explored
14 more in CFS. And as Dr. Michele, you said yesterday,
15 she was asking about the timing and the duration, there
16 just isn't enough basic research on post-exertional
17 malaise.
18 The third concept I want to bring up is a
19 concept I've been learning about recently. It's called
20 fatigability. It's a concept from geriatric medicine,
21 and the difference between fatigue and fatigability is
22 fatigue has to do with the perceived sensation of not

1 having enough energy to do certain activities.
2 Fatigability not only talks about the
3 subjective sensation of fatigue, but in relation to
4 what activities. So rather than just asking people
5 about how tired are you? Are you tired today? You're
6 asking people about, are you tired when you try to make
7 the bed? Are you tired when you're trying to brush
8 your teeth? And putting it and relation to that. And
9 the reason why that's important is in the elderly we
10 know that people self-pace.
11 They match their activity to their energy
12 level and it's similar in CFS. So if you're testing a
13 drug and someone tells you it decreases their fatigue,
14 you have to think about, okay, is it also because they
15 decreased their activity at the same time? Because if
16 they did decrease their activity at around the same
17 time, that drug might be effective for fatigue, but
18 it's not really helping the person improve their
19 function. So those are my comments.
20 DR. MONTOYA: I think that based on our
21 experience it's important to, yes, to try to capture
22 all the symptoms, all the issues that affect the

1 patient's day-to-day lives, but at the same time to
2 carefully separate one from the other.
3 In our experience in using certain antivirals
4 in a group of CFS patients, we have noticed that a
5 group and we have a paper, a peer review process now
6 for a double-blinded, randomized, placebo-controlled
7 trial that shows that an antiviral could be helpful in
8 a small group of patients and in those patients we have
9 noticed that clearly there is a cognitive improvement
10 that occurs earlier than the physical fatigue
11 improvement and it was only captured when we went to
12 our main endpoint that was the multidimensional fatigue
13 inventory questionnaire, when it was captured by one of
14 the subscores that emphasizes the cognitive fatigue.
15 So it was only when we pay attention to that
16 subscore that it became clear that there was a benefit
17 in that trial. And you could imagine the following
18 scenario, which has occurred in our patients where if
19 they have the early cognitive improvement, the first
20 thing a patient wants us to do something, because they
21 feel better in that area, and you can see how that
22 feeling of cognitive -- more clarity could lead to more

1 activity inadvertently and then leads to a crash, et
2 cetera.
3 So separating what constitutes fatigue,
4 separating the physical fatigue from the cognitive
5 fatigue has been helpful for us and could be helpful in
6 other trials. The other aspect that we have noticed is
7 the statistical methods appear to matter. So if you
8 just simple measure what happened at the end of the
9 trial and compare that time point in your endpoint with
10 a baseline, again you may not get the statistical
11 significance that you are pursing, because the disease
12 is inherently very highly fluctuating.
13 So patient status changes day-to-day, week-
14 to- week, month-to-month, and there are statistical
15 methods like the so-called mixed effects linear
16 regression methods that allows to capture what happened
17 in all the time points of the endpoint over time. And
18 when you plot the two, then significant differences
19 come evident between the placebo and the treatment
20 groups.
21 And by the way, that difference between using
22 this statistical method versus the other was the same

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1 issue that investigators in Norway faced when they
2 analyzed the rituximab data. It became clear that
3 rituximab in the patient population was doing something
4 when they used these statistical method that takes into
5 account all the points, all the time points in the two
6 groups and not just the beginning and at the end.
7 And lastly, I think that in addition to
8 carefully choosing the endpoints, we have also noticed
9 that it may be key for the design of clinical trials to
10 keep in mind when you randomize the patients whether
11 they have vital onset, abrupt onset or not, the
12 duration of the illness, it's really hard to believe
13 that a patient with CFS of two years duration will have
14 the same pathogenesis as someone with 20 years
15 duration.
16 So that needs to be taken into account. The
17 female/male ratio appears to be important, and the
18 severity of the disease at baseline before they are go
19 into the clinical trial.
20 MS. SPOTILA: I want to put a big exclamation
21 point on the time issue and the variability of the
22 condition. I think that's absolutely critical and I

1 can give you an example. It ties into what Dr. Munos
2 was talking about in terms of data measurement and
3 automatic data collection. I started wearing a FitBit
4 in January.
5 So I went back and checked my data to tell
6 you that my lowest day was 839 steps in 24 hours. My
7 best day where I was really working hard was 3,630
8 steps, which is 36 percent of what's recommended for a
9 normal person, but that was my maximum effort. But
10 that doesn't just tell you about the difference between
11 the healthy recommendation and my max, it also shows
12 you the huge variation in my functionality between 839
13 and 3,630 and how dramatically different those days
14 were.
15 So if you only checked my steps in the first
16 week and the last week, you missed 839 or 1,100. You've
17 got to measure that data all way across and it will be
18 more expensive for data analysis, but it will give you
19 a real picture of functionality over time.
20 MS. WILLIAMS: Yeah, I'm just going to concur
21 with what others have said.
22 DR. CORBIN: So I'd like to concur as well,

1 but I'd like to highlight a couple of things. One is I
2 think it's very important to follow the symptom that's
3 most distressing to the patient, and as we've heard,
4 that's also going to be the most challenging thing for
5 research given the heterogeneity of symptoms.
6 And I was struck by what Lily mentioned about
7 function, and that's something that I think we, as
8 clinicians, find very important, but the functional
9 scales that are out there will measure certain
10 activities, but these may not be activities that are of
11 interest or important to the patient sitting in front
12 of you.
13 So for example, I think it was one of
14 Denise's sons who could read a book for two hours. Was
15 that you? Somebody's son couldn't read a book at all
16 and then was able to read a book for two hours. I can
17 guarantee there's no functional scale that's been
18 validated that says, how long can you read a book?
19 So I think there may be some different
20 challenges with doing CFS research that we should
21 definitely look at function as an outcome, but we may
22 need to work on changing some of the ways that we

1 measure function to be more specific for this patient
2 population.
3 DR. CHU: I just wanted to make a quick
4 comment about what Dr. Corbin just mentioned. The
5 paper I was reading was by Basil Elbida (ph), who's a
6 National Institute of Aging Program Officer, and in it
7 he did talk about some measures of fatigability. And
8 so that's true that there are no validated measures of
9 fatigability yet. But one of them, for example,
10 Dutchwin (ph), it did talk about duration of activity
11 including cognitive activities, but that's not a valid
12 survey yet.
13 And the second piece of it is he did talk
14 about in the paper using devices like the FitBit
15 accelerometers actigraphy to look at, to objectively
16 measure activity and then sort of correlate that with
17 fatigue, but those measures are in progress.
18 DR. BATEMAN: When I looked at this question
19 I answered it; there were three points I wanted to
20 make, and one was a literal answer to this question
21 which asks what symptoms could be endpoints? And I
22 thought that was a little bit narrow, but -- because I

1 think we might not be able to use symptoms as endpoints
2 necessarily, but -- so I answered that question first.
3 And I do believe that almost every major
4 symptom of this illness, particularly in the priority
5 order is quantifiable and could become a reliable
6 outcome measure, and I made a list starting with what I
7 thought would be the most useful and I started with
8 cognitive impairment. Then the ability to remain
9 upright or orthostatic intolerance. Measures of
10 function and measures of post-exertional malaise, and
11 certainly pain and sleep are easily quantifiable.
12 And we use those tools clinically all the
13 time to assess treatment and treatment progress in our
14 clinic. So I think they can be translatable to
15 endpoints for research. We also -- this is the second
16 part of the question, actually have a lot of objective
17 measures that have been mentioned in the literature
18 that could immediately be assessed and perhaps
19 considered for inclusion as outcome measures, and that
20 includes all the measures of orthostatic intolerance we
21 have, beside lean tests, and tilt table tests.
22 We have cardiopulmonary exercise testing. We

1 have the immune tests that have been talked about and
2 we have a growing literature of gene expression
3 particularly in relation to certain activities such as
4 a stressor or an exercise stressor and what me might
5 see. So all of those are going to be the potential for
6 objective tools as outcome markers.
7 The last thing I wanted to say is that
8 symptoms are tricky in the measurement of -- as an
9 outcome marker, because as a patient's ability to
10 function increases, they increase their function. They
11 do more. And they'll do more to the point of eliciting
12 symptoms.
13 So sometimes symptoms are -- unless you
14 control for function in a clinical trial, in other
15 words tell people not to change their level of function
16 at all, sometimes symptoms become -- they tell you the
17 wrong message. And I see that naturally people
18 increase their activity until they're limited. So
19 those are things that need to be taken into account in
20 the design of studies.
21 DR. KLIMAS: And I would underscore that.
22 There was a very good example of a clinical trial,

1 placebo-controlled study, done beautifully at the
2 University in Antwerp. It was a growth hormone. They
3 had 8 of 24 people go back to full-time employment from
4 disability.
5 Their primary outcome variable was quality of
6 life and it didn't change. So it was a failed clinical
7 trial. But clearly, the function truly improved. So
8 it's extremely important to make note and makes us more
9 and more think that maybe function should be our
10 primary outcome variable, not symptoms, because
11 patients will push to symptoms. They do it all the
12 time, every time, no matter what you tell them.
13 DR. MONTOYA: Just one point, Nancy, to
14 illustrate how tricky that can be. We at the very
15 early stages in our clinic, we used to ask the
16 patients, give us a percentage of how much you can do
17 physically. And then they would say, well, right now
18 before starting your therapy, I can only do 20 percent.
19 And then a year later after multiple visits, there was
20 clearly an improvement in the patient situation and
21 then we'll ask the question again, and they will say 20
22 percent.

1 And then say, well, but you clearly are much
2 better than last time you said 20 percent. And what
3 has happened in certain patients is that the 20 percent
4 is very relative, obviously. So the 20 percent at the
5 beginning, before they were clearly better, was the 20
6 percent of the world that they have adjusted and
7 downsized.
8 But without realizing that world had expanded
9 to a bigger world where it was still 20 percent. So it
10 really is very tricky to just if you go with certain
11 measures. Another scale besides the MFI-20 that we
12 have found helpful that appears to track, appears to
13 track the patients improvement is the very simple scale
14 of the fatigue severity scale, FSS, in our hands seems
15 to work.
16 DR. MICHELE: Thank you so much. I think
17 that is absolutely critical and I'm so glad that people
18 brought out that point, because I think that that
19 applies not just to chronic fatigue syndrome, but it's
20 a natural human approach to things, and I know it
21 certainly applies in other fields such as COPD, where
22 we have patients all the time who come in and you ask

1 them how short of breath they are, and they'll tell
2 you, oh, I'm not very short of breath at all.
3 And you'll say, well how many steps can you
4 go up? And they say, oh, I don't go up steps anymore.
5 I always take the elevator because I get short-winded
6 when I do that. So it's just a natural approach to
7 things, but it's a real confounder for clinical trials
8 that we absolutely have to take into account.
9 So with that, I think we'll move on to
10 question number three. And this question, what are the
11 key factors that you take into account when making
12 decisions to prescribe as clinicians or use as
13 patients, therapies to treat symptoms associated with
14 CFS and ME? And this is intended to get at some of
15 that clinician intuition kind of piece that we heard
16 Suzanne Vernon speaking about earlier.
17 DR. CORBIN: So I think the first thing that
18 comes into mind as far as a key factor goes is the
19 patient input. So with all patients I see, whether CFS
20 or other diseases, my initial words to them are what
21 are they hoping to accomplish and what do they want to
22 achieve, and make sure that I'm in partnership with

1 them. Which I think, especially for me, is critically
2 important. People come to the Center for Integrative
3 Medicine. They have no interest in acupuncture.
4 I don't want to push the acupuncture on them
5 if that's not of interest to them. I want to have a
6 discussion about it, but -- so that they feel they have
7 the information to make the decision, but the first key
8 factor is patient preference, their concerns and their
9 input.
10 Then I've just bullet pointed my other
11 comments for time. I would like to treat the most
12 disabling symptom first. I like not to make too many
13 changes at once. Sometimes I look at a patient and
14 say, oh, wow, we could change this and do this, and do
15 this. And then I think that just muddies the water so
16 much you have no idea what's helping, what's not
17 helping, and you run the risk of increasing side
18 effects and then start chasing your tail.
19 I like to start low and go slow, recognizing
20 that many patients with CFS have a different tolerance
21 to medications than patients without CFS who might use
22 the same medication. I also like, especially with the

1 pain management piece, to consider retrying a
2 medication which worked in the past.
3 So I hear from patients a lot that a low dose
4 of amitriptyline, for example, used to help them sleep
5 and they think it did have an impact on their pain, but
6 after a few months it quit working and they haven't
7 been using it in two or three years.
8 If you can identify a treatment that had
9 worked in the past, rather than just throwing it out
10 for good, I think sometimes it makes sense to revisit
11 things that have been successful. And after the body's
12 had a chance to not see them for a while, it may be
13 successful again.
14 I also like to try to kill two birds with one
15 stone, as possible, and minimize the amount of
16 medications. And so if there's a medication that may
17 help sleep and pain, that's going to win over a
18 separate medication for sleep and a separate medication
19 for pain.
20 And then I also think of each patient as
21 being their own clinical trial. So we don't have a lot
22 of research to guide us, but we do have the patient

1 experience, and so as we're hearing about function and
2 symptoms, that becomes very important even in the one-
3 on-one clinical trial that we're doing with our
4 patients.
5 I also like to be very mindful of financial
6 and time burdens, especially with the integrative
7 therapies that might be offered. Because something
8 like acupuncture could require somebody to travel from
9 their home, go to an acupuncturist, spend money that's
10 -- that treatment is not covered by insurance, go home.
11 And it's not a onetime deal. You need to give it at
12 least three to five treatments to know whether or not
13 it's going to work, and then if it works for you,
14 trying to limit the amount of time between -- or trying
15 to increase the amount of time between appointments is
16 a goal.
17 Our therapists are very good at teaching
18 people things they can do on their own. My overall
19 goal is to return as much of the care to the patient,
20 to the patient, and our providers are good at that. If
21 massage is helpful, they'll have a spouse come in and
22 learn some techniques, so that they can do massage

1 without getting carpal tunnel themselves.
2 Our acupuncturists will teach people
3 acupressure, and we try to be very, very mindful of the
4 financial and the time burdens. And along those lines,
5 if there's a therapy covered by insurance, I like to
6 highlight that with a patient, what's covered versus
7 what's not.
8 And then some of the other things that we're
9 heard about. Physical therapy -- I can't just send my
10 patients to the physical therapists. They come back
11 much, much sicker. You have to work with a physical
12 therapist who understands the condition. And the same
13 thing is true for psychology. You can't send somebody
14 to the psychologist who doesn't have a knowledge of
15 CFS.
16 You need to send someone to the psychologist
17 who can work with them on building tools to actually
18 improve their symptoms.
19 DR. KLIMAS: Cindy?
20 DR. BATEMAN: I would say that the key
21 factor, the primary factor I take into account is how
22 to return a sense of control to the patient to do self-

1 management. And this rests on this balance between
2 quality of life and the ability to function better, and
3 we take those things into account, and the treatment
4 has to be completely individualized to the patient and
5 you have to -- it's quite important to take into
6 consideration the risk benefit analysis every time you
7 do an intervention.
8 And that not only is the risk in terms of
9 safety, but in terms of cost, all kinds of costs it is
10 for the patient, versus whether or not it's actually an
11 effective treatment. I mean many times I'll ask a
12 patient about a medication and they'll tell me how much
13 acetaminophen or how much ibuprofen they're taking.
14 And I'll say, well, but does it help your
15 pain? And they'll say, no, it doesn't. And I say,
16 well, why do you take it? Because I have so much pain
17 and it's a pain medicine. So really trying to educate
18 patients about how to judge that risk benefit when
19 we're doing interventions and empowering them to make
20 those decisions day-to-day for all aspects of their
21 symptoms.
22 And then we kind of have a hierarchy of

1 managing comorbidities, managing other medical problems
2 primarily. Second, is teaching pacing and that
3 includes activity, physically and cognitively, but also
4 the orthostatic component. Patients naturally do what
5 we call a recovery position, which getting more supine,
6 and we've used a really interesting measure of upright
7 activity in our clinic that's been very, very helpful,
8 that upright activity is defined as feet on the floor,
9 and supine or recovery activity is when you're lying
10 down or have your feet up.
11 And I've discovered for most of my CFS
12 patients, the time they spend in upright activity is
13 somewhere between two to six hours per 24 hours. Most
14 patients are well-adapted. And our goal is to get that
15 higher. So we work on pacing and then primarily help
16 the patients learn how to manage cognitive symptoms,
17 this restorative sleep we've talked about, manage pain
18 appropriately and orthostatic intolerance and to avoid
19 deconditioning.
20 And when we prioritize the symptoms and
21 individualize them to the patient, and with a light
22 touch, try to understand the best treatment for that

1 patient, it's really empowering for them for self-
2 management.
3 DR. KLIMAS: Jose?
4 DR. MONTAYA: So concur with Cindy. The
5 first priority is to see how can we prevent that the
6 patients go into this wild fluctuations of their
7 disease, and if there is anything that they can do to
8 reduce the fluctuations. I used to use the words
9 cognitive behavioral therapy and physical greater
10 therapy, until Lily Chu taught me that could be a
11 misuse by some people to say that that's the treatment.
12 So we stopped using those two terms and we are now
13 partnered with a very good program in Palo Alto, where
14 patients are taught to deal with the feelings of guilt
15 about adjusting and downsizing your life to prevent
16 these wild fluctuations and address, as Cindy
17 mentioned, the sleep issue.
18 And then as an infectious diseases
19 specialist, I try to go to see if we can in a
20 reasonable way and the most objective possible way to
21 address the issues of infectious triggers. The very
22 first level that we try is doing a PCR, the polymerase

1 chain reaction test, PCR for Herpes 6 and EBV.
2 We do have a small cohort of patients that
3 are what we call chromosomally integrated, HSV6 with
4 viral loads of several millions in their blood, and
5 those patients are put in a very separate special
6 protocol, a very aggressive antiviral therapy. And so
7 those have to do separately because it's a different
8 nature of the disease.
9 And then those who are PCR negative, which is
10 the vast majority, undergo a series of biological
11 testing, antibody testing, to see if we can, in a
12 reasonable way again, see whether the trigger is HSV1,
13 HSV2, BCV, especially for those with significant pain
14 in one side of their bodies, herpes 6, EBV, in the
15 herpes viral world.
16 And then according to the epidemiological
17 history carefully obtained, we see if there is a risk
18 factor for queue fever or brucella, where we have a
19 very tiny small group of patients that when properly
20 identified, they seem to have responded really well to
21 the therapy of these pathogens.
22 And I cannot thank enough to the group of

1 physicians in the area that help us with the symptom
2 targeted therapy, because as I have gone into
3 infectious diseases, my skills in the other areas of
4 internal (ph) medicine has decreased. So I get the
5 help of my colleagues in the area in managing the pain
6 and sleep issues with appropriate treatment.
7 DR. KLIMAS: Just one sec. We're going to
8 keep this really tight now, because we're getting
9 really close on time, so target.
10 MS. WILLIAMS: Okay. I just want to make one
11 comment that hasn't come up and that is patient
12 compliance. And I, you know, I spent 30 years in
13 health policy and know a lot about the healthcare
14 system. And yet as a patient, I'm not always compliant
15 with some of the recommendations, not necessarily the
16 medications, but the cutting back, et cetera.
17 In fact, my doctor, who's quite a character
18 himself was at an event a few months ago and there was
19 another one of his patients there who he introduced me
20 to, and he said, well, you know, this is my other
21 patient who takes my advice better than you do. So I
22 think that when we think about physicians making

1 recommendations either for pharmaceutical help or
2 pacing and other kinds of really self-management, the
3 whole patient compliance side, I think is something we
4 have to think about and both as patients and
5 physicians.
6 MS. SPOTILA: Just in terms of the risk
7 benefit analysis need how I as a patient think about is
8 that a treatment or a medication that I want to try,
9 first thing I always ask is, is there a study, a good
10 study on it? And the answer is usually no. So then we
11 move on to what's the mechanism of action? Is there an
12 indication that it will help sleep, so it's worth
13 trying, and working through that.
14 And then I will ask, are there risks of
15 serious side effects like liver toxicity or something
16 like that. I don't even bother to ask about headache,
17 dizziness, constipation, is it going to make me drowsy,
18 is it going to make me dizzy? I don't even bother to
19 ask, because I'm already dealing with all that stuff.
20 So unless it's going to have some sort of big
21 impact, which I will find out when I try it, I don't
22 bother. And then my risk tolerance, I'm probably a

1 little more risk adverse than most patients, but my
2 risk tolerance shifts based on the amount of data,
3 based on what we know about the drug, and what we know
4 about its mechanism of action, and based on what we
5 know about CFS patients.
6 And so I work with my doctor to do a
7 calculation and then start very, very low and go up
8 very slowly, and the same thing for coming off a med if
9 it doesn't work, coming down very, very slowly over a
10 long period of time. And I work with a doctor who's
11 not a CFS specialist. So my experience might be more
12 similar to a lot of the patients who aren't here today,
13 they work with their local doctor, maybe the person who
14 diagnosed them, and they're not going to try all of the
15 antivirals.
16 They're not going to try all of the things
17 that the specialists are using, and I think that's a
18 perspective we have to keep in mind. There are a lot
19 of us working with doctors who are not trying all the
20 latest things, so we need good data to bring to them to
21 show it's worth trying X drug or X treatment.
22 DR. CHU: Okay, so I just wanted to say that

1 it seemed like from our survey that factors that played
2 into why patients stopped or changed their medication
3 included side effects and cost, as well as dependency
4 potential, and withdrawal potential of some of the
5 sleep and pain medications out there.
6 Another reason was, as Dr. Corbin had
7 mentioned, decreased effectiveness over time,
8 especially with sleep medicines. For me personally,
9 aside from just what some people have already
10 mentioned, both as a patient and as a prescriber, I
11 think about long-term side effects of medications.
12 It seems like most medicines in CFS,
13 Ampligen, other antivirals, you have to take for a long
14 period of time. And so I think long-term side effects
15 are worth considering. Secondly, because a lot of
16 people affected with CFS are women of child-bearing
17 age, I also think sometimes about the teratogenic
18 effects of medications and also about any effects on
19 breastfeeding, because people are taking other
20 medications.
21 They have other medical conditions and
22 they're taking other supplements, you have to think

1 about interactions. And finally, as Jenny alluded to,
2 I think about the experience of the treating physician
3 with specific treatment, especially with cutting edge
4 treatments.
5 DR. BATEMAN: I just wanted to make a quick
6 statement about symptom management versus treatment of
7 the core disorder because there's some angst about that
8 concern. And after my several decades of experience, I
9 want to say that symptom management and the ability to
10 do self-management is really important for quality of
11 life and to stabilize the illness to a point that we
12 can see what the illness is, right, out of all its huge
13 variation.
14 And I also say that I think symptom
15 management has improved function a little bit, but that
16 the core illness remains severely disabling even with
17 very good symptom management. So we need to have
18 efforts on both fronts, because we don't have a core
19 treatment. We need to apply the treatments we have, so
20 that we can then move forward on core treatments.
21 DR. CHU: Can I have one last comment?
22 DR. KLIMAS: Go right ahead.

1 DR. CHU: I just wanted to emphasize that
2 also in our survey with pacing that was considered one
3 of the top treatments in terms of coping with day-to-
4 day function. And on the other side of it though,
5 exercise programs that are administered by
6 professionals and are recommended by some medical
7 authorities were noted by 62 percent of patients as
8 worsening their health. Now this does not mean that
9 all exercise is bad. It means that exercise has to be
10 done in specific ways, such as taking into account
11 orthostatic intolerance, meaning as someone mentioned
12 earlier, exercises lying down or sitting down.
13 And also you have to take into account the
14 time and the frequency and the intensity of the
15 exercise. And as Dr. Corbin mentioned, the unfortunate
16 situation is a lot of physicians, therapists, other
17 health professionals, do not know enough about exercise
18 and CFS to prescribe it in a way that's beneficial and
19 not harmful to patients.
20 DR. KLIMAS: Thank you very much. It was
21 really very, very helpful. It was a great set of
22 comments. I'm a clinical immunologist and I'll just

1 pitch in, because it didn't get mentioned that there
2 are treatments that would enhance or modulate immune
3 function that are also often used by various providers,
4 myself included. We are really running out of time,
5 but we have one really important final question, which
6 is what would your -- if you had a drug that you would
7 like to explore, or an intervention you'd like to
8 explore, what would be your top one or two or three
9 choices? I just want to say them, not discuss them,
10 because we're just going to run down, running down the
11 group here.
12 DR. BATEMAN: My priority list were
13 antivirals and immune modulating drugs on top. Next
14 would be symptom management drugs like for pain,
15 stimulants for cognition, sleep meds, and then meds for
16 orthostatic intolerance which would include midodrine,
17 beta blockers, fludrocortisone, and desmopressin.
18 DR. CORBIN: I'm good with that list.
19 DR. KLIMAS: You're good with that list?
20 That was good, Lisa. Lily?
21 DR. CHU: Yeah, I agree with that list
22 mostly. I think the important thing is to subgroup the

1 subjects either by history, labs or other tests,
2 because what has been shown to be effective either in
3 studies or in anecdotes has always been done in
4 subgroups. It's not everyone with CFS benefited from
5 it. So I think that's really important. But
6 otherwise, antivirals, immunomodulators as mentioned.
7 Orthostatic intolerance treatments are really
8 important, because it has such a huge impact on
9 people's function and there are treatments out there
10 for it. Someone else had mentioned in our group,
11 rifaximin for IBS related symptoms in CFS can help some
12 people, too.
13 DR. MONTOYA: Antivirals are primarily
14 targeting herpes viruses and I agree with Nancy
15 wholeheartedly about the role of immunomodulators. It's
16 becoming more and more obvious to us by many reasons,
17 for many reasons, that it is the immune response to the
18 infectious agent what appears to driving the symptoms
19 and what we try to do by suppressing the infectious
20 agent with the antiviral or antimicrobial is to prevent
21 the immune cascade that comes afterwards. But in some
22 patients it might too late and you may have to tap into

1 the modulation of their immune system.
2 MS. WILLIAMS: Yeah, I'll concur with the
3 rest of the panel on their suggestions.
4 MS. SPOTILA: Ditto, and I would add we need
5 a trial of rituximab, a large scale, double-blind,
6 placebo-controlled trial of that drug. And if there
7 are any products out there that will affect anaerobic
8 threshold in VO2 max performance, please, please, study
9 them now, because that I think could have great
10 potential to improve the functionality of patients.
11 Audience Question and Answer Period
12 DR. KLIMAS: Okay. So we have questions from
13 the audience. We're digging through the yellow cards,
14 and I think there was one kind of interesting question
15 that should be addressed, and this goes to the point
16 that there are so few expert sites, something that
17 CFSAC has discussed endlessly, and that it's very
18 difficult to enroll in clinical trials from a distance,
19 and is there some way to have distance designed into
20 clinical trials? How do we cope with access to
21 patients and patients' access to clinical trials?
22 I can start that one. There's an example we

1 have, of course this happened to be an easy one, sort
2 of easy, we didn't think it was easy, to implement at
3 the time, but we have right now a spouse CBT protocol
4 that is a video group session that is done long
5 distance and people can enroll from long distance and
6 the labs are done at the local Quest lab, and we
7 designed a study that you didn't have to come to the
8 site to participate in.
9 Now that doesn't happen to be a drug
10 intervention, but with very safe drugs where the
11 efficacy can be tested and the safety using distance
12 models, I don't see why you couldn't design clinical
13 trials with distance in mind.
14 Anyone have any ideas about that? Any
15 thoughts? Then let's move on. Let's pick another one.
16 We have two questions here that ask about
17 immune markers, viral markers, immune modulators, and
18 so on. You heard Lily say that something like 70
19 percent of the patients have had natural killer cell
20 functional study done in this survey, and yet it's "not
21 in anybody's guidelines to do these things."
22 And it shows how far those of us that

1 practice this care actually go -- that we believe
2 strongly that the biology is there, the science is
3 there to justify these types of measures, and that the
4 measures actually influence the care of the patients.
5 And I'll say that for myself. That I'm an
6 immunologist; of course I'm going to measure the immune
7 system, and if I have a way to treat the immune
8 abnormalities I have, I will try to find a way to treat
9 those, and those are certainly the clinical trials I'd
10 be the most interested in pursuing.
11 And I'm sure with Jose, the same way. It
12 might not be in the guidelines to PCR for EBV, but you
13 have -- you're an infectious disease expert and you
14 have the tools to treat those things. Of course, you'd
15 want to measure them. And so we do have a bit of a
16 problem here, a disconnect between guidelines that feel
17 20 years old, even though they keep being revised more
18 recently, and the actual way we practice medicine and
19 take care of patients.
20 DR. CHU: I think one of the messages I got
21 from my surveys, a lot of patients mentioned that they
22 knew about these tests, natural killer cell function,

1 repeated cardiopulmonary exam, various types of brain
2 imaging studies, neuropsych testing, tilt table -- but
3 they weren't able to afford them.
4 Their insurance didn't cover it or their
5 physicians didn't prescribe it, because they didn't
6 know anything about it.
7 DR. KLIMAS: We have two questions that are
8 directed at Jose and his Stanford work. One is asking
9 if he subgroups out tick borne diseases. And then the
10 other is saying what's the prevalence of HSV and CMV in
11 your practice, and do you use cidofovir for HSV
12 positive patients?
13 DR. MONTOYA: So we have tried to pursue the
14 tick borne illnesses and we have tried it through PCR.
15 Antibody testing has not helped us, has not been
16 helpful. However, we do have a small group of patients
17 in whom we have reasonable laboratory test results to
18 believe that they can be behind the triggers and we
19 obviously try to address them with antimicrobial
20 therapy appropriate to whatever has been found.
21 It has been really hard to come up with any
22 conclusion, because the numbers of patients are really

1 small for the tick borne illnesses group. For herpes
2 simplex, we primarily go with acyclovir or the
3 acyclovir-like drugs. Occasionally we jump to
4 valganciclovir. That is a stronger, potentially more
5 toxic and it's really hard for herpes simplex, for HSV,
6 I assume that that's the question, not Herpes 6, it's
7 really hard to justify cidofovir, but if the
8 (inaudible) where we have very good evidence that HSV
9 is progressing and causing the problem, we will not
10 hesitate to use it.
11 We use it certainly without any doubt in
12 transplant patients who are dying of HSV and we have
13 nothing else to offer; we don't hesitate to use
14 cidofovir. One of the things that we encountered and I
15 hope you understand is that practicing in a medical
16 center that is very conventional in many ways, you
17 really have to avoid hurting any patient in trying to
18 do good or else your program will be shut down.
19 And so it's something that we're trying to
20 follow Bernard's invitation to innovation to bold
21 thinking, to think out of box, to get into Bernard's
22 box. At the same time, we have to know what is the

1 environment that we are working in.
2 DR. KLIMAS: So there's one final question
3 that I think is a great final question for this panel
4 and it sort of comes right off of Suzanne's talk
5 actually, which is how one might be able to better
6 pool, share, breakdown the barriers of data sharing in
7 this group of scientists and investigators and
8 clinicians that care for these patients, and how we
9 might move forward in that way. If you have any
10 comments?
11 DR. CHU: Well, when I first heard that, one
12 of my concerns was how is that affected by certain
13 privacy laws and also by the consent process, because
14 when patients consent to a study or to a registry,
15 there usually should be some idea of who their data is
16 going to and what the purpose of that is and that could
17 be a little difficult to leave it open ended.
18 DR. MONTOYA: I think that we are in
19 desperate need for this with the creation of a clinical
20 trials network group for CFS, something similar to what
21 was done for AIDS in the '80s where within 15 years of
22 having found that AIDS was causing all these issues and

1 that's within 15 years highly effective treatments were
2 found and hundreds of millions of dollars were spent in
3 order to arrive to that.
4 I think that one group or one person would be
5 very hard to make the impact that we are all looking
6 for. It will have to come from a major effort,
7 nationwide, multicenter studies, and that requires a
8 whole infrastructure, the best groups at the FDA,
9 statisticians, the people who have been familiar with
10 the disease for years that are mostly present here and
11 others that are not in this meeting.
12 But it's the only way I can see making the
13 impact that we all desperately want. We need to have
14 the infrastructure and that costs money. I think that
15 would be like doing a bailout for CFS, similar to the
16 bailout that was given to the banks and all that stuff
17 years ago. I think that's what is required to get this
18 disease where it deserves to go.
19 MS. WILLIAMS: Can I just add one thing? You
20 know the CFIDS Association has developed a research
21 institute without walls and part of the sort of the
22 rationale or what we're trying to do is to make sure

1 that all of our researchers are connected. And I think
2 that something like that built out on a larger scale
3 could certainly be effective.
4 We also have a biobank which we are gathering
5 data from patients and also from healthy controls. So
6 I think sort of the way that we have begun to work with
7 our own research requiring people who get a grant from
8 us to share their data with each other, bringing these
9 folks together, not just people working a single grant,
10 but bringing all of our grantees together and really
11 making sure they're connected.
12 It's a direction that we are moving in and
13 perhaps there's some way to build that out in a larger
14 way.
15 DR. KLIMAS: And that's actually what I was
16 going to say too, is that there's a number -- people
17 may not realize because it sounds like we're starting
18 from scratch here, but oh my gosh, this isn't scratch.
19 My Lord, these things are very, very far along.
20 The CFIDS Association has their biorepository
21 and dataset. We have this chronic fatigue initiative;
22 has five groups that collected 200 patients, 200

1 controls, there's a very sophisticated biorepository
2 system with saliva. Someone asked for saliva yesterday
3 -- saliva, stool, blood, and tears collected in a
4 biorepository with a very excellent database.
5 That REDCap platform we use to collect that
6 is a sharable resource through my institute. It's
7 housed at Nova and we are happy to share it. I've
8 already shared it with Alison Bested's new set up in
9 Canada in Vancouver. So we have an international
10 collaboration. I'd be happy to share it with others
11 that want to -- and those of you that are already in
12 the study of course have open access to it.
13 So we all want these walls to go flying down,
14 and we're keen to do this type of sharing and I don't
15 think we've been all that close chested with our
16 datasets. I think we've been rushing and certainly
17 Suzanne said that the path when she helped set up with
18 the CDC Research Group and Dr. Unger and others, these
19 great big open efforts to jump into big, big datasets
20 with the computational challenges she set up at the
21 Bambury (ph) meetings.
22 So I think we're moving in that direction and

1 that there is data -- oh, and by the way, there's
2 another biorepository from the XMRV sitting at the NIH.
3 So there's at least three biorepositories that are
4 multi-group biorepositories. And then there are sites
5 like ours where we have literally hundreds -- I know
6 Dan Peterson's shared many of his very valuable samples
7 with scientists that are interested. We got freezers
8 and we know how to store stuff correctly. So we know
9 where we have some really amazing resources available
10 for pharma and for other scientists.
11 DR. MONTOYA: And at Stanford we have a
12 biobank of 200 CFS untreated patients, 100 treated
13 patients, and 400 healthy controls that are also
14 available for those who want to collaborate.
15 DR. KLIMAS: We have a longitudinal dataset,
16 150 patients with four points in time; the good day,
17 bad day studies; a biomarker discovery project NIH
18 funded. And then we have many, many years of other
19 longitudinal datasets. We never throw anything away.
20 We ask the right permissions from the get go, so that
21 we can share these resources. So there's a lot there,
22 and I think it's an exciting time. This was a very

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1 valuable panel.
2 DR. MICHELE: Incredibly so, and I would like
3 to take this opportunity to thank all the panelists. I
4 think there was an incredible amount of very important
5 information that was shared here today. I need a
6 moment to digest it all and kind of stick it in my
7 brain. And so with that, we're going to break for
8 lunch. Please be back here promptly at 12:30. We will
9 start Panel 3 on time and try to keep things moving
10 forward. Thanks everyone.
11 (Lunch Break) Panel 3: CFS and ME Clinical
12 Trial Endpoints and Design
13 DR. COX: If folks can take their seats,
14 we'll get going here in just a minute. Thank you. All
15 right, well, thank you everybody, and welcome back from
16 lunch. And we're starting our afternoon session, our
17 third panel, which will be on Chronic Fatigue Syndrome
18 and Myalgic Encephalomyelitis Clinical Trial Endpoints
19 and Design. And we have a series of four speakers, and
20 then we'll have some time for questions.
21 So hopefully folks have handy the yellow
22 sheets for writing questions down and as we go through

1 the speakers, please do write those questions down and
2 then we'll collect them as we get closer to the Q&A
3 session. And maybe at this point, I'll turn to my co-
4 moderator and we'll introduce ourselves as we work our
5 way down the panel here.
6 DR. DIMITRAKOFF: Thank you, Dr. Cox. It's
7 really a privilege and an honor to be here. I'm Jordan
8 Dimitrakoff. I'll be co-moderating this session with
9 Dr. Cox from FDA, and basically my interests in chronic
10 fatigue syndrome and myalgic encephalomyelitis actually
11 emerged from my work with patients with chronic pelvic
12 pain. So then a fair amount of work in the area of
13 biomarkers and clinical trials in chronic pelvic pain
14 syndrome for the past 10 years at Harvard Medical
15 School.
16 DR. COX: All right. Thanks Jordan. And my
17 name's Ed Cox. I'm the Director of the Office of
18 Antimicrobial Products which is within the Center for
19 Drugs and Sandy over there is my boss. And my
20 background is in infectious disease, internal medicine
21 trained physician and I've been at the FDA, I don't
22 know, for probably 10 or 12 years, involved in the

1 regulation of antimicrobial products for infectious
2 diseases of all types.
3 And then also in the area of ophthalmic
4 products and immunosuppressive agents for patients who
5 receive solid organ transplants. And it's interesting,
6 the area that I oversee, there are the full spectrum of
7 range of challenges in the area of clinical trial
8 designs and endpoints. So it's a topic that's near and
9 dear to my heart, trying to work through these clinical
10 trial design issues and endpoints and I look forward to
11 a series of very informative talks. Now, I'll turn to
12 Dr. Rowe.
13 DR. ROWE: Hi. I'm Peter Rowe. I'm a
14 Professor of Pediatrics at Johns Hopkins and I started
15 working on chronic fatigue syndrome about 20 years ago
16 now. I had been running a diagnostic problems clinic
17 and we started getting patients with CFS referred to
18 us, because truthfully nobody else wanted to take care
19 of them, and we ended up making some observations about
20 the similarity between their symptoms and those with
21 recurrent orthostatic intolerance problems. And from
22 there have been continuing to try and ferret out a

1 number of the clinical risk factors and different ways
2 to treat adolescents with chronic fatigue syndrome.
3 DR. SNELL: My name's Christopher Snell. I'm
4 an exercise scientist. I know exercise sounds a little
5 bit of an anathema to chronic fatigue syndrome, but
6 hopefully I'll explain the connection later on. I've
7 been involved in chronic fatigue syndrome research for
8 over 15 years. I got into it like a lot of people
9 almost accidentally through actually knowing somebody
10 with chronic fatigue syndrome.
11 I think that's the way we really need to
12 publicize the disease. We should have politicians
13 adopt a chronic fatigue syndrome patient for a week and
14 get to actually know them personally. And this was a
15 graduate student of mine who came down with chronic
16 fatigue syndrome and so, you know a real person with a
17 disease.
18 And said, well, you know, can we do something
19 to help. And we took a look at the illness and
20 decided, well we have a ready-made measure of fatigue
21 here that nobody's using. Let's apply it to this
22 population and see what happens and we never looked

1 back from that point. So thank you,
2 DR. UNGER: My name is Beth Unger and I'm
3 currently at the Centers for Disease Control and
4 Prevention and the Chronic Viral Diseases Branch. My
5 background and training is as an experimental and
6 anatomic pathologist, and I was at Emery University and
7 started collaborating with a group at CDC related to
8 human papilloma virus, and took the opportunity to join
9 that group, because of the multidisciplinary nature of
10 the work, and the opportunity to really address public
11 health questions.
12 And because chronic fatigue syndrome was
13 there, they had just had a peer review and were charged
14 with coming up with a molecular approach to
15 understanding chronic fatigue syndrome. And so that
16 became part of my interest as well. And so I had the
17 privilege of working with the group at CDC since 1997
18 on CFS.
19 DR. SLAGLE: Hi. I'm Ashley Slagle. I'm a
20 fellow working with the study endpoints and labeling
21 development staff at CDER. My background is in
22 measurement science, and so I have developed and

1 evaluated clinical outcome assessments across a range
2 of conditions and have become very interested in
3 clinical outcome assessments for chronic fatigue
4 syndrome, because there's a real need there and so this
5 has been very exciting work.
6 You know when I was doing my graduate work, I
7 had the opportunity to collect some primary data and I
8 learned during that experience that it's so important
9 how you ask the questions in a survey or a
10 questionnaire and that's how I got into this. And at
11 the same time, my mom had an experience where in a
12 hospital they needed to figure out what a patient was -
13 - what medications the patient was taking. And three
14 people had asked him, what are you taking for your
15 pain, knowing that he was a cancer patient with a lot
16 of pain.
17 And each time he said no. And then my mom
18 said, what are you using for your pain? And it turned
19 out that he was using a very strong opioid patch, that
20 when you say the word taking, he didn't interpret it in
21 the way that the clinicians meant it to be interpreted.
22 So it's critical that we find good

1 assessments that ask the questions in the right way.
2 DR. DIMITRAKOFF: Great, thank you so much to
3 all the speakers on the panel and putting on the
4 interesting discussion that we had in the morning and
5 the very productive suggestions that emerged from this
6 discussion. Without further ado, we'll just hear Dr.
7 Peter Rowe, about the clinical trial designs in the
8 past, looking into the future of CFS clinical trial
9 design. Clinical Trial Designs in CFS
10 DR. ROWE: Thank you. I appreciate the
11 invitation from Dr. Michele and her colleagues to be
12 part of this symposium and have been very impressed
13 with the effort on the part of the FDA in improving the
14 process of making more effective therapies available
15 for people with CFS.
16 I've been asked to talk about clinical trials
17 in CFS and you will be happy to know I will not review
18 all of them. That would, without doubt, tax the
19 attention spans of even the healthiest people in the
20 room.
21 I will draw from my experience in the last 20
22 years as a CFS researcher and clinician, and I want to

1 address what has and hasn't worked, to look at lessons
2 from specific trials including the Florinef trial in
3 which I was most directly involved.
4 I then want to look at the ideal patient
5 population for studies. And I'll draw on some of this
6 section from other illnesses in which, like CFS, we
7 don't really have a full grasp of the pathophysiology
8 of symptoms, but have nonetheless identified effective
9 therapies.
10 I will talk a little bit about the ideal
11 endpoint, but others are going to be addressing that
12 today, so I'll be brief there. And then I want to end
13 with some potential designs that might help decrease
14 the heterogeneity of the disease that we've been
15 hearing about today, and help us identify the signal
16 from an effective therapy from the background noise of
17 all the other comorbid conditions.
18 I want to sketch out for you, before we begin
19 the main talk, what my main themes are. The first is
20 that because CFS is so heterogeneous with variable
21 onsets and types of symptoms for each individual and
22 varying combinations of the comorbid conditions, we're

1 going to need to address this and take this into
2 account in our study designs, in order to identify
3 effective therapies.
4 And the design issues that come up the most
5 are the careful selection of groups or subgroups which
6 we've heard about before; the decisions on which groups
7 of patients to include; at what point in the illness we
8 include them -- early or with established symptoms; we
9 need to look at how we include people with different
10 levels of disease severity.
11 And with any illness in which there's a lot
12 of heterogeneity, another point I'm going to make is
13 that small studies are almost certainly doomed to
14 failure from the outset. We are going to need much
15 larger studies in order to detect clinically important
16 but modest differences between patients.
17 I think the outcome measures that we have
18 available for us, available now, are actually fairly
19 serviceable and why we need to choose them judiciously.
20 I want to suggest that the imperfections in measurement
21 tools don't seem to me to be the biggest impediment to
22 identifying effective treatments.

1 So with that, let's look at the first of the
2 trials in the modern era for CFS and that's the
3 acyclovir study. We know that CFS often follows
4 Epstein-Barr virus infection, and it had been
5 hypothesized that persistent symptoms from EBV or
6 symptoms of CFS might be due to EBV. Acyclovir
7 inhibits the replication of the virus and it was being
8 used at the time on a compassionate basis.
9 So those were the issues and the background
10 for this study. There had been some preliminary
11 observations of an improvement in symptoms. So this
12 trial had a number of design features that were quite
13 laudatory. It was a randomized crossover trial. Each
14 individual acted as his or her own control, and that's
15 a quite economical way to reduce variability between
16 individuals in a study.
17 There was also a clear requirement that
18 patients undergo an evaluation at the NIH, and this was
19 a fairly extensive evaluation to confirm the diagnosis.
20 They had to meet the 1988 criteria for the diagnosis of
21 the disease. And importantly, the study didn't enroll
22 an undifferentiated group of CFS; they had to have some

1 likelihood based on their serology of being a candidate
2 to improve in response to acyclovir.
3 Note that the group that was enrolled had a
4 mean duration of illness of 6.8 years, which is an
5 issue we'll return to several times later. Well, in
6 this study each patient received IV acyclovir or
7 placebo, and the order of treatment was randomized.
8 They got it in hospital for seven days and then they
9 received 30 days of outpatient oral therapy.
10 The outcomes included measures of their daily
11 energy. The wellness score, which a zero to a hundred
12 scale, asking people how they felt, and that was
13 measured each day along with temperature and weekly
14 measures of fatigue, vigor, anger, depression, and
15 anxiety, that were drawn from the profile of mood
16 states questionnaire.
17 Three of the 27 subjects had to be withdrawn
18 because they developed transient renal failure in
19 response to the IV acyclovir. Of the 24 who completed
20 the study, 21 rated themselves as improved during one
21 stage of the study or the other.
22 The interesting thing was that the patient

1 impression of improvement was evenly distributed
2 between the 11 who felt better during the acyclovir
3 phase and the 10 in the placebo phase. This is one of
4 the few studies in CFS that actually has a high placebo
5 response rate, and one of the interesting things is
6 that in CFS we usually see quite a low placebo
7 response.
8 Anxiety, depression, those symptoms were
9 worse during the acyclovir period of the study, and the
10 wellness score was also a bit worse. So while it
11 wasn't a large study, this trial was able to identify
12 some adverse effects of acyclovir therapy at least in
13 the doses used in this study and it introduced a number
14 of design features that I would argue we would do well
15 to continue using today, including the crossover
16 design; enriching the study population to increase the
17 likelihood of enrolling those who could benefit from
18 the study drug; and insisting on a clinical evaluation
19 to confirm the diagnosis, as well as fairly simple
20 outcome measures.
21 Subsequent studies have evaluated a large
22 number of interventions. And a recent systematic

1 review in 2006 showed that there had been 56 randomized
2 trials and 14 non-randomized trials of therapy. The
3 categories included: behavioral interventions like
4 cognitive behavioral therapy; graded exercise therapy
5 and other rehabilitation strategies; immunologic
6 treatments like acyclovir, intravenous immunoglobulin,
7 staphylococcal toxoid, Imunovir and terfenadine;
8 corticosteroids like hydrocortisone and fludrocortisone
9 or Florinef. Other treatments that I've lumped in a
10 sort of miscellaneous category: fluoxetine,
11 galantamine, NADH, growth hormone, dextroamphetamine,
12 and some complementary and alternative measures.
13 Well, how did these treatments fare? The
14 authors of the systematic review drew three conclusions
15 overall. They thought that a number of the RCTs
16 suggested that CBT, graded exercise, and rehab may
17 reduce symptoms and improve physical function. The
18 immunologic and antiviral treatments may have
19 beneficial effects, but also can be associated with
20 harmful side effects. And their main conclusion was
21 that most pharmacologic treatments have not shown
22 beneficial results.

1 Well, why might that be the case? Sometimes
2 we're dealing with wrong hypotheses, wrong drug.
3 Sometimes the trial is negative because there's
4 virtually no chance that it'll work based on that
5 hypothesis. It's very reasonable though given the gaps
6 in our scientific knowledge to speculate that there are
7 as yet unidentified mechanisms of the illness.
8 Perhaps, as somebody suggested yesterday,
9 even a single mechanism that explains all the symptoms
10 of the illness, and that a pharmacologic therapy will
11 eventually address the problem. But the other
12 possibility is that sometimes we have the right drug
13 but the wrong study methods, and that's what I want to
14 focus on today.
15 We'll be looking at methodologic reasons for
16 why the studies that have been conducted might have
17 failed, so that we can avoid the same errors in the
18 future. As we heard yesterday, a central challenge in
19 treating CFS, and we heard this this morning as well,
20 is that while patients have a common range of symptoms,
21 there are many differences between individuals, both in
22 the types of triggers, the kind of onset, whether it's

1 abrupt or gradual, and in the number of comorbid
2 conditions.
3 These include pain, migraines, irritable
4 bowel syndrome symptoms, temporomandibular dysfunction,
5 dysmenorrhea or painful periods, allergies, orthostatic
6 intolerance, joint hypermobility, anxiety and
7 depression just to name a few of the more prominent
8 ones. This heterogeneity in the onset and the comorbid
9 conditions creates a methodologic challenge that unless
10 the groups have approximately the same number of
11 comorbid problems, the studies that we do risk
12 comparing apples and oranges.
13 The clinical heterogeneity can be reduced by
14 careful subject selection. We've heard many comments
15 about the case definition used for studies. So we need
16 clear case definitions and clear eligibility criteria
17 for the subsets under study.
18 Uneven distribution of a comorbid condition
19 could mean that an intervention is doomed from the
20 start. So in a large study, the process of
21 randomization usually creates equal groups. You'd
22 distribute the comorbidities equally. But in a small

1 sample, an over representation of a prominent comorbid
2 condition, if it's untreated, could overwhelm the
3 effects of whatever the study intervention is.
4 A second design challenge is that flare ups
5 in these comorbid illnesses occur with regularity. In
6 the clinical setting, all of us who treat patients with
7 CFS can deal with those flare ups as they arise. But
8 the randomized clinical trial isolates one variable,
9 the study intervention drug, and it tries to minimize
10 the other things that you intervene with.
11 And so the -- and that's in an attempt to
12 isolate the signal from the therapy, from the other
13 background health problems, but you can have
14 fluctuations in a variety of the things that people in
15 this room have reported.
16 For example, if endometriosis flares up; if
17 you get sinusitis; if you get migraines; if you're
18 having recurrent syncope; all of those can overwhelm
19 the effect of the treatment under study. Similarly,
20 given the heterogeneity of the disorder, unless there's
21 an incredibly powerful medication that applies across
22 all of the heterogeneous subgroups, then a small

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1 clinical trial will not be sufficient and will need
2 much larger sample sizes.
3 To illustrate those concepts, I want to show
4 some data from a cohort study we've been doing in
5 pediatrics and I'm not sure this is going to be easily
6 visible. We'll be presenting this next week at the
7 Society for Pediatric Research meetings. But in this
8 four year cohort we identified patients who, at the
9 beginning, had what's called in a fairly clumsy medical
10 term, non-IgE mediated milk protein hypersensitivity.
11 It's a delayed hypersensitivity. And we
12 found that 25 percent of the subjects in this study, at
13 baseline, had this delayed milk protein problem. Their
14 initial SF-36 physical function scores were
15 significantly different than the group who were not
16 milk sensitive.
17 Over the next 12 months, we treated everybody
18 with multimodal therapy and we treated the milk
19 sensitive patients with a milk-free diet. And you can
20 see on this graph that they caught up to the other
21 patients. So the statistically significant differences
22 were no longer present on the diet. They looked like

1 the other patients.
2 But if you hadn't recognized that problem and
3 the milk allergic patients were in your clinical trial
4 and exposed to milk on a regular basis, that can easily
5 overwhelm the effect of any other intervention.
6 Next, I want to look at the sample sizes of
7 the trials that have been performed thus far. We know
8 that if you have a huge and really quite dramatic
9 treatment effect of a drug, you don't need a large
10 study and we've seen this a few times in medicine.
11 I remember as a trainee working in the bone
12 marrow transplant unit after acyclovir had been
13 introduced to help those patients, and they were either
14 going to live or die, and the trials were not large.
15 But that's an uncommon event in medicine. Here are
16 some of the CFS trials that were done at an early
17 phase.
18 We talked about the acyclovir that had just
19 24 people. The initial IVIG study had just 15 per
20 group. In the terfenadine study it was just 15 per
21 group. And I think most of us as CFS clinicians, use
22 antihistamines to treat chronic fatigue syndrome

1 patients who have allergic problems.
2 Terfenadine's an antihistamine. But to think
3 that an antihistamine might show a large enough
4 difference in symptoms that with 15 subjects per group,
5 you'd have a massive effect on their overall symptom
6 profile, really in retrospect seems completely
7 fanciful.
8 And so this slide has a number of studies
9 that I think were doomed to fail. Small trials do have
10 some merit when they identify some adverse effects. So
11 the hydrocortisone trials showed that after a month or
12 more on hydrocortisone that you could induce
13 potentially dangerous adrenal insufficiency.
14 But in general, small studies risk missing
15 the target, if we are looking for a therapeutic effect.
16 Now contrast the small negative trials with the sample
17 sizes used in the larger studies for a condition,
18 fibromyalgia that has a lot of similarities with CFS.
19 It's defined by its symptoms. We lack a clear
20 understanding of the pathophysiology.
21 So this study of pregabalin in fibromyalgia
22 enrolled 529 people. They had 131 in the placebo

1 group, and about the same number in each of four
2 treatment groups with different doses. The primary
3 outcome in this study was really actually very simple.
4 It was a daily pain scale.
5 And with that huge sample size, they were
6 able to show that a fairly modest proportion of
7 patients, 21.4 percent, had more than a 30 percent
8 improvement in their pain score. So a large sample
9 allows you to detect a small, but for some people,
10 clinically meaningful change.
11 Here's the slide from the journal showing the
12 differences between groups and you can see at the eight
13 month point, it doesn't look that impressive, but it
14 was for a few people, and this is an important point to
15 take into consideration as we think about regulatory
16 issues.
17 Now, what about CFS studies that have had a
18 big sample size? And here is where I need my uniformed
19 colleagues to provide me with some help, because anyone
20 who ventures into discussion of the PACE trial probably
21 needs an armed guard. But I want everybody to focus on
22 methods and not on their preconceptions about this

1 study.

2 So this study looked at specialist's medical

3 care in England and compared it to specialist medical

4 care plus adaptive pacing, cognitive behavioral

5 therapy, and graded exercise therapy. They had 641

6 people and they had about 160 per group.

7 You know already where I'm going with this.

8 Their primary outcomes were things that we've used a

9 lot in CFS studies; the SF-36 physical function score

10 which goes from zero to a hundred -- a hundred being

11 good health; and the Chalder fatigue scale which has a

12 score of zero to 33. There are problems with both

13 scales, but they would normally be expected to

14 interfere with detection of a treatment effect.

15 The SF-36 has a ceiling effect. And the

16 Chalder scale is interesting because it asks patients

17 to rate fatigue on 11 different items and to compare

18 that fatigue as to whether it's better or worse than

19 usual. So the baseline comparison is with their usual

20 function.

21 We've heard from a lot of people whose usual

22 function doesn't change very much. So if they answer

1 the Chalder fatigue scale, they'd have a very low
2 fatigue score, but would be really quite impaired. So
3 this is not always a very sensitive measure.
4 It's serviceable. It's been used in a lot of
5 trials, but it misses some things. The secondary
6 outcomes were the clinical and global impression scale,
7 work and social adjustment, a six-minute walk, and then
8 a variety of symptoms that we've all talked about --
9 sleep, depression, different CFS symptoms and post-
10 exertional malaise; all relevant to improvements in
11 general function.
12 So despite what I would consider the
13 potential for missing an important degree of change due
14 to the outcome measures being a bit insensitive, the
15 study showed small but statistically significant
16 differences both on the fatigue scale and the SF-36
17 physical function scale.
18 In the group that received specialist medical
19 care and CBT, there was a 3.4 point difference on the
20 33 point Chalder fatigue scale, and 11 percent improved
21 by two points or more. Not really very impressive. On
22 the physical function scale, 13 percent improved by

1 eight points on a hundred point scale. Again, a very
2 modest improvement, but statistically significant due
3 to the relatively large sample size.
4 And here's what the figure looked like when
5 you compared all of the groups in the study. Note that
6 the Y-axis is a bit truncated at the bottom and that
7 this visually looks a bit more impressive than it
8 actually is. I suspect that most of my clinician
9 colleagues in the room would agree with this comment,
10 and that is that if all you've been able to do with
11 your treatment is change your fatigue score by three
12 points on a 33-point scale over a year, that that's the
13 kind of thing that would have made us hang up our
14 licenses and our office headings and quit CFS in
15 frustration.
16 We usually do better than that. But again, I
17 want us to dissociate the concepts about -- whatever
18 our views are about CBT or whether we think this trial
19 was based on the hypothesis that CFS is largely a
20 behavioral problem and focus on the methods lesson,
21 which was -- this one was positive, mainly by virtue of
22 the fact that there was a large sample size and they

1 were able to detect a relatively small clinical
2 difference.
3 So with that, let me move on to the Florinef
4 trial that I was a participant in. This was a two
5 center collaboration that we conducted with Stephen
6 Straus', the late Stephen Straus at the NIH where we
7 examined the efficacy of fludrocortisone or Florinef to
8 treat neutrally mediated hypotension in those with CFS.
9 And our component of the study was funded in
10 part by the CFIDS Association and a grant, RO1 grant
11 from the NIH. The hypothesis for the study came from
12 observations in the clinical care of patients. So here
13 was a 16-year-old that illustrates that.
14 She had been healthy and active until nine
15 months before the visit to see me. She had the
16 insidious onset of fatigue. Was now sleeping 12 hours
17 a day, awakening unrefreshed; had to lie down after
18 showering and was much more tired after an active day.
19 Very familiar symptoms to everybody with experience
20 with this illness.
21 And as a result of all these problems she was
22 unable to attend school. The main finding on her exam

1 was that she was fairly acrocyanotic. She had a purple
2 dislocation in the dependent limbs. When we subjected
3 her to a 10 minute standing test in the clinic, her
4 heart rate went up 41 beats during that time, which is
5 excessive.
6 We then went on to a formal tilt test and
7 that showed that she reproduced her symptoms of
8 fatigue, warmth, lightheadedness, nausea, and at the 17
9 minute point of 70 degree head up tilt, she became
10 presyncopal. Her blood pressure dropped from the mid -
11 - sort of 117 over 81, down to 78 over 48, which would
12 not allow you to remain upright very long.
13 And so we diagnosed her with CFS, postural
14 tachycardia syndrome and the neurally mediated
15 hypotension. Treated her with an increased intake of
16 salt and fluids and Florinef and we brought her back in
17 a month to see how things were coming along.
18 Well, she had had an improvement in all of
19 her symptoms within two weeks and she resumed working
20 at two jobs; one feeding livestock at the family farm,
21 could spend time with friends, full school attendance,
22 would only get tired after 45 minutes of swimming, and

1 her repeat standing test showed an objective
2 improvement in heart rate variables compared to
3 baseline.
4 So with that as the kind of clinical
5 background that we'd seen a few times, we went into the
6 Florinef trial with these study questions. Will
7 individuals with CFS and NMH -- so they had to have
8 both -- have a greater improvement in self-reported
9 well-being and objective orthostatic tolerance nine
10 weeks after starting treatment with Florinef, then
11 after starting the placebo?
12 Patients were eligible if they were 18 to 50,
13 satisfied the Fukuda criteria, had undergone some
14 evaluation to exclude other causes of chronic fatigue,
15 and these were patients in whom we could provoke
16 hypotension during the first two stages of the upright
17 tilt test.
18 They had to have at least moderate severity
19 of symptoms in order for us to detect a change, but
20 they needed to be ambulatory and so they couldn't be so
21 severely affected that they were unable to walk.
22 The study was a randomized, placebo-

1 controlled, double-blinded study where we stratified
2 patients by center where they were enrolled and by
3 disease duration with the cut point at three years. We
4 had them on Florinef and a gradual start up dose, but
5 they were on the full study dose of 0.1 milligram a day
6 for seven weeks.
7 We recommended an increase in fluid intake,
8 but asked them to stick with their usual sodium intake
9 during the period of the trial. This is what it looked
10 like. Subjects came in, were screened, had a tilt
11 test. If they were positive, they got randomized to
12 the drug or placebo, and we repeated the tilt test or
13 tried to get them to come back to repeat the tilt test,
14 towards the end of the treatment.
15 And again, we need to be very careful when we
16 impose objective measures which are great for science,
17 but not good for the patients, as we had a fair bit of
18 dropout on that final tilt test part of the study. The
19 primary outcome was the percentage with a clinically
20 important 15-point improvement in well-being as
21 measured by the wellness score that had been used by
22 Straus' group in the acyclovir trial.

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1 And this asked, how have you felt in the last
2 24 hours, and they recorded a number between zero,
3 which is dying, and a hundred being as good as you
4 could expect a person to feel. And this simple little
5 measure correlates beautifully with the SF-36 and a
6 variety of other much, much longer quality of life
7 measures. So we like it a lot.
8 The secondary outcomes were changes in
9 different symptoms scores including the Wood Mental
10 Fatigue Inventory; another simple one-page measure of
11 some of the cognitive dysfunction and we looked at the
12 percent who were tolerating one further stage in their
13 tilt test.
14 When we calculated the sample size of this
15 studied, we assumed that this 15-point improvement
16 would be clinically meaningful, and that 35 percent of
17 those treated with Florinef would have that kind of
18 improvement and only 10 percent in the placebo group.
19 So we came up with a sample size of 100; 50
20 per group. We enrolled a group that had a mean age in
21 their mid-30s, two-thirds female with a disease
22 duration that had a mean of more than six years, and

1 over 70 percent in the groups had been sick for more
2 than three years.
3 So what did we see? And the answer is not
4 much. We were absolutely spot on with the proportion
5 of improvements in the placebo group, but far below our
6 prediction for the Florinef group. So our formal
7 conclusion -- and there were no differences in any of
8 the secondary outcomes. So our formal conclusion was
9 that Florinef was not efficacious when used alone in
10 treating NMH in adults with CFS.
11 So I returned to my clinic. And I thought
12 well, this was not what I expected. We were expecting
13 to show that this worked and this would be available
14 for people with CFS. And at the time I was an
15 erstwhile clinical epidemiologist who believed his
16 data. I thought, well, if the drug didn't work, I
17 better take people off it. Maybe we're mistaken; maybe
18 this was some other effect. So I went back to this
19 girl that we treated and after the randomized trial,
20 any attempt to wean her Florinef was associated the
21 return of really quite impressive and immediate
22 fatigue, despite a good level of conditioning. In

1 other words, she was very fit.
2 And so you couldn't blame the worsening on
3 deconditioning. Her wellness scores off the drug
4 ranged from 50 to 70; on the drug, 85 to 90. So how to
5 reconcile the study results and the clinical
6 observations or as I term this with apologies to the
7 American country music star, George Jones, darlin' tell
8 me my lyin' eyes are wrong.
9 So one potential problem with this group was
10 that the duration of CFS was quite unlike those we see
11 in clinic. They had a mean disease duration of more
12 than six years. Subgroup analyses that we defined
13 before unblinding the study showed that for those who
14 had less than three years of CFS, we had a higher rate
15 of response, and for the younger patients we had a
16 higher rate of response.
17 But the conclusion we drew was that patients
18 with CFS may be more refractory to treatment if they've
19 had the illness for a long period of time. Well what
20 does this tell us about the ideal patient population?
21 And I borrowed the next couple of slides from Dr. Mark
22 Demitrack who was a conference participant at a very

1 exciting conference last October, organized by Beth
2 Unger's group at the CDC and the CFIDS Association, and
3 this was looking at deconstructing clinical trials.
4 Dr. Demitrack is a psychiatrist who some of
5 you may remember his work on low cortisol levels in CFS
6 back in the early 1990s. He's an excellent
7 methodologist and he has emphasized that in depression
8 trials, past treatment resistance influences the rate
9 of response to a new intervention. So here's a slide
10 from his study of vagal nerve stimulation and
11 pharmacotherapy for depression.
12 And what you see on the bottom are the number
13 of treatments that had been failed before entry into
14 the trial. If you'd failed two to three treatments,
15 your rates of response or remission were sort of in the
16 -- response was in the mid-50s, remission in the 30s.
17 As the number of failed prior treatments increases, you
18 have much, much lower rates of response and remission.
19 So that if you failed more than seven
20 treatments, there is no response to this therapy, and
21 that reflects a much larger experience with the Star*D
22 trials in depression. These had huge sample sizes,

1 over 2,000, and they showed that if you had failed --
2 if you'd never had treatment of your depression or had
3 limited treatment, the response rate to a new drug was
4 27.5 percent. It dropped to 21 percent after you'd had
5 one prior treatment failure. After two treatment
6 failures, it was down to 16 percent and so on.
7 So he concluded in a paper he wrote in
8 pharmacogenomics in 2006 that because CFS, by
9 definition, develops after a substantial period of time
10 has elapsed and as many treatment studies have obtained
11 treatment samples based on self and clinician referral
12 to tertiary care medical centers, the populations under
13 study often represent patients who are among the more
14 refractory to any further treatment intervention.
15 Now, in saying that, I don't think he
16 intends, and I certainly don't intend to diminish our
17 clinical and ethical responsibilities to study those
18 with more severe or more prolonged illnesses. But if
19 we're going to be purely mercenary about getting drugs
20 approved for this condition, it suggests that to
21 include those individuals in our CFS trials, may set
22 the bar impossibly high for detecting a true treatment

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1 effect and get these treatments on the books.
2 At the minimum, we need to stratify by
3 disease duration and perhaps calculate our sample sizes
4 based on the group that have had very short duration of
5 illness. Now there are some caveats. Not all of the
6 studies have had people who have had prolonged illness.
7 The PACE study was a positive trial with 2.7 years
8 duration, but a couple of the ones with fibromyalgia at
9 the bottom, patients had four, eight and a half years
10 duration, and the two trials in the middle I've
11 selected because they represent the rituximab trial and
12 a couple of dextroamphetamine trials that show that if
13 the treatment is effective, assuming these are results
14 that stand the test of a larger replication study, you
15 can overcome the issue.
16 So this is something we need to pay attention
17 to. On to the ideal endpoint, I want to look at a
18 couple of slides from the rituximab study. This trial
19 used a fairly simple baseline visual analogue scale
20 looking at a score of one meaning no symptoms, up to
21 10, very severe symptoms and they used a fatigue score
22 that was calculated from the visual analogue for

1 fatigue, post-exertional worsening, need for rest and
2 daily functioning.
3 And they did a follow-up visual analogue
4 scale comparing the last two weeks versus baseline in
5 this scale that looked at major worsening, moderate,
6 and slight worsening, versus no change or the same
7 range of improvements. On the right you see the
8 fatigue score and by the 24-week point of their
9 intervention, they were seeing significant differences
10 in the results. And when you look at the larger patient
11 reported improvements as major or moderate, they had a
12 highly significant difference.
13 Again, small trial needs to be replicated,
14 but very simple trial endpoints. Others will discuss
15 this point more, but I think some of the reasonable
16 study endpoints would be visual analogue scores for
17 fatigue and specific CFS symptoms that include both
18 frequency and the severity or impact, fatigue scales,
19 measures that might be specific to an outcome of
20 interest.
21 So if you're looking at a drug that affects
22 cognitive function, maybe a questionnaire of executive

1 function outcomes would be important. A general
2 quality of life measure, an activity measure. We've
3 heard a lot about numbers of steps per day. That was
4 used in the clonidine trial in Norway that's about to
5 be published for adolescents, but other questionnaires
6 look at activity, functional measures, and then these
7 global clinician measures of change.
8 I would point out that we heard from Joe
9 yesterday, that there's often a level of confusion and
10 that creates a methods problem. If we're asking people
11 to compare how they are now versus two weeks ago, we
12 may be asking the wrong people and better answers may
13 come from the clinician or a family member who's
14 evaluating that.
15 I also want to reflect on a clinical
16 observation that was communicated to me by a patient.
17 We asked this young man how he was doing. He'd come
18 back to see me after about three months of an
19 intervention, and I said, Ben, how you feeling?
20 He said, ah, about the same. And at that
21 point his mother who's sitting behind him is rolling
22 her eyes, whacking him in the shoulder. Ben, tell him

1 what you did yesterday. Well, we went out and played
2 18 holes of golf. And then we came back and went to
3 the pool for a while and then we shot some hoops and
4 then we went to the movies, but I still feel the same.
5 And the point of that story is this guy was
6 used to such a level of fatigue that he made the very
7 healthy choice that I see over and over again, of
8 expanding his activity level until he generated that
9 fatigue, rather than resting so much that he had no
10 fatigue. So we've got to watch that we don't use
11 fatigue as the only outcome measure and I think people
12 made that point earlier today.
13 I want to end with some comments on potential
14 study designs that decrease the heterogeneity in this
15 disorder. We've talked about sample size issues, but
16 we also have to look at more creative trial designs and
17 these include stratification to address the duration of
18 illness or its severity, different subsets. We needed
19 run-in periods where we treat comorbid disorders or
20 identify responders.
21 We need to look at randomized trials of
22 withdrawing ostensibly effective therapies at crossover

1 designs and possibility N of one trials. So here's the
2 structure of our current approach. We take
3 undifferentiated CFS patients. We randomize them to an
4 intervention or placebo, and then we measure the
5 outcome.
6 To reduce some of the heterogeneity, we might
7 try for a run-in program of active treatment. For
8 example, if everybody got some CBT or graded exercise
9 or specific attention to their main symptoms, like
10 allergies, like migraines, that would help reduce the
11 amount of fluctuation they were having day-to-day in
12 the trial period. Now that's probably going to be
13 easier in countries where there are networks of
14 specialists for CFS treatment, provided that specialist
15 treatment is actually effective.
16 As everybody in this room knows, we're pretty
17 far from that situation here, but if we included a run-
18 in period in the design of a trial, that would be very
19 attractive to patients who would then get essentially a
20 tune up, and they might be more willing to join the
21 trial, but it would also help at a methodologic level,
22 so I think that's a win-win.

1 A second approach would be to take patients
2 like the young woman I mentioned to you, and we took
3 her off her drug just to reassess, but we could do that
4 formally. Once they've responded to a given drug,
5 randomize them to either continue that medication or
6 withdraw it. This has been used in seizure studies, in
7 rheumatologic studies, and the alternative to this is
8 you begin a trial and you treat everybody, and then
9 after a certain point stop the treatment and then
10 randomize the responders to that drug to either
11 continue or withdraw the drug.
12 Listening to the testimonials about Ampligen
13 the other day, this design would seem to me to be much
14 more attractive and economical as a way of testing they
15 hypothesis that Ampligen is efficacious for subgroup.
16 It takes a fair bit, though, for people to stop a drug
17 that's effective. So there are complicated issues
18 there.
19 Clinical trials that look at crossover
20 designs have the chance to use each person as their own
21 control. That assumes that there's no carryover effect
22 of the drug in the first period, so the washout period

1 has to be long enough. All of those designs use one
2 enrichment strategy or another.
3 Others are described in a monograph from the
4 FDA that I've included on the next slide. But this --
5 one of the enrichment approaches would be to identify
6 the subgroups that we expect to respond to a drug. So
7 for example, droxidopa is one that's one on the
8 horizon; used in Japan for treating orthostatic
9 intolerance. If it becomes available here, we would
10 want to select only those who have profound or
11 prominent orthostatic intolerance to treat in a trial
12 with droxidopa.
13 So the reference was to a monograph by Dr.
14 Temple on enrichment strategies. I've listed the
15 paper by Mark Demitrack. And last, I want to thank the
16 people who supported our work over the last 20 years
17 and that includes some grants, on occasion from NIAID,
18 Department of Defense, and the CFIDS Association.
19 We've been the recipient of an endowed chair
20 in CFS work that has allowed me to continue on, and I
21 get help from -- my team is me, and a volunteer parent,
22 Coleen Marden (ph) who's been helping me with the

1 cohort study, a number of summer students and a lot of
2 help with private philanthropy that's kept us going. So
3 I'm going to end there and move on to the next one.
4 Thank you.
5 DR. COX: Great. Now I'd like to invite
6 Christopher Snell to the podium and he's going to talk
7 to us about repeated cardiopulmonary exercise test
8 results as clinical endpoints in myalgic
9 encephalomyelitis, CFS research. So Chris? Exercise
10 Challenge Studies in CFS
11 DR. SNELL: We heard this morning that we
12 need to come up with some new ideas to solve this
13 problem, and so I'm looking out in the audience today
14 and one of the scary things is how many people I
15 actually know, and know well. You know there's a small
16 group of very committed and hardworking physicians; a
17 slightly larger group of equally committed and long
18 suffering patients. It's a little like being a member
19 of an exclusive club that nobody actually wants to be
20 in.
21 I'm also a little embarrassed when I come
22 here because people come up to me and they say thank

1 you for all you've done for us. And I think, I haven't
2 really done anything. I have no answers. All I do is
3 I tell people it's a real disease and I'm still trying
4 to find out why. Preaching to the converted maybe good
5 for the ego, but it's not going to move the field
6 forward. If we're going to do that we need a new group
7 of sinners brought into the fold that we can actually
8 convert.
9 A little bit of self-promotion before I start
10 the presentation. I thought I'd changed the slide
11 actually. I put the Workwell website up there. We're
12 no longer operating out of the University of the
13 Pacific. The university closed the lab down without
14 any discussion or any acknowledgement of anything that
15 we've done in the last 10 years. So we've set up
16 independently. We have an independent premises now. We
17 have the equipment. We're doing the testing that we've
18 always been doing. We're also operating out of
19 physicians' offices, including Dan's office in Tahoe.
20 So Workwell Foundation is where to contact is from now
21 on.
22 So I indicated when we started, my background

1 is exercise science. And so it was never on the
2 horizon that I would be looking at pathology. We were
3 working with athletes. We were testing firefighters
4 for functionality. You know these are people that will
5 exercise until they die on the bike.
6 And so, when we started to get involved in
7 chronic fatigue syndrome, it brought a completely
8 different mindset to the picture. So now we're looking
9 at a group of people that are exercise intolerant, and
10 we're asking them to do an exercise test. But the
11 beauty of exercise testing is that it assesses
12 function. And one of the things that surprised me when
13 I got into the field, that nobody really had an
14 objective measure of fatigue. You know you say well
15 I'm tired, I feel fatigued. Well say well how much.
16 Well five on the scale.
17 So that doesn't mean anything to me. I need
18 some hard numbers. That's not real science as far as
19 I'm concerned. We have tests out there that we use all
20 the time with athletes who are so concerned about their
21 performance that they'll take the test over and over
22 again. They use it to monitor training. Interestingly

1 they have their own off-label drug trials going on that
2 they assess through exercise testing and physical
3 function, and they get way more publicity than any drug
4 trials involved in any mainstream illnesses let alone
5 chronic fatigue syndrome. But it applies equally well
6 to professional and high-level athletes, as it does to
7 people with certain pathologies.
8 It's just a matter of asking the right
9 questions. It has advantages. It's non-invasive. We
10 don't have to stick a needle in anybody. I actually
11 think it's a biomarker, but we sent a paper up last
12 year and I put biomarker in the title and one of the
13 reviewers nearly had a fit, telling me this is not a
14 biomarker. So I added the World Health Organization
15 definition in, and it's a biomarker. And they even
16 give blood pressure as a biomarker for cardiovascular
17 disease. A lot of the measures we use are used for
18 differential diagnosis between cardiovascular disease
19 and pulmonary disease, and metabolic disorders.
20 And so it provides diagnostic, prognostic
21 information and it evaluates an individual's capacity
22 for dynamic exercise. And you can substitute the word

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1 work for exercise if you don't like the exercise word.
2 It's just that I'm so used to using it that I've tried
3 to train myself and I can't. But that's all we're
4 really talking about, is a capacity to do work. And a
5 definition of fatigue that I like is a reduced
6 efficiency as a result of doing work. So you do work,
7 you don't recover, you're not as efficient anymore.
8 So it's not rocket science. It's based
9 around human physiology. We are energy producing
10 machines. It's what we do. It's called metabolism. It
11 uses every bodily mechanism. Everything is involved.
12 And we have a built in reserve capacity. Evolution has
13 put that into us. It's known as the fight or flight
14 syndrome. We can find extra resources of energy
15 whenever needed, and most persons with chronic fatigue
16 syndrome know that. You know, if they need to do
17 something, they can do it.
18 Disease states reduce this capacity. The
19 problem is, in the absence of stress, that reduction is
20 not always seen. It's like your good day. Well,
21 there's nothing wrong with that person. He or she is
22 perfectly well. I saw Matt the other day riding a

1 horse. Or they were at the fun fair, or they went to a
2 game. They don't see people the next day when they're
3 in bed, and the day after that and the day after that.
4 So exercise is an effective way to induce
5 stress. It stresses all the systems. It will have an
6 effect. So by stressing the system, we can start to
7 look for differences between normal healthy individuals
8 and individuals with the pathology. So if we only look
9 at cardiac output at rest, then we don't see any
10 difference between those individuals. We start to
11 stress the system, and those differences start to
12 become immediately apparent.
13 So a simple goal of exercise testing, assess
14 the function of the cardiorespiratory system. So CFS
15 may or may not be involved with the cardiorespiratory
16 system, but the cardiorespiratory system is the way
17 that we produce energy. So we're looking at how
18 efficiently that operates.
19 And that determines your functional capacity,
20 how much work you can do. Highly individual. We focus
21 on aerobic capacity. And what that means is that how
22 efficiently is the body able to utilize oxygen. So

1 it's exactly the same principle that your car works on.
2 The more efficiently your car can use oxygen, the less
3 gasoline you use, the more energy you can produce, the
4 greater output you get.
5 There are two main energy systems. You've
6 probably heard of these systems. It's a little of a
7 simplified way of approaching it, but essentially
8 there's an aerobic metabolism, that means with oxygen.
9 It is oxygen dependent. It's highly efficient. It's
10 time intensive so we can engage in aerobic activity for
11 extended periods of time. It predominates at lower
12 workloads. So at submaximal workloads, we're operating
13 aerobically with oxygen. Byproduct, carbon dioxide. So
14 we're all contributing to global warming.
15 Anaerobic metabolism, it's a sort of a
16 misnomer to say no oxygen is needed. You don't stop
17 breathing when you do work anaerobically, otherwise you
18 die. But essentially the energy system doesn't need
19 oxygen to produce the energy. It contributes more at
20 higher workloads. And the byproduct of anaerobic
21 metabolism is lactic acid.
22 So as exercise intensity increases, your

1 capacity to produce energy aerobically decreases, and
2 you start to increasingly rely on the anaerobic energy
3 system.
4 Now if you get into a debate over lactic acid
5 with exercise physiologists, it's one of the areas that
6 people like to disagree about. It actually is an
7 energy substrate, and particularly highly trained
8 individuals have an extra capacity to reutilize lactic
9 acid for further production of energy. But for most of
10 us it's associated with pain, reduced muscle function,
11 altered enzyme activity, and ultimately cessation of
12 activity. So the lactic acid will continue to build up
13 in the blood stream, eventually you have to stop, even
14 if you don't want to.
15 So definitions, maximum amount of oxygen the
16 system can deliver and combust, i.e. use; sometimes
17 called maximum oxygen consumption. Often in research
18 you'll see it referred to as peak oxygen consumption.
19 It gets out of that argument about was it really
20 maximum, but if it says peak oxygen consumption,
21 they'll give you a definition of how they've evaluated
22 peak, and you can determine how close that was to the

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1 most the person could give. I'll come back to that in
2 a little while.
3 Anaerobic threshold is particularly
4 interesting because it really defines most people's
5 limits for activity. So it's the point at which you
6 can't continue to work, you can't continue to exercise.
7 So aerobic production is no longer sufficient to
8 produce energy, you have to rely on the anaerobic
9 system; increasingly the buildup of lactic acid is
10 going to prevent you working, eventually.
11 This point is highly individual. So normal
12 individuals, their anaerobic threshold can be anywhere
13 between 50 or 40 to 60 percent of their maximum. Highly
14 trained individuals, I've seen numbers where endurance
15 athletes, such as Tour de France cyclists, have
16 anaerobic thresholds at 90 percent of their peak. So
17 they can go up to within 10 percent of their maximum
18 before they start to build up lactic acid, and that's
19 partly genetics and partly adaptation to training.
20 Adaption to training is an important concept
21 when you look at exercise. And really we look at that,
22 when we look at training effect, we're looking at how

1 do people adapt to exercise. Interestingly, when you
2 look at most of the graded exercise studies done with
3 chronic fatigue syndrome patients, even if they were
4 done with healthy people, they're not at an intensity
5 that is going to produce a training effect. You're not
6 going to see a training effect. So whatever effect
7 they see has got to be something else, and it's
8 unlikely to be quantified by any change in oxygen
9 consumption.
10 So the topic of my talk today is endpoints
11 for clinical trial designs. So I'm going to talk about
12 how do we measure this capacity to produce energy,
13 because not all measurement systems are created equal
14 and unfortunately people tend to think that they might
15 be. They're certainly not all created equal
16 economically, which very often factors into research
17 much more than it should do.
18 So we'll get people call us sometimes, say
19 well we're really interested in the work that you're
20 doing with exercise testing. What's it going to cost
21 to set up? So we start to tell them and we don't think
22 it's particularly expensive. It's $40,000 to $50,000

1 worth of equipment, and you want a trained individual
2 that's good at their job and they can do it. So you
3 need an exercise physiologist, which is really a
4 technical capacity. They don't get paid six figures.
5 So in the scheme of things, it's not hugely expensive.
6 But usually the next question is, is there a cheaper
7 way of doing it?
8 The other interesting question we get is
9 that, well we would never get the CFS patients to do
10 the exercise test. You might not get them to do a
11 graded exercise program; we have no problem getting
12 people to do exercise tests. We have a bigger problem
13 with the sedentary controls, because they want to know
14 what's in it for me. The CFS patients, if you explain
15 to them, well this is going to quantify your fatigue,
16 it validates your illness, it's useful information, and
17 they'll go like an elite athlete until you have to
18 pries them off the bike. It's quite sobering to
19 actually watch an exercise test, and if we could do it
20 we would just videotape everybody and show somebody a
21 videotape. Say look, this person is not faking it,
22 they're not malingering.

1 So two ways of measuring this are directly.
2 So we do a, apologize, a graded exercise test. That's
3 not the same as a graded exercise program. We've had
4 hate mail about that. So you recommended graded
5 exercise. Yes, graded exercise tests, it's not the
6 same as a graded exercise program. Or indirectly,
7 usually measured by recording a heart rate response,
8 and onset of fatigue, to a graded exercise protocol. So
9 distinction, directly, indirectly.
10 And there are a whole bunch of tests out
11 there. And so the easiest are what we call field
12 tests. These are the sorts of things that you might do
13 with your elementary school class or a group of
14 athletes even. There's the Cooper 12 minute test,
15 which essentially just measures how far you can move,
16 how far you can traverse in 12 minutes. There's a
17 Rockport one mile fitness walking test, obviously
18 sponsored by the shoe people. So they just do a timed
19 mile walk.
20 And then the infamous six minute walk test.
21 I'll come back to the six minute walk test. I have
22 issues with the six minute walk test, but it was

1 designed for a specific purpose. It was really for
2 cardiovascular patients that couldn't do the 12 minute
3 walk test. It's a quick and dirty measure of looking
4 at somebody's indication for cardiovascular disease.
5 And it's reasonably accurate at predicting that.
6 Then we have step tests, just stepping up on
7 a box or a stool. Treadmill tests, the standard moving
8 belt treadmill. And cycle ergometer tests, cycling on
9 a bicycle that's calibrated to provide a certain amount
10 of information.
11 So first, the field tests. So we see a group
12 of athletes there. They're probably doing the 12
13 minute test, and they're running the 12 minute test.
14 Obviously, if you run it, you cover way more distance
15 than if you walk it. And then there's a woman in a
16 hospital corridor, counts as a field. She looks like
17 she'd doing the six minute walk test to me. They're
18 easy to administer. Everybody likes easy. It's that
19 big button, right, in the ad. Just give me the easy
20 button.
21 You can test large groups of people all at
22 once. So I can test a whole room full of people at the

1 same time. So it's cheap. Require minimal equipment.
2 If you really want to get fancy, you can put a heart
3 rate monitor on the person, or what's everybody wearing
4 these days, the Bizbit (sic). Yes, the FitBit thing.
5 So disadvantages. We're not monitoring blood
6 pressure and heart rate. So we've got a sick
7 population here that might be at risk for other things,
8 such as cardiovascular disease, and we're not looking
9 at blood pressure and heart rate. Aerobic capacity,
10 remember that capacity to utilize oxygen is estimated.
11 So it's like doing your taxes. Will they accept the
12 estimated tax or do they want an accurate calculation
13 of how much tax you owe?
14 May result in inadvertent max testing in some
15 populations. This is a biggie. It's supposed to be a
16 sub-maximal test. It's why people like it. One of the
17 issues we have with our maximal testing is that it may
18 be unethical to do it on people that you know it's
19 going to make sick, and I struggle with that at times.
20 So if I could come up with a sub-maximal test that
21 worked equally well, I would be on it like white on
22 rice.

1 There have been studies done that have looked
2 at cardiovascular patients where they found that over
3 50 percent of the cardiac patients, what they do is
4 they put portable equipment on to measure their oxygen
5 consumption. And they found that at least 50 percent
6 of the people in some studies were actually exercising
7 maximally, compared to the other 50 percent where the
8 six minute walk test was a sub-maximal test. I'll come
9 back to this when we start to look at case controlled
10 studies where we're comparing people on a test and
11 we're not equating effort, because we know that chronic
12 fatigue syndrome patients won't try if you ask them to
13 do exercise. That was meant to be a joke.
14 Motivation and pacing plays a big role in the
15 results. Motivation and pacing. Think about that. I'm
16 a confirmed couch potato, so I don't even have to be
17 sick. And somebody says I just want you to walk as far
18 as you can and you sit in six minutes. And you think
19 well you know how far is it from my couch to the
20 refrigerator. Well I've moved it actually next to the
21 couch so I don't actually even have to get up.
22 And so it's new territory for you. So this

1 is not even somebody's who's sick. So what do you tend
2 to do when it's new and an unknown? You back off a
3 little bit, don't you? Well, let me just see how this
4 goes. You come back in a few weeks, oh I've done this
5 before, no big deal, you're likely to do it a little
6 bit better.
7 You also have to be a little careful in these
8 studies, is you know, who was monitoring the test? Was
9 it somebody involved in the research or did you pull in
10 a graduate student that hadn't turned an assignment in
11 on time or something. I do experiments in class
12 sometimes and I say don't give anybody any feedback
13 while they're doing the test because it's going to
14 alter the results. How hard is that for students to
15 do? It's virtually impossible. They've been trained
16 all through their life to encourage people, so they
17 encourage people. So motivation and pacing play a big
18 role in the results.
19 Okay, so both Peter and I will need an armed
20 guard when we leave, because I'm also going to talk a
21 little bit about the PACE trial. I'm going to
22 primarily talk about the endpoints that's what the

1 topic of my talk is. And I'm going to talk about the
2 only, the only true objective measure they had in the
3 whole study, which was the six minute walk test.
4 So we saw that there were about 110 people in
5 each of the treatment arms of the study. The data for
6 the six minute walk test is based upon 69 percent of
7 that 110. I can't do 31 percent of 110, but 31 percent
8 of 110 people didn't complete the six minute walk test.
9 Why?
10 Baseline distance, 341 yards. I think I
11 converted that correctly, because of course Britain
12 like the rest of the world is in the metric system.
13 Over here we kept the Imperial system. Nobody calls it
14 the Imperial system here, but that's what we used to
15 call it in Britain. 341 yards. Fifty-one week
16 distance, 414 yards. These are the endpoints, so it's
17 the delta between those two that was the endpoint for
18 the six minute walk test.
19 I did a little bit more math on that, because
20 I was interested. I said well, that didn't mean
21 anything to me. What can I convert that to so that it
22 gives me an indication of effect size? So one of the

1 things that we're concerned about in research is, is
2 this effect large enough to actually be a meaningful
3 difference. So I converted it to miles per hour, not
4 kilometers per hour. Interestingly in Britain they
5 still use miles per hour. 1.9 baseline, 2.3 endpoint.
6 That's not very fast. That's of walking around the
7 office, going to the water machine, going to get a cup
8 of coffee. So it's not speed walking.
9 So I took that a little bit further. So
10 there are tables of energy equivalents that are not
11 particularly accurate, but they're used quite often to
12 indicate the energy costs of activities. And some of
13 the patients out here may have suffered from that, the
14 use of these tables, that they were never developed for
15 individual prescription. They were a research tool.
16 And they came up with something called a MET, or a
17 metabolic equivalent. And this is supposed to be based
18 upon baseline metabolism.
19 So they calculated everybody in the world's
20 basal metabolism, and then they averaged that and came
21 up with the MET. No, they didn't. I think they took a
22 40-year-old sedentary guy and calculated his basal

1 metabolism and said the rest of the world is exactly
2 the same as that.
3 So if you look in these tables, two miles an
4 hour equates to about two METs, which, for real
5 scientists, we can now convert that. One MET is worth
6 3.5 milliliters per kilogram per minute of oxygen. So
7 I can double that to make seven milliliters per
8 kilogram per minute of oxygen. That would mean that
9 the patients were severely disabled, and unlikely to be
10 candidates for a heart transplant because they wouldn't
11 survive it. So not a particularly meaningful endpoint
12 in terms of improvement for how long the trial -- was
13 it 52 weeks of graded exercise? And quite likely
14 influenced by motivation.
15 So the next round of tests, we look at
16 treadmills, cycle ergometer and step test. Indirect
17 estimation, they employ regression equations, derived
18 from experimental data, to estimate VO2 Max and
19 anaerobic threshold from performance on field tests.
20 You can do it by time, or you can do it by heart rate.
21 So that's indirect.
22 Limitations of indirect assessment may not

1 apply to special populations, disease states. They're
2 biased by the tested population, and biologic heart
3 variability of heart rate in response to exercise, it
4 is enormous. American Heart Association don't
5 recommend using heart rate as an indicator of effort on
6 exercise tests. It's not reliable.
7 So danger of using regression equations, you
8 have to make assumptions. So the assumptions are that
9 there's a steady state of heart rate achieved. There's
10 a linear relationship between measured variable and
11 oxygen consumption. Response to any given age group is
12 consistent. And mechanical efficiency of every
13 individual is the same. The individual is not on
14 medications.
15 So there's a wealth of evidence to suggest
16 that it may not apply in disease. Biologic variability
17 of heart rate is well documented. It can differ by 25
18 percent across individuals. Temperature, medications,
19 environmental noise, elevation, time of day, illness,
20 could all affect heart rate. Tested population is
21 going to bias it. Outside of normal ranges, regression
22 equations start to break down.

1 Okay, so I hope I've got time left. Direct
2 assessment of aerobic capacity, maximum oxygen
3 consumption and anaerobic threshold. We do it through
4 gas exchange. So aerobic metabolism burns oxygen and
5 produces carbon dioxide. We measure oxygen in, we
6 measure carbon dioxide out. When I first started doing
7 it we used things called Douglas bags. And you have a
8 huge room with a big rack in it, and you had big
9 plastic bags that people breathed into, and then you
10 had somebody run in, and as soon as the bag was filled
11 you whipped it off and took it over and gave them
12 another bag. And you would just then extract the gases
13 out of the bags and measure it. We've got high tech
14 equipment that does breath by breath analysis now that
15 measures it in real time.
16 It's strongly correlated with endurance
17 performance capability. It's dependent on
18 cardiovascular limitations, ability of heart, lungs and
19 circulatory system to deliver oxygen to working
20 muscles.
21 Anaerobic threshold, we can measure it using
22 gas exchange. We also get something called the

1 respiratory exchange ratio. This is the ratio between
2 that oxygen and carbon dioxide. It really is the best
3 measure of effort. We know that once that starts to
4 get above 1.1, once the carbon dioxide starts to exceed
5 the oxygen, then that person is getting close to their
6 limits. They're giving close to maximal effort. It
7 cannot be faked. Generally breathing during exercise
8 is involuntary. It's extremely difficult to control.
9 And even if you did, you're not going to get an RER
10 above 1.1, and so the test is invalidated.
11 So indirect measurements can vary by 25
12 percent. We don't get ventilator threshold. We don't
13 get respiratory exchange ratio. We can't compare
14 effort across individuals, how hard was this person
15 working compared to how hard was that person working.
16 So determining aerobic capacity is crucial when
17 assessing level of function. Oxygen uptake and
18 anaerobic capacity are two parameters that are closely
19 correlated to aerobic performance. Direct measurement
20 of aerobic capacity, much more accurate, especially in
21 special populations and disease states.
22 I'm going to cut to the chase a little bit

1 now, because I'm running out of time, and I'm going to
2 highlight some of our research. Our initial round of
3 testing using single exercise tests couldn't clearly
4 distinguish between CFS and deconditioning. What did
5 was the post-exercise response, or the post-exercise
6 morbidity. People were sick after the exercise if they
7 were diagnosed with chronic fatigue syndrome generally.
8 So we determine, how do we tap into that drop
9 off after the exercise test. So we just threw two
10 exercise tests together, let's bring them back 24 hours
11 later, give them a second exercise test, and look at
12 the objective measures again. Our first attempt at
13 doing this, we saw a significant difference in oxygen
14 consumption, CFS compared to controls. Controls
15 usually do a little better on the second test. CFS did
16 considerably worse.
17 We replicated that with a larger population.
18 That first study was an N of six for CFS and six
19 controls. We replicated it with 51 CFS and 10
20 controls. Slightly different results. We didn't get
21 such a dramatic drop off in oxygen consumption, but one
22 of the measures we did look at was workload. We get

1 that on a bike. It's exclusive really to a bike. And
2 we saw a big drop off on second test workload at
3 ventilatory or anaerobic threshold in the CFS
4 population, that wasn't apparent in the CFS population.
5 All that suggests is that a big drop off in
6 efficiency, in utilizing oxygen post-exercise, so now
7 at a much lower level of work, I have to start relying
8 on my anaerobic energy system. So I'm starting to get
9 less work from more effort and greater buildup of
10 metabolites.
11 Lots of reasons why people may fail to
12 reproduce. That's for the rest of my colleagues to
13 find out. Objective measures of fatigue in CFS/ME,
14 functional endpoint in clinical trials, better than a
15 six minute walk test. It reveals abnormalities across
16 multiple systems. RER, built in measure of effort. I
17 can compare my treatment group with my controls, and
18 say yes, they were both working as hard. Any
19 differences must be due to the treatment. That's what
20 we all want to be able to say when we run a trial of
21 anything. Single exercise tests may be insufficient to
22 distinguish between CFS and sedentary controls.

1 Just to finish up, and just to emphasize that
2 this is not witchcraft. There are people out there
3 doing this. I just put cardio-pulmonary exercise
4 testing into clinicaltrials.gov and there are just
5 under 400 clinical trials around the world that
6 currently include cardio-pulmonary exercise testing in
7 their protocol. And it's fairly widespread, so I
8 didn't find a continent that was not using cardio-
9 pulmonary exercise testing in a clinical trial for some
10 purpose. Thank you.
11 DR. DIMITRAKOFF: Thank you, Dr. Snell. Next
12 we'll hear from Dr. Elizabeth Unger from the Centers
13 for Disease Control and Prevention. She'll talk to us
14 about the measures of chronic fatigue syndrome in a
15 multicenter clinical study that the CDC is conducting.
16 Thank you. Measures of CFS in a Multi-site Clinical
17 Study
18 DR. UNGER: Thank you very much for the
19 opportunity to come and participate in this workshop. I
20 think this is a really very important opportunity to
21 increase communication about this very important
22 subject.

1 So what I'm going to do today is tell you
2 about this study that we're conducting; first of all,
3 the background of why we're conducting it, who we're
4 working with, and what are the measures that we're
5 collecting and why we think this is a start that will
6 have some relevance to the question of what are good
7 measures in this illness?
8 You've heard over and over again that
9 physicians worldwide do recognize a condition like CFS,
10 but there are different case definitions in use, and
11 even with the same case definition, there's substantial
12 heterogeneity in the patients.
13 And it was already explained, the
14 difficulties that this can produce in clinical trials
15 and in evaluating response to all sorts of therapies
16 and the factors that were already mentioned, duration
17 of illness, the severity and types of symptoms,
18 comorbid conditions, medications, and even basic
19 demonstrations.
20 And so our study design and objectives were
21 to really capitalize on the clinical expertise of
22 physicians with expertise in care and treatment of CFS

1 patients. And, again, just as the FDA has explained,
2 for the purposes of this workshop, CFS, or CFS/ME is
3 kind of a generic term. And we asked our clinicians to
4 enroll any patients that they considered to be CFS,
5 CFS/ME, post-infectious fatigue, anything that fit
6 under this umbrella diagnosis.
7 The goal was to collect standardized data on
8 the major domains of illness from CFS in patients from
9 these practices. And we thought that it would be
10 important to evaluate how much heterogeneity there are
11 between patients and their practices and provide some
12 evidence and data from these standardized ways of
13 collecting information to address the question of CFS
14 subgroups.
15 So our only exclusion criteria were HIV
16 positivity and an age at diagnosis of older than 62
17 years. You know, probably the most important part of
18 our study is who we have participating with us, and
19 there are seven clinical centers, and -- Benjamin
20 Natelson's center in New York City, Beth Israel Medical
21 Center; Nancy Klimas' center for neuroimmune disorders
22 in Miami, Florida.

1 And as part of the Open Medicine Institute
2 consortium, we have Dr. Lucinda Bateman's Fatigue
3 Consultation Clinic in Salt Lake City, Utah; Dr.
4 Charles Lapp's Hunter-Hopkins Center in Charlotte,
5 North Carolina; Andy Kogelnik's Open Medicine Clinic in
6 Mountain View, California; Richard Podell's clinic in
7 Summit, New Jersey; and the Sierra Internal Medicine
8 Incline Village, Dr. Daniel Peterson. So this was a
9 contract mechanism, and CDC was -- felt very, very
10 fortunate to have these experts willing to enlist their
11 patients to participate in our studies.
12 Now, the protocol was developed in
13 collaboration with the CDC, but by the participating
14 clinics. And our goal was to make this fit into the
15 clinical practice as much as possible so as not to
16 create a burden either on the clinicians or on the
17 patients, and particularly not on the patients. The
18 protocol was IRB-approved at all participating sites,
19 and this first phase is really only cross-sectional
20 data.
21 Physical examination at the time of clinic or
22 with one -- within one year was collected, and then

1 questionnaires for self-reported measures of illness
2 were completed by the patients, and we relied on the
3 medical record abstraction by clinic personnel.
4 Now, a lot of the important information we're
5 collecting is not particularly standardized, but we are
6 getting a lot of important information out of this, and
7 this is data that we're asking -- that we've asked
8 permission to get from the clinic records.
9 And the new patient intake form is scanned,
10 whatever the clinic uses to collect information on new
11 patients. Then, of course, basic demographics, their
12 detailed medical history, the history of their present
13 illness, their medication lists. Whatever laboratory
14 tests have been done by the clinicians, we're
15 collecting those tests and what the results are. Family
16 history, infection and immunization history, and
17 physical examination.
18 So while that information is not
19 standardized, we're collecting whatever each site has,
20 and even that will be interesting, to review different
21 clinics' approaches to collecting this information.
22 The patient self-collected instruments, the

1 three at the top were collected at the clinic so that
2 the patients could be monitored and supported by clinic
3 personnel while they were completing these forms. All
4 the other forms -- and I think you've heard about most
5 of these a little bit throughout the day and yesterday
6 -- were collected within a week of the clinic, and a
7 lot of them were put online so the patient could
8 complete in a paced way, as they felt they had time.
9 So I'd like to give you just an interim
10 analysis, and we've just, just begun this finalizing
11 the data. We were able to include 393 participants in
12 this interim analysis. We expect a total of 450 when
13 enrollment is really completed. And the distribution
14 among the seven clinics is shown here. It's fairly
15 evenly distributed, and that's, of course, one of the
16 goals of our study, is to be sure that we're taking a
17 look at all seven clinics.
18 And I'm going to go through a number of
19 slides describing the data that we have, and in the
20 interest of time, I'm going to just emphasize the high
21 points and also just try to give you an idea of how we
22 expect that we will use the data once this is really

1 finalized, because this is just an interim analysis.
2 In this slide, the factors that have a little
3 star beside them did differ statistically between the
4 clinics. And the mean age at -- the mean age of the
5 patients at the time of the study was 48.6 years, but
6 that did vary, and that's the top graph. And I should
7 emphasize that a lot -- the things that we find that
8 vary statistically doesn't necessarily mean that it's a
9 biologically meaningful difference, and we'll have a
10 lot more work to do to really determine that.
11 Seventy-one percent of the patients were
12 female, and the proportion female in each clinic, there
13 was a variation. What we found was 95.4 percent of the
14 patients were white, and this, of course, is not really
15 representative of CFS, but this is representative of
16 the clinic populations, the clinics that we're working
17 with. And we think this is a really good sign of
18 access to care that we have to address in a concerted
19 effort.
20 The mean BMI was 27.2; 58.1 percent were
21 married; 78 percent had greater than a college
22 education; and 98 percent were insured, and that is

1 another big difference from the general population.
2 What was consistent across the clinics -- there was
3 really no difference at all -- was that 75 percent were
4 not working.
5 The age at diagnosis, the mean age was 38.2
6 years, and about two-thirds of them had a sudden onset.
7 The range in this -- the proportion that was a sudden
8 onset was between 52 percent and 76 percent, and that
9 did differ by the clinic. The mean duration of illness
10 was 15 years, and the figure below there is just a --
11 gives you a distribution of the duration of fatigue at
12 each of the clinic sites.
13 Now, this slide is a compilation of different
14 measures of fatigue that we've looked at, and one of
15 the advantages of using multiple standardized
16 instruments to measure the same part of the illness is
17 to see what information we're getting from each of the
18 instruments, to see also which instruments we could
19 possibly reduce, and because we're going to be doing
20 follow-ups, we're going to see which instruments give
21 us the most reliable indication of change.
22 So at this point, this is just cross-

1 sectional. And I've -- I'm going to be emphasizing the
2 PROMIS instruments, which are a set of instruments that
3 were developed by NIH for use across a whole broad
4 spectrum of illnesses. They're very highly validated,
5 and they're very brief. And so the PROMIS instruments
6 have a lot to recommend them for use if they will work
7 in this population, and they, to date, have not really
8 been validated in CFS.
9 The PROMIS scores of fatigue was 68.3, and
10 the scores across the clinics were different, the
11 PROMIS scores in fatigue. The bar graph there shows
12 the MFI scores by clinic, and MFI is scored by multiple
13 domains. Physical fatigue is the first bar, and it
14 goes across.
15 The lowest scores on the -- sorry. The
16 lowest -- so MFI and the subscore of reduced activity
17 did differ by clinic, but all of the other MFI scores
18 were similar across the clinics. And the general
19 fatigue was the one measure that we had a big ceiling
20 effect on. Thirty-seven percent of the patients were
21 at the maximum score. And this was not in any of the
22 other subscores.

1 The PROMIS fatigue correlated with the MFI
2 subscales on three of the MFI subscales, the general
3 fatigue, physical fatigue, and reduced activity, but
4 did not correlate with -- well with the other two,
5 which is the reduced motivation and the mental fatigue.
6 And we've talked about how fatigue might not
7 be actually as important as measures of function. And
8 the SF-36 has been an instrument that's been used in a
9 number of studies. And what the SF-36 shows very
10 clearly -- again, it's got a number of subscores. You
11 can see that the bars are all very low except for two
12 of them, and there's relative -- those two relatively
13 high scores are on vitality -- sorry, are on mental
14 health and role emotional, indicating that those areas
15 of function are preserved in CFS. And that, again, is
16 pretty consistent across all of the clinics.
17 We included a measure of daily activities in
18 a vertical manner, which is, as Cindy described, either
19 standing or sitting with your feet on the floor, and
20 that mean level was 7.6 across the clinics. The hours
21 of activity with your feet up, horizontal, was 12.8,
22 and that did show a difference across the clinics.

1 We asked about exercise, mild exercise,
2 numbers of times per week that this was done, and there
3 was a difference in this response across clinics, the
4 average being 3.4 times a week.
5 For measures of pain, we included the Brief
6 Pain Inventory, and, again, the PROMIS scores. And in
7 the Brief Pain Inventory, over 80 percent of the
8 patients had pain in the last week. And in the Brief
9 Pain Inventory, it's only those 80 percent that go on
10 to complete the rest of the inventory.
11 The percent of patients taking pain
12 medication did differ by the clinic, and the severity
13 scores in the BPI differed across clinics, but there
14 was a very good correlation between the PROMIS pain
15 interference with activity and the BPI pain
16 interference.
17 In measures of sleep, we noted severe sleep
18 impairment in the PROMIS scores in the sleep questions
19 that we had included as well as in the CDC Symptom
20 Inventory. And there were differences between clinics
21 in the PROMIS sleep-related impairment and in the times
22 awakening not rested.

1 Now, I'm going to show you a series of
2 patterns here, and this is just a distribution of the
3 scores on various questions that were asked in the CDC
4 Symptom Inventory. And the Symptom Inventory score is
5 a combination of both intensity and frequency of that
6 symptom. And each of the clinics is a different-
7 colored bar, and the various -- let's see if I can
8 point -- like this gives an idea of the severity, so
9 bar -- this is the lowest to the highest.
10 And so the only thing you need to do is kind
11 of look at the patterns, and you can see that for some
12 symptoms, the -- it's just about everybody's over on
13 the right, where it's most severe, and as you go down
14 each one, we're seeing a shift to the left, which is
15 less severity.
16 And most of these patterns don't differ
17 between the clinics, the ones that are -- have a little
18 star, there was some difference between the clinics in
19 these scores. But what this does show you is that for
20 some symptoms, such as the concentration and the memory
21 problems right there in the middle, there's almost a U
22 shape, where there seems to be one population that has

1 the very severe function problems and another one that
2 doesn't have any at all.
3 And so I started with those that had the
4 highest scores, moving on down to the least
5 problematic, at least on this measure, and you can see
6 that the fever was the one that had the very lowest
7 scores.
8 We included questions from the DePaul Symptom
9 Questionnaire, and that questionnaire also measures
10 severity and frequency of the symptoms, and the -- both
11 the severity and the frequency scores kind of followed
12 each other. Their scoring does not call for
13 integrating them, but gives them each separate scores.
14 And so in the interest of time, I'm just showing you
15 the severity scores for some of these.
16 And, interestingly, the sensitivity to noise
17 and the alcohol intolerance were the factors that
18 showed the most difference across clinics. And some of
19 these measures, such as unsteady on feet, dizziness, or
20 fainting, part of the autonomic measures, again, shows
21 a very uneven distribution across the patients.
22 And, finally, I'd like to close with just an

1 example of how we think that the PROMIS scores are
2 going to help us. At the top, the first line on this
3 gives the scores that we have in our CFS patients in
4 this study for fatigue, sleep disturbance, sleep-
5 related impairment, pain interference, and pain
6 behavior.
7 And then below that, there are -- actually,
8 it's only two studies, but five different conditions
9 that have used these same measurements, so we can make
10 a direct comparison. And chronic pelvic pain, you can
11 see that the fatigue score is less, and for the promise
12 score, the T score of 50 is considered average;
13 anything above 50 is worse. And ten-point differences
14 is definitely a significant difference between them,
15 functionally.
16 And whereas sleep is about the same between -
17 - in the chronic pelvic pain, and pain behavior -- that
18 is pain that's influencing what you're able to do -- is
19 approximately the same in the chronic pelvic pain as in
20 the CFS patients in this population.
21 The other measures, again, are very
22 interesting: spinal cord injury, muscular dystrophy,

1 post-polio syndrome, and multiple sclerosis, and you
2 can see that the fatigue in these situations are all
3 much lower, and sleep is much lower, pain is much
4 lower.
5 And so this is just an interim analysis, and
6 I would like to emphasize that I think that this
7 interim analysis so far has shown us that there is a
8 heterogeneity in the CFS population as a whole. There
9 is a little bit between clinics, but more in the
10 patients than between clinics.
11 This is also giving us a hint that phenotypic
12 measures themselves may be limited in their ability to
13 distinguish robust phenotypes -- or robust subgroups,
14 and that's why we're proposing to expand this study to
15 some other measures. And it could very well be that
16 other biologic correlates will be needed in order to
17 better define subgroups.
18 The other study -- the other factor is that
19 the data from these kinds of studies will allow us to
20 evaluate how well these questionnaires work. For
21 example, the MFI General Fatigue Scale, in this
22 population, really, from the specialty clinics, did --

1 was limited by its already reaching the maximum in 40
2 percent of the patients.
3 The final datasets will allow comparison of
4 the instruments measuring the domains of CFS illness,
5 and, importantly, we have follow-up plan to allow the
6 measures to correlate with changes in illness status.
7 We have additional measures of cognition and
8 exercise capacity that are planned in a subset of this
9 study population, and this study is going to be
10 included -- or expanded to include healthy controls as
11 well as ill controls, the -- and ill comparison groups,
12 I think, are really important to really understand how
13 these measures will distinguish CFS from other patient
14 populations as well as pediatrics.
15 Okay. So, finally, the most important thing
16 is to acknowledge and thank everyone involved in this
17 study, most importantly the CFS patients study
18 participants. They really had to fill out a lot of
19 questions, and we understand the burden that this is,
20 and we really appreciate it. We appreciate our expert
21 clinicians.
22 And one of the things that we found most

1 rewarding is our on-site visits with each other, and
2 the clinicians also appreciate the opportunity for
3 networking. So I think this is just a little beginning
4 step of networking, and I see more and more evidence of
5 the need and anxiousness to start with this
6 interacting.
7 And, of course, at the CDC, I need to thank
8 my colleagues, everybody that's been involved with
9 this, particularly Sally Lynn and the others that are
10 in bold who worked really, really hard to get this
11 preliminary data organized and summarized for this
12 session. And thank you.
13 DR. COX: Thanks, Beth. And now we'll hear
14 from Ashley Slagle. She's an ORISE fellow within the
15 Study Endpoints and Labeling Development Team, which
16 was within CDER, FDA. And she'll be talking to us
17 about clinical outcome assessments to evaluate
18 treatment benefit in clinical trials for CFS and ME.
19 And I'll remind folks too -- I know we've
20 been trying to move to keep as close to schedule as
21 possible. If you do have questions, if you'll write
22 them down on the yellow pages, we'll be collecting

1 those shortly, and we'll certainly do our best to try
2 and get some questions in while also trying to be
3 mindful of the time schedule too. So Ashley? Clinical
4 Outcome Assessments to Evaluate Treatment Benefit in
5 Clinical Trials for CFS and ME
6 DR. SLAGLE: Thank you. Well, good
7 afternoon. First, I would like to thank the conference
8 organizers for inviting me to participate today. You
9 know, it's so critical that we find effective therapies
10 that can help CFS and ME patients significantly improve
11 how they feel and function. And so to be able to
12 participate that -- in that effort in any way that I
13 can is very important, and I'm really pleased to be
14 here.
15 Of course, to find effective therapies, I
16 think one of the critical steps is that we need to be
17 able to assess those therapies in a well-defined and
18 reliable way. So my discussion today is going to focus
19 on some regulatory and other considerations for
20 assessing treatment benefit or effectiveness in
21 clinical trials of CFS and ME.
22 So I am not speaking on behalf of the FDA.

1 As was mentioned, I'm a fellow in the FDA, working with
2 the Study Endpoints and Labeling Development staff. And
3 so the views expressed here are my own, but they are
4 based on my experiences working during this fellowship.
5 Okay. From the regulatory perspective, it's
6 necessary that drug developers document substantial
7 evidence of treatment benefit from adequate and well-
8 controlled clinical trials. The regulations also
9 specify -- specifically indicate that the methods of
10 assessment of a subject's response be well-defined and
11 reliable. This is important. It means that well-
12 defined and reliable become the key criteria by which
13 the FDA judge outcome assessments.
14 And the evidence of treatment benefit is used
15 to support the conclusion of effectiveness for drug
16 approvals, but also for claims that are made in
17 labeling and promotion, so communication that's
18 provided to patients with CFS and ME.
19 So what does this mean, that outcome
20 assessments are well-defined and reliable? Well,
21 generally speaking, it means measuring the right thing,
22 or the concept of interest, in the right way, in a

1 defined population or targeted context of use.
2 Specifically, it means that the score that
3 quantifies the thing that you're measuring does so
4 accurately and reliably, and the effects that are seen
5 in the outcome assessment can be interpreted as a clear
6 treatment benefit.
7 So let me define treatment benefit. FDA
8 defines the treatment benefit as the impact of
9 treatment on how patients feel, function, or survive.
10 Now, feels is a patient's physical sensation or some
11 perceived mental state that -- or related to their
12 health within their typical daily life. So pain,
13 weakness, cognitive problems might be -- are good
14 examples of feelings.
15 Function is a patient's ability to perform an
16 activity that's a meaningful part of their daily life.
17 Now, FDA describes three different methods that either
18 directly or indirectly assess treatment benefit in
19 clinical trials, and these include measures of
20 survival, biomarkers, and clinical outcome assessments.
21 So for the purposes of assessing treatment
22 benefit in CFS and ME clinical trials, of course

1 survival is an important outcome, but in order to use
2 survival as an outcome, it would take very long
3 clinical trials, which would unnecessarily prolong the
4 time that it takes for treatments to reach the market.
5 So I'm -- for the rest of this talk, I'm
6 going to focus quickly on biomarkers, but then spend
7 the remainder of the discussion talking about clinical
8 outcome assessments.
9 Now, a biomarker is an objective measure of
10 biologic process, pathologic process, or biologic
11 response to a therapeutic intervention. An example
12 might include immune function markers. What's
13 important to remember about biomarkers when assessing
14 treatment benefit in clinical trials is that they do
15 not directly tell us how a patient feels, functions, or
16 survives.
17 Instead, biomarkers may provide indirect
18 evidence of treatment benefit by showing a biologic
19 treatment response, but to use biomarkers as evidence
20 of treatment benefit to support regulatory approval, it
21 would be necessary to understand how that biologic
22 response relates to how patients feel, function, and

1 survive in their daily life.
2 So you want to understand what is the
3 association between -- or the replacement value of the
4 indirect biomarker assessment and the directly
5 meaningful treatment benefit. Unfortunately, in CFS
6 and ME, there are no scientifically agreed upon
7 biomarkers yet to use as of course assessments.
8 And remember, as we heard this morning, that
9 if treatments are approved on the basis of a biomarker
10 that's used as a surrogate endpoint in the accelerated
11 approval process, there's still a need to prove a true
12 treatment benefit in subsequent trials if we don't
13 fully -- if that link isn't fully established yet. And
14 if those subsequent trials fail, then the drug could be
15 removed from the market. And so that's why it's
16 critically important to find clinical outcome
17 assessments that can directly tell us how patients are
18 feeling and functioning, and it's a direct evidence of
19 treatment benefit.
20 So then let's turn our attention to clinical
21 outcome assessments. Like I said, clinical outcome
22 assessments may allow us the opportunity to more

1 directly assess how patients feel and function. A
2 clinical outcome assessment is based on a report by the
3 patients themselves, or a patient-reported outcome;
4 based possibly on a clinician-reported outcome; or
5 another observer who doesn't need clinical training,
6 such as a caregiver or a parent.
7 And unlike a biomarker, a clinical outcome
8 assessment may be influenced by human choices,
9 judgment, or motivation, because they depend on the
10 cooperation, interpretation, and reporting by a person.
11 But regardless of who's doing the reporting, all
12 clinical outcome assessments ultimately produce a score
13 that may be used to test for statistical and clinically
14 meaningful differences in trials.
15 Clinical outcome assessments can provide
16 critical understanding of a drug's benefit or harm, and
17 so therefore they require rigorous development and
18 evaluation before they can be used to assess treatment
19 benefit in clinical trials, particularly trials that
20 are meant to support drug approval. So only with that
21 careful development and evaluation can one ensure that
22 the assessments have adequate validity and reliability

1 to support claims of treatment benefit.
2 Now, assessments that are reported by
3 patients, clinicians, or other observers are not all
4 clinical outcome assessments to evaluate treatment
5 benefit in clinical trials. There are assessments
6 that, while reported by patients or clinicians or
7 caregivers or other observers, are useful for very
8 different purposes. They may be useful for diagnostic
9 purposes or prognostic purposes; used to select
10 patients for a clinical trial; used for epidemiologic
11 studies, or understanding the natural history of a
12 condition.
13 And oftentimes, assessments that are useful
14 for these other contexts are not really great outcome
15 assessments in clinical trials; at least not without
16 some modifications. So, for example, an instrument
17 that is really great at identifying which patients have
18 CFS or ME versus those who don't, that same instrument
19 may be terrible at detecting treatment differences
20 within patients in a clinical trial.
21 And then one more broad point I'd like to
22 make, across multiple conditions, including CFS and ME,

1 I've heard concerns expressed that clinical outcome
2 assessments must be used in conjunction with a
3 biomarker. This isn't true. Clinical outcome
4 assessments may be used independently in clinical
5 trials. Remember that FDA's requirement is that any
6 assessment is well-defined and reliable.
7 Okay. The elements that are listed here will
8 impact whether an instrument is considered well-defined
9 and reliable, and I'm going to discuss each more
10 specifically in the subsequent slides.
11 Now, whether or not a clinical outcome
12 assessment is appropriate very much depends on its
13 context of use. The context of use in this case is
14 that we're talking about the outcome assessments used
15 in clinical trials, but context of use also includes
16 many more specific considerations.
17 So the disease definition, which must be
18 explicit and specific; relevant disease
19 characteristics, for example, the severity level of
20 disease. An outcome assessment that's appropriate for
21 patients with a very severe level of disease, for
22 example, who may be bedridden, might be very different

1 from an outcome assessment that should be used in
2 patients who still have close to normal daily
3 functioning. What's important is that the assessment
4 match the population that it's being used in.
5 The selection of an appropriate instrument
6 also may depend on other clinical characteristic of the
7 population, so patients with different comorbidities,
8 the demographic characteristics of the population. For
9 example, age is very important. A self-reported
10 assessment might work very well in adults, but in
11 children who can't report for themselves, we couldn't
12 use the same outcome assessment.
13 The context of use considerations also
14 include the study, the study design; the other
15 endpoints that are being used, and how this clinical
16 outcome assessment will fit in with those other
17 endpoints; and then, of course, the type of labeling
18 claims that are being sought.
19 One of the biggest challenges in CFS and ME
20 related to the context of use is that the disease
21 definition isn't entirely clear, but there are ways
22 around that. What is important is to identify a

1 rational set of clinical trial entry criteria, and
2 being careful to exclude other conditions, to the
3 extent possible.
4 Of course, in clinical practice, many other
5 comorbidities exist, but it's important to have as pure
6 of a population in your clinical trial as possible to
7 limit any unwanted variability that might obscure
8 treatment effects. Of course, there is a need to
9 identify the most precisely defined population, but
10 researchers and the FDA recognize that patient
11 selection really needs to be practical too so that you
12 can recruit sufficient patients. There are a number of
13 potential subpopulations within CFS and ME, and I've
14 listed several here, but we know that there are more.
15 So you've probably realized by now that the
16 things that we want to measure, the concepts that we
17 want to measure, and the context of use go hand in
18 hand. We can't consider one without considering the
19 other. So it's critical to define your context of use,
20 define what concepts are important to measure, and then
21 select your outcome measure.
22 And, actually, yesterday's -- one of the

1 goals of yesterday's meetings was to help us really
2 start to better understand what are the important
3 things that we should be measuring in different
4 populations of patients with varying experiences?
5 In thinking about the things that may be
6 important to assess in CFS and ME clinical trials, I've
7 listed here a fairly comprehensive list of symptoms. Of
8 course, not all patients experience all of these
9 symptoms, and this list doesn't reflect all of the
10 things that all patients experience.
11 It also focuses primarily on symptoms and
12 doesn't reflect some of the more multifactorial
13 experiences that patients have, such -- you know,
14 family concerns, social concerns, financial impacts,
15 and general quality of life. And we know all of these
16 things are important, but these impacts are very
17 difficult to assess in clinical trials, particularly
18 because they're multifactorial.
19 And we heard an example this morning of a
20 clinical trial that failed, although the patients --
21 they were -- they were getting better. They were going
22 back to work. The outcome assessment assessed quality

1 of life, which was probably not the best measure to
2 use, and it -- so you don't know when a -- when a
3 treatment fails, if it's -- is the drug really not
4 effective, or was the outcome assessment that you used
5 not the appropriate one?
6 So the goal is to identify the experiences
7 that are important to patients in the various
8 subpopulations, identify those things that are
9 important and can be feasibly and accurately measured
10 in a clinical trial setting, and identify those things
11 that you would hope to see a drug therapy have some
12 impact on, then find the outcome assessments to measure
13 those things.
14 And, again, yesterday was a great start at
15 generating that list of things that we should be
16 thinking about measuring in clinical trials. So I've
17 tried to represent visually here how to think about
18 what to select when you're measuring something in a
19 clinical trial.
20 So the yellow circle represents all of the
21 things that the broad group of CFS and ME patients
22 might experience. The green circle represents a

1 particular, well-defined subpopulation of patients who,
2 for example, experienced post-exertional fatigue or
3 malaise. The blue circle represents the effects of a
4 drug treatment. Where the green and the blue circles
5 overlap represents the right thing to assess in a
6 clinical trial of this particular subpopulation in
7 order to document treatment benefit.
8 Now, in this slide, we have all of the
9 original circles that I described, but we also have the
10 addition of this rust-colored circle. It represents
11 the assessment of something that is not experienced by
12 or relevant to the subpopulation that was in this
13 particular trial. Even though it's relevant to the
14 broader population and it may do a good job of
15 distinguishing between the population -- your clinical
16 trial participants and those who shouldn't be in the
17 clinical trial, this would not pick up a treatment
18 benefit in the clinical trial of that population, if
19 you were to measure those things.
20 So, again, it's key to define the right
21 things and good measures of those things upfront so you
22 don't have to look back on trials and wonder if it's

1 truly the drug failing or if it's your outcome
2 assessment that's failing.
3 Because CFS and ME are highly symptomatic
4 conditions that seriously impact functioning and daily
5 life, I'm going to discuss some issues that are
6 specific to patient-reported outcome measures. And
7 here's a specific example highlighting a concern of the
8 content of a patient-reported outcome measure.
9 So say, for example, an investigator intends
10 to assess a study population of primarily bedridden
11 patients, where minimal physical activity is very
12 difficult. So the concept of interest, or what -- the
13 thing that we would want to measure is physical
14 functioning. We want to see if patients are able to
15 improve their physical activities.
16 So an investigator could look for an
17 assessment that assesses physical functioning. Makes
18 sense. But if you look closely at the assessment, and
19 this is based on an actual example that happened in
20 another condition, you see in the items that there's a
21 question, "Do you have trouble running to the bus?" So
22 it says it's assessing physical functioning, which you

1 want to assess, but the items assessing that are not
2 appropriate. Clearly, this would not be appropriate
3 for a bedridden population.
4 So this is why it's so important to consider
5 every specific item or question in a questionnaire and
6 how those items contribute to the domain scores and
7 then the overall score of the instrument. So to avoid
8 using questionnaires that don't appropriately target
9 the population, the FDA would look at individual items
10 that make up those scores to determine if the items and
11 the instrument are appropriate in that context of use.
12 Now, in this case, the colored boxes
13 represent scores that are turned into endpoints in a
14 clinical trial. So as an example, if the overall
15 concept to be measured is fatigue, then it's important
16 to consider what items and domains make up fatigue.
17 Domain A might include items that promote -- produce a
18 domain score that relates to physical tiredness, while
19 Domain B might represent mental tiredness. There could
20 be a Domain C that represents emotional tiredness.
21 There are other domains of fatigue that possibly should
22 be included.

1 This is where it is critical to talk to
2 patients in the intended population to really fully
3 understand what are the meaningful aspects of a broader
4 concept that we should be measuring in clinical trials
5 to understand treatment benefit?
6 So there are some other considerations for
7 selecting clinical outcome assessments for use in
8 clinical trials, and one is the recall period. We know
9 that people have difficulty recalling or averaging
10 experiences over long periods of time, so for symptoms
11 that vary over the course of a day or even hours,
12 asking a patient to recall over several weeks is
13 unlikely to give us very reliable results. And I think
14 this is particularly important in patients who are
15 having some cognitive difficulties. It makes it even
16 more difficult to think about -- thinking about your
17 experience over the last week, two weeks, 30 days.
18 The length of a questionnaire is also
19 important to consider. Investigators need to think
20 about responder burden. You know, unlike some
21 epidemiological studies, where patients are completing
22 assessments just one time, in a clinical trial,

1 assessments are completed multiple times, sometimes
2 daily, and so lengthy questionnaires really don't lend
3 themselves to being used in clinical trials with these
4 repeated assessments.
5 And, again, thinking about the symptom that
6 we've heard a lot over the last two days is that
7 patients who are having cognitive difficulties and sort
8 of hit a wall after reading for so many minutes, if
9 they're trying to fill out a very long questionnaire,
10 it may become impossible after just a few questions.
11 The mode of administration should be given
12 some consideration. Electronic data capture does help
13 to limit missing data, but you have to be careful. If
14 an instrument was developed for a paper administration,
15 if you just transfer it onto an electronic platform,
16 you have to be careful that you haven't changed the way
17 that patients are interpreting those questions, and you
18 don't want it to impact how patients respond to that
19 assessment.
20 And then once you've assured content
21 validity, the recall period, the length of the
22 questionnaire, the mode of the administration is

1 established, then it's important to evaluate the other
2 psychometric measurement properties of an instrument,
3 and this includes reliability, construct validity, and
4 the ability to detect change.
5 So now I'm going to turn our attention to
6 talking about some existing instruments. This slide
7 identifies just some of the many patient-reported
8 outcome assessments that have been used in CFS and ME.
9 It certainly doesn't represent all of them.
10 What this slide does highlight is that there
11 are already quite a few existing instruments that have
12 been identified, which represent the many different
13 symptoms and domains that may be relevant to various
14 subpopulations within CFS and ME.
15 However, many of these have been developed
16 for purposes other than as outcome assessments in
17 clinical trials, or they have not been specifically
18 developed for CFS and ME subpopulations, so they need
19 to be evaluated carefully and potentially modified
20 before they're used in clinical trials.
21 In addition to patient-reported outcome
22 assessments, there are also clinician-reported outcome

1 assessments and observer-reported outcome assessments.
2 I've listed a couple of clinician-reported outcome
3 assessments here, and so far we haven't found any
4 observer-reported assessments that may be useful for
5 assessing experiences in young children or other people
6 who are unable to report for themselves.
7 So I'd like to point out some of the
8 challenges that we've identified in existing
9 instruments, when we consider them for use as outcome
10 assessments in clinical trials. And I don't want to
11 pick apart specific instruments. That's not my goal.
12 But I hope that by identifying some of these broader
13 concerns, that it can help guide instrument selection
14 for clinical trials.
15 So there are some instruments, and the
16 Karnofsky Performance Scale is an example of this, that
17 have been developed for diagnostic purposes or as a
18 classification tool. And these types of tools rarely
19 can capture the appropriate concepts that are relevant
20 to treatment benefit.
21 Some of the assessments have been developed
22 as epidemiologic assessments, so they're very

1 comprehensive, which is great for an epidemiologic
2 study, but they're too long for use in clinical trials,
3 especially with repeated administration. The recall
4 period is often way too long for patients to report
5 accurately, and they include a lot of symptoms that not
6 everyone experiences.
7 There have been some generic measures that
8 have been developed for a broad population, and they're
9 not specific to CFS and ME. The concerns here are that
10 these measures include items that aren't relevant at
11 all to the population; for example, the can you run to
12 the -- how much trouble do you have running to the bus?
13 Or they might be missing some items that are very
14 important to measure in this population.
15 In some cases, there are conceptual framework
16 concerns. There are -- for example, there are
17 checklists where you're checking "yes" or "no," whether
18 you have a symptom or not, but there's no conceptual
19 framework or no scoring algorithm that's available to
20 produce a score that can support an endpoint.
21 I see also problems with conceptual framework
22 issues in general measures of fatigue, where items ask

1 about fatigue generally, but they don't consider
2 including items within the various domains of fatigue
3 that are relevant to CFS and ME patients. And in some
4 cases, the measures don't account for activity level,
5 which we're hearing is very important to consider when
6 you're thinking about symptoms in CFS and ME.
7 There are also some concerns with individual
8 items in some of these measures. In some cases, the
9 items are very confusing, where they ask -- one item
10 will ask about trouble falling asleep or trouble
11 sleeping too much, which leaves patients unsure how to
12 respond to that.
13 The items may be too general. Sometimes they
14 ask about, "Are your signs or symptoms of disease
15 present?" Well, what signs or symptoms of disease? And
16 then in other cases, some of the items are just not
17 really relevant and don't make a lot of sense, or
18 patients don't know how to interpret them, so items
19 like "I feel fit" or "I feel peppy" are not really
20 clear and relevant.
21 So all of the concerns that I highlighted in
22 my last slide, of course, will impact whether an

1 instrument is well-defined and reliable and therefore
2 appropriate to support drug approval and labeling
3 claims. And, unfortunately, none of the instruments
4 I've reviewed so far are ideal to assess treatment
5 benefit in clinical trials of CFS and ME patients, but
6 it's important not to let the perfect be the enemy of
7 the good.
8 So what are our options? Well, the ideal
9 option is to continue looking and find existing
10 measures that are appropriate within specific
11 subpopulations. But if this isn't possible, another
12 really good option is to modify existing instruments to
13 make them well-defined and reliable for a particular
14 clinical trial. And there are many instruments that
15 are already existing that we can consider to modify,
16 and we can remove the problems that we already know
17 exist in some of these instruments.
18 And then, outcome, the final option is to
19 develop a new instrument, but with all of the work
20 that's already been put into many of these existing
21 instruments, all that we know and we continue to learn
22 about the CFS and ME population, I don't think that

1 developing a new measure is necessary.
2 So as we think about modifying or developing
3 instruments for use in CFS and ME, I would like to
4 describe a process through which the FDA is able to
5 work with the public to do this. This process is
6 called the drug development tool qualification process,
7 and it's outside of a specific drug development
8 program.
9 So what this allows is for various groups to
10 work together and come to the FDA through this process
11 and receive consultation and advice from the FDA on the
12 instrument that they're putting together for use in
13 future clinical trials. And the idea is that these
14 instruments would be available publicly and they could
15 be used across many clinical trials within the same
16 context of use.
17 And I think this is a really good approach to
18 instrument development or modification, because the FDA
19 is participating, various groups are coming together
20 with a lot of different expertise, and it helps to
21 reduce scientific uncertainty and risk to the
22 pharmaceutical companies, ultimately, who would use

1 these outcome assessments in their clinical trials.
2 And I've provided some links here with
3 some additional information and an email address if
4 you're interested in finding out more information about
5 the DDT qualification process. Thank you. Audience
6 Question and Answer Period
7 DR. COX: Thanks, Ashley. So now we'll try
8 and take some questions, and we'll also be watching the
9 clock too so that we don't go too far over.
10 DR. DIMITRAKOFF: Thanks, Dr. Cox. I had the
11 sense that we -- that this panel actually deserves a
12 whole day, but I do think that the talks were quite
13 productive and insightful. So probably start with a
14 question for everyone on the panel. So the question,
15 basically, is it's clear that we need large clinical
16 trials because of the heterogeneity of ME, but those
17 big trials are usually paid for by pharma, who Dr.
18 Munos told us won't invest because of how ill-defined
19 the disease is. Patients do not have the resources to
20 bridge this gap. So comments from the panel? Dr. Rowe?
21 DR. ROWE: Yeah, I think this is a big
22 problem. Others had commented that we need something

1 like what was available for the HIV network or what we
2 see being available for patients with pediatric cancer.
3 Almost every patient that shows up in our institution
4 is slotted into a multicenter trial. That requires
5 some sort of effort. I'm not sure where it would come
6 from.
7 When we submitted our first grant to the NIH
8 for the study of Florinef, it had a priority score of
9 326, which my colleagues emphasized was you're dead and
10 buried, and I think the only reason that study
11 eventually got overturned by -- or the scoring got
12 overturned by NIH counsel was that we were able to say,
13 "Look, your internal intramural researcher, Steve
14 Straus, wants to work on this. He's putting resources
15 into it. How do you explain the discrepancy between
16 that vote of confidence and the review committee?"
17 And then a second problem we had was when we
18 were halfway through the Florinef trial, we proposed
19 studying midodrine in a crossover trial, and the review
20 committee didn't give it a score because there was no
21 mechanism for funding clinical trials at the NIH. Since
22 we were currently being funded for a clinical trial by

1 the NIH, I was a little puzzled by that.
2 But in the end, I think that comment was
3 correct, that the first trial would have -- was
4 addressing pathophysiologic mechanisms, and the NIH
5 focuses on that. So they are not a clinical trials
6 agency, for the most part. So I think that's a big gap
7 that we're struggling with, is that if studies don't
8 come from pharma, I don't know who would fund them.
9 DR. DIMITRAKOFF: Dr. Snell?
10 DR. SNELL: You know, clearly, because it's a
11 multidimensional illness and the endpoints are likely
12 to rely on expertise from different individuals,
13 coordinating the whole thing is a major task and a
14 major economic problem. So, yes, it needs something to
15 drive it.
16 DR. DIMITRAKOFF: Ashley?
17 DR. SLAGLE: I think that one of the things
18 that we can do is try to encourage pharmaceutical
19 companies to complete these trials, and in my world,
20 one of those things we can do is to develop good
21 outcome assessments and so that there's lower risk to
22 the pharmaceutical companies in conducting these

1 trials. If they know what they're shooting for, you
2 know, if they have well-established measures that they
3 know that they can use that have been developed in
4 consultation with the FDA, then I hope that they'd be
5 more likely to engage in clinical study (inaudible).
6 DR. DIMITRAKOFF: Dr. Unger? Thanks.
7 DR. UNGER: Yeah. It goes back to what was
8 in the first panel, reducing the risk for the drug
9 companies and showing, once we get a critical mass of
10 data and infrastructure, then they will come. And
11 that's -- and I believe that that's true. And just to
12 -- CDC doesn't do clinical trials, but we're supporting
13 it by trying to make some of the first data -- a start
14 on the data and a construct.
15 DR. DIMITRAKOFF: I just want to throw my two
16 cents into the discussion. We actually had some
17 discussion with some other colleagues during the lunch
18 break, and I think one of the very promising mechanisms
19 for doing this is actually through a partnership
20 through the NIH, so there is a partnership grant
21 program. It's an RFA, which actually provides
22 researchers with access to the NIH Clinical Center

1 resources.
2 So it's a shared grant mechanism which allows
3 people to do clinical trials utilizing the NIH Clinical
4 Center research. So that might be probably similar to
5 what Dr. Rowe was doing back in the day with Dr.
6 Straus, but maybe that's something that could be
7 potentially a good start.
8 DR. COX: All right. The next question here
9 is asking -- or citing a survey where 18 percent of
10 respondents diagnosed with ME/CSF (sic) have only that
11 diagnosis. The high rate of comorbidity may be an
12 additional challenge for design of clinical trials, and
13 it's asking if there's any suggestions from the panel
14 about how this challenge might be addressed with
15 regards to clinical trials.
16 Dr. Rowe, do you want to start off?
17 DR. ROWE: I mean, one option might be to do
18 what they've done in fibromyalgia, where I think they
19 faced the same issue with these multiple comorbidities,
20 and yet they have a number of approved drugs. And I
21 think part of it is just you've got to have a huge
22 enough sample size that there is a random distribution

1 of the comorbid problems.
2 So that's one option. The other is that any
3 two people with the illness next to one another have a
4 lot of differences, and so using each as his or her own
5 control is another way of getting around that problem.
6 DR. DIMITRAKOFF: We're trying to -- just
7 trying to be mindful and respectful and respectful to
8 all the people that asked the questions, given the
9 limited time, and that's why we're just trying to
10 probably address some more questions.
11 So there is a question for Dr. Unger, given
12 the results from the CDC trial. So the question
13 basically says, "You mentioned that
14 infection/immunization is in part in your database that
15 you have assembled. Have you looked separate at any
16 connection between immunization and onset or
17 exacerbation of symptoms or relapse, and are the data
18 maintained in such a way that such an analysis could be
19 done?"
20 DR. UNGER: We don't have onset specifically
21 correlated with the infections or immunizations, but
22 this was -- this is our first chance to actually look

1 at the data in this way. And so from that first
2 collection of information, then we can decide what
3 additional questions and how to go forward in the next
4 design.
5 And that was not -- because that wasn't a
6 standardized kind of question, the data -- cleaning up
7 the data -- so to the point where we can analyze it --
8 is taking us a bit longer, but we will have that
9 information, and just at a first look, there is --
10 there are interesting differences in numbers of
11 infections and immunizations. So we think this will be
12 an important data point, but it will only be the
13 beginning of looking at it.
14 DR. COX: Thank you. So a question for
15 Ashley, and it's asking about in the -- at the time
16 that a study's being designed, does the FDA assist with
17 the development of the trial and also -- and coming to
18 agreement on outcome measures? And there's -- yeah,
19 it's essentially just asking does the FDA advise, so
20 feel free and happy to turf it to me if you want to.
21 DR. SLAGLE: There are two processes, at
22 least for developing outcome assessments. You can

1 think about going through the IND or NDA process, where
2 you're developing a specific drug product, and you're
3 working -- going through the IND process with the FDA.
4 And in that case, during that -- the course of normal
5 meetings through that drug development process, you
6 would, of course, if you're bringing information to the
7 FDA about your clinical outcome assessments, you will
8 receive a response. You're likely to receive a
9 response.
10 The other option is to go through this
11 qualification process that I mentioned that is outside
12 of the drug development -- a specific drug development
13 process. And then the FDA is specifically providing
14 consultation to the developers of that instrument, and
15 then ultimately, once it's qualified, that instrument
16 could be used in multiple clinical trials.
17 And, Dr. Cox, if you would like to
18 DR. COX: Yeah, no, all good points. And
19 just sort of, you know, on a broader -- on a broader
20 level, just thinking about this topic, you know, when a
21 clinical trial's being designed, when an endpoint is
22 being selected, we welcome the opportunity to talk with

1 those that are designing the trial and think it's a
2 very important step in the clinical trial design.
3 So for those that are designing trials, for
4 those that are, you know, designing endpoints that
5 they're going to use in trials, please do. Come and
6 talk to us at the point that you are designing your
7 trial. We welcome the opportunity to engage at that
8 point, and we think it's very important for us to do
9 so.
10 DR. SLAGLE: Can I say one more thing?
11 DR. COX: Yeah, please.
12 DR. SLAGLE: The earlier the better. When
13 you're designing assessments, the earlier you start
14 talking to the FDA about it, the better off you are.
15 Pre-IND phase, even if -- that might be a little bit
16 early, but the earlier, the better. Don't wait until
17 the Phase III trials to start talking about outcome
18 assessments.
19 DR. DIMITRAKOFF: Okay. Just a question for
20 Dr. Snell. What is a substantial improvement from
21 baseline in, number one, VO2 max, and, number two,
22 steps walked, as in the Ampligen trial?

1 DR. SNELL: I mean, VO2, you would expect,
2 you know, to see progressive improvement with a
3 training effect. Given that we don't have a lot of
4 data that might show a treatment effect for something
5 other than training -- so the real problem is that if
6 there's a VO2 deficit, we don't know what's causing it,
7 and so if it's -- let's say it's an immune problem,
8 then -- and you fix the immune problem, and all of a
9 sudden the VO2 goes up, you know, you could use a
10 number of different criteria. There are different
11 disability categories rated by oxygen consumption.
12 So if somebody moved from severely disabled
13 to moderately disabled, that would seem to be a
14 reasonable way of looking it -- at it, a 5 percent
15 improvement, 10 percent improvement, and relate that to
16 functionality, then that would be another way of
17 looking at it.
18 What you'd expect to see with an athlete is
19 that you're going to see progressive improvement over
20 time, up to a ceiling, but it's fairly dramatic. You
21 know, you'll see big improvements in VO2 from training
22 in two weeks.

1 As for the steps, we don't have criteria for
2 that. It's not a -- it's not necessarily helpful
3 unless you decide it's related to something else, that
4 there's not a lot of data to show how much -- how many
5 steps you're going to get.
6 There's probably data for the six-minute walk
7 test in terms of distance and the way they grade
8 cardiac disease, but does that apply to chronic fatigue
9 syndrome? I don't know. You need specific data for
10 the population for a test like that, to see where the
11 baseline is.
12 DR. DIMITRAKOFF: We'll go for another five
13 minutes, with everyone's permission and participation.
14 So, Dr. Cox, you actually have the next question.
15 DR. COX: Just one more quick question for
16 Chris Snell on this. It's asking about insurance
17 coverage or payment for exercise testing. Is that
18 something that -- in your experience, that is covered
19 and
20 DR. SNELL: We don't third-party bill, but we
21 advise anybody we see in the clinic to send it in to
22 the insurance company, and the insurance company

1 usually copies the letter when they pay people, and we
2 get a reasonable response to people getting paid.
3 DR. COX: And the underlying diagnoses that
4 they are willing to --
5 DR. SNELL: I -- somebody asked me that
6 earlier, and --
7 DR. COX: Okay.
8 DR. SNELL: -- I can't remember. We actually
9 give them the code number, so I'll look it up, and
10 DR. COX: Great. Thank you.
11 DR. DIMITRAKOFF: So there are two questions
12 from Dr. Grobstein, and one of them is -- there are
13 several, actually, from Dr. Grobstein, and I just pick
14 a couple.
15 One of them is to Dr. Unger and the other one
16 is to Dr. Slagle. The question for Dr. Unger is: "The
17 FDA says patient population must be well-defined for
18 clinical trials, yet CDC's study does not ask
19 participant clinics to use any particular definition.
20 How do you reconcile these two views of how to do
21 trials?"
22 DR. UNGER: Okay. So ours isn't a treatment

1 trial, and we're not -- so we're collecting data on
2 what CFS -- ME/CFS looks like in the -- in the clinics,
3 what the clinicians who treat these patients -- what
4 they look like. That objective data can then be used
5 to derive a case definition of more or less
6 specificity, depending on the use and the indication.
7 And, you know, there are times when you would
8 want a very broad case definition, and then there are
9 times when you would want to restrict it. For example,
10 if you're -- in Dr. Rowe's study, he required postural
11 hypotension, because he was trying to intervene on
12 that. That's a different -- that's a different use of
13 a case definition. So there's -- that, I think, is the
14 distinction.
15 DR. DIMITRAKOFF: Thank you. Just a
16 question, again, from Dr. Grobstein to Dr. Slagle, you
17 briefly pointed out the problems with various commonly
18 used outcome measures, including the Karnofsky scores.
19 You say the role of the instruments -- so you say that
20 the instruments are not ideal. Does this mean we can't
21 do trials, because we have no instruments until we
22 modify the existing instruments or develop new ones?

1 DR. SLAGLE: I don't think -- it shouldn't
2 hold up progress on trials. I think that not having
3 great instruments does add a little bit more risk to
4 the trial. There may be a treatment benefit that's
5 there that's not able to be picked up by the
6 instruments that are used.
7 If there's a huge treatment effect, then even
8 a very broad instrument that may not be specific enough
9 can probably detect that treatment. So I think mapping
10 -- or matching the instrument to the population and
11 measuring the right thing as best as you can, even if
12 it's not ideal, is still an appropriate way to move
13 forward. But we should also be working to modify
14 instruments so that they can be more -- better defined
15 and more reliable.
16 DR. COX: A broad question here, if any of
17 the panelists would like to comment. So the essence of
18 the question asked about what we -- the knowledge that
19 might be gained from brain mapping and the impact that
20 that might have on studies in patients with ME/CFS. Any
21 thoughts on that from the panel? I know it's a fairly
22 broad question.

1 DR. DIMITRAKOFF: Is that brain mapping of
2 the patients or the researchers?
3 DR. COX: I -- it's more the -- it's -- yeah.
4 It's the general research. Any thoughts? It's a big
5 question, so if you're hesitant, we'll just move to the
6 next one. Okay. Fine. Here's a question. I don't
7 know if anyone has any facts or statistics on
8 differences in racial and ethnic groups and the
9 prevalence of CFS, if anyone can comment on that?
10 DR. UNGER: From CDC's population-based
11 studies and Lenny Jason's population-based studies, CFS
12 is very common in racial/ethnic minorities, and it's of
13 equal or increased prevalence, so it just -- it depends
14 a little bit on how the study was done. So, yeah, and
15 just going back to the brain-mapping, I think this is,
16 you know, the future. There's going to be a lot of
17 data that's coming from brain imaging studies. New
18 England Journal of Medicine published something where
19 they could measure pain by functional magnetic -- yeah.
20 DR. DIMITRAKOFF: MRI, yeah.
21 DR. UNGER: Yeah, MRI. So I think this will
22 eventually have an impact. It may be a little bit too

1 soon. And the interesting thing is studies like that
2 and the gene profiling, you end up going very, very
3 deep and getting a lot of data on a very few patients.
4 And that's one approach, and you'll probably -- you're
5 going to get something there, but given the
6 heterogeneity of the illness, we also have to go broad
7 and -- so that we can go deep and make sure that when
8 we go deep, we have a uniform group that we're going
9 deep on.
10 And I think some of the confusion in the
11 literature has been on these different comorbidities,
12 different stages of the illness, and so we're getting
13 different views of the illness.
14 DR. DIMITRAKOFF: And building on what you
15 said, just to add up to the MRI studies, I think it
16 might also be important in the future to kind of like
17 use the paradigm that Dr. Snell was referring to. You
18 might need to stress the system, so to say, so just a
19 baseline evaluation or a single measurement might not
20 be ideal, and we might need to follow people.
21 DR. UNGER: Right. And CDC's -- and other
22 people have definitely found that the difference at

1 baseline are very different from after -- putting the
2 disease in motion in responding to all kinds of
3 stresses, exercise, cognitive, infections.
4 DR. COX: Yeah, so Jordan and I would like to
5 thank all of our speakers for, really, a series of
6 excellent presentations and the audience for all your
7 questions. I think at this point, we will have to move
8 to the break, so we'll take a 14-minute break. Speakers
9 will be up here for another minute or two if you have
10 particular pressing questions. We apologize to those
11 whose questions we did not get to. We'll start back at
12 3:30 with the next session. Thank you all very much.
13 DR. DIMITRAKOFF: We can pass those questions
14 to the people who are there (inaudible).
15 FEMALE SPEAKER: Oh, okay.
16 (Whereupon, a short recess was taken.)
17 DR. MANGAN: Panel Number 4. Thank you. My
18 name is Dennis Mangan. I'm one of the moderators for
19 Panel Number 4, the final panel for the meeting. And
20 we're going to be doing a summary and a path forward.
21 The point of this session, of course, is to do a little
22 recap of what we've heard over the past two days, make

1 sure we heard what we thought we heard, and then to be
2 able to document this and to be able to pass it along
3 to the FDA and to the other federal agencies and to --
4 essentially to everybody.
5 Again, my name is Dennis Mangan. I'm a
6 former NIH employee. I was the chair of something
7 called the Trans NIH Research Working Group, ME/CFS
8 Research Working Group. And now I'm sort of retired,
9 but I'm a passionate advocate for research on chronic
10 fatigue syndrome and other medical illnesses.
11 My co-moderator today is Dr. Chowdhury.
12 DR. CHOWDHURY: Hi, good afternoon. I'm Dr.
13 Chowdhury, and my affiliation is up there. I'm at the
14 Food and Drug Administration, in the division of
15 Pulmonary, Allergy, and Rheumatology Products. And I'm
16 a colleague of Dr. Terri Michele, who has been
17 very instrumental in putting this symposium together and
18 working hard on the background and also put these two
19 days.
20 My introduction to the chronic fatigue
21 syndrome has been, as Dr. Michele earlier mentioned,
22 with realignment within the FDA when all the drugs

1 for this disease was transferred to our division. And
2 I've been involved in this for the last couple of years
3 and working hard and hopefully will see some drugs
4 coming down the pike, ultimately, needing approval for
5 this devastating disease.
6 So what we will do briefly here is introduce
7 ourselves, which I just did, and pass down the table
8 here for those folks who are new, to introduce
9 themself, and for those who have been introduced
10 previously, perhaps just to say "hello" and move on,
11 and then we'll go to the questions.
12 So Dr. Chu, if you can briefly introduce
13 yourself. You have been in the panel up here before,
14 so it can be very, very brief.
15 DR. CHU: Yes. So just to remind everyone,
16 I'm a patient. I'm also a physician and a board member
17 of the IA CFS/ME.
18 DR. DIMITRAKOFF: I'm Jordan Dimitrakoff from
19 Boston. I'm a urologist, actually, seeing patients
20 with chronic pelvic pain syndrome, and I have developed
21 an interest in seeing patients with chronic fatigue
22 syndrome as well as learning more about the

1 pathophysiology and the treatments for chronic fatigue
2 syndrome.
3 DR. KLIMAS: I'm Nancy Klimas from South
4 Florida, and I'm a clinician and an investigator. And
5 I'd be curious how many people from pharma are in the
6 room, or biomarker discovery? Very good. Thank you.
7 DR. LEE: And I'm Nancy Lee. I am the
8 Designated Federal Officer for the Chronic Fatigue
9 Syndrome Advisory Committee. I am the Director of the
10 Office on Women's Health at the Department of Health
11 and Human Services.
12 What I know about chronic fatigue syndrome is
13 probably what I have learned in my two years as the
14 DFO, so I am in no way an expert, but I have been with
15 the federal government for about 25 years. I was at
16 CDC as a medical epidemiologist for 23 years, and then
17 now I'm at the Department. And I am an internist by
18 training.
19 DR. MAIER: My name's Susan Maier, and I am
20 the new Dennis Mangan at NIH. I am in the Office of
21 Research on Women's Health. I'm the Deputy Director
22 there. And I'm also the chair of the Trans NIH Myalgic

1 Encephalomyelitis/Chronic Fatigue Syndrome Research
2 Working Group. A lot of words, but we're a coordinated
3 working group. We have members from almost every
4 institute in the center on that working group, and we
5 are going to become the face of ME/CFS at NIH. And
6 I'll leave it there and save the comments for later.
7 MR. MILLER: Robert Miller. I'm a ME/CFS
8 patient. I'm also a Ampligen patient. I've had ME/CFS
9 since 1982, and I've been on Ampligen since 2000, on
10 and off. And I'm very happy to be here. Thank you.
11 DR. MICHELE: Hi, I'm Terri Michele. I think
12 probably everyone here knows me by now.
13 MS. ROTH: Hello. I'm Jody Roth. I'm the
14 industry rep today, and I'm from Eli Lilly and Company.
15 I'm the Director of Regulatory Affairs for Biomedicines
16 Group, and I appreciate the opportunity to be here
17 today. I've been in pharma over 19 years and hope to
18 bring some of the experience and the discussion around
19 what it might take to get into this indication. Panel
20 Discussion
21 DR. MANGAN: Very good. Thanks to the panel
22 members for taking time out of their busy schedules to

1 be here and to participate in this panel discussion.
2 Again, like Panel 2, we're going to have a series of
3 questions that we're going to pose to the panelists and
4 go down the table here and ask them to give their
5 impressions of what they've heard over the past two
6 days.
7 And the first question that we're going to
8 ask is what were the key messages on drug development
9 that you heard at this meeting over the past two days?
10 And I'll start with Dr. Chu.
11 DR. CHU: I heard -- two of the main messages
12 that I received were -- was that, first, there needs to
13 be more data from Mr. Munos early on the first panel.
14 And I agree with him. I think there's a lot of even
15 basic information on CFS that has not been well-
16 researched yet.
17 I do think, however, that patient
18 organizations have tried very hard to raise money and
19 also to collect this data, but we need the support of
20 the federal government to invest in the research for
21 this, in both the basic and the clinical research.
22 The data out there is that about $6 million a

1 year is being spent on CFS research. And that is very
2 much in disproportion to the $18 to $24 billion
3 annually that is lost in both direct and indirect costs
4 due to this disease.
5 We keep hearing in past years that there are
6 not enough young investigators who put in grant
7 applications for CFS. And I think, in part, that's
8 because of the last 20 years, there hasn't been that
9 much of a great support.
10 I used to be a young investigator in
11 geriatric medicine, and I got there because I had
12 mentors. I knew there was funding available. I can
13 see why there would not be a huge pipeline of junior
14 investigators, and that's partly because they don't see
15 their senior investigators, if they have any role
16 models, getting the funding that they needed. So
17 that's point one.
18 Point two is about the open access data that
19 people have mentioned. Aside from the fact that there
20 was a question during our -- my panel, the second
21 panel, about how do you access trials if you're not in
22 the same geographical area as the center, I also want

1 to address the issue of including severely ill
2 patients, homebound patients, bedridden patients.
3 Part of this is, as a geriatrician, I used to
4 visit people at home, and there was a huge difference
5 between the patients I saw in clinic versus the patient
6 I saw when I visited them at home. And right now,
7 practically all studies of CFS -- with two -- with the
8 exception of two I've heard about -- have been in
9 clinics and not based outside of clinics.
10 There are things that can be done outside of
11 clinics, like blood draws, ultrasounds, et cetera. Some
12 of those tests are now available that weren't available
13 in the past. So that's two points I wanted to make.
14 DR. DIMITRAKOFF: All right. I think one of
15 the -- there were a couple of messages for me. Number
16 one message for me during this meeting is that it is
17 actually possible to have a drug for ME/CFS, and I
18 think that's very encouraging. I think this is good
19 news for the patients, for the researchers, for the
20 clinicians trying to help patients with ME/CFS. And I
21 think this is -- this is really, really, really
22 optimistic, and this is good news.

1 The number two message for me is that I think
2 that we would all agree that there is a great deal of
3 support and enthusiasm from the FDA, from the federal
4 government, supporting the development and accelerating
5 the development and potentially approval of a
6 medication or medications for ME/CFS.
7 And I think for this, we all have to applaud
8 Dr. Kweder and Dr. Michele, who helped put together
9 this meeting. And I think this is really a great
10 message for the community. Thank you again, Dr. Kweder
11 and Dr. Michele, and everyone at the FDA, and everyone,
12 actually, being here. Thank you to the patients for
13 being here. You probably deserve most of our applause,
14 and for all the clinicians and researchers and the drug
15 companies that are represented here.
16 The third message, just listening to Dr. Chu,
17 is actually something that we have been discussing over
18 the past year. I'm involved as a member of the Chronic
19 Fatigue Syndrome Advisory Committee at the Department
20 of Health and Human Services, where I'm actually very
21 fortunate to work with both Dr. Michele, Dr. Nancy Lee,
22 who's here on the panel, and Dr. Susan Maier from the

1 NIH. So we actually had a -- have been having a
2 discussion over the past year about young investigators
3 and bringing young investigators to the field.
4 And I think this meeting actually validates
5 the importance of this discussion, the importance of
6 how important -- sorry for the repetition -- it is for
7 young people to get involved in ME/CFS at the very
8 early stage of their career.
9 We have been discussing different mechanisms
10 of providing young investigators with support early in
11 their career and also trying to retain established
12 investigators in the field of ME/CFS. A lot of those
13 discussions have been tainted by pessimism, actually,
14 and by the fact that people don't see a lot of
15 motivation for coming and staying in the field.
16 But I think from now on, if somebody actually
17 has doubts, I would actually point them to this
18 conference, and I would ask them to look at the webcast
19 and the video cast, because I think this is the best
20 motivation. And, as someone said earlier, this is
21 really a territory for a young investigator to conquer.
22 And I always tell my students, just giving an

1 example, like people usually try to go to cancer
2 biology or cancer pathology. I do tell them that this
3 is -- that this condition is probably the greatest
4 intellectual challenge in medicine, and people can
5 really help patients with ME/CFS, but at the same time,
6 they can really make a career working in the area of
7 ME/CFS. So I think that's one of the key messages for
8 me, that we all have to work together, and we have to
9 help bring new young people into the field.
10 DR. KLIMAS: He's got good points. I also
11 take a positive note on this, and in general, I think
12 that one thing this meeting shows us, that we're much
13 further along. We don't give ourselves credit for much
14 of what we already have in hand and have going. We
15 have clinical trials groups. We don't have to talk
16 about forming them. We have them. We already have all
17 these different investigators that are linked together,
18 doing clinical trials. They're experienced, and
19 they're experienced clinical trials investigators who
20 have the patient population.
21 We have many, many years of experience with
22 these various and sundry instruments we've been talking

1 about that asses the domains of the illness and
2 function. So what I'm encouraged about, frankly, was
3 Dr. Robb and Dr. Slagle's talks that said we can do
4 things quickly. We will help you. We want to help
5 you. Help us -- let us help you design your trials.
6 Come do this. And I have every intention to take
7 advantage of that, and I'm hoping that we'll have
8 pharma partners that will join in with that.
9 DR. LEE: Thank you. I'm a public health
10 person for 30 years, and so that's sort of the lens
11 that I look through. And one of the things you learn
12 in public health is the value of partnerships. And I
13 was pleased -- I really enjoyed all of the talks today.
14 This was a fabulous meeting, and I really appreciate
15 the FDA for the work they've put together and all of
16 the participants in the audience and up here, because I
17 have learned a lot and got a lot of inspiration.
18 One of the things that I heard early this
19 morning was from Dr. Munos about partnerships. And
20 that was -- if you'll recall, that was one of the
21 strategies he said that we needed to do. And so, you
22 know -- and sort of in a strategic way, that's how

1 public heath works. They reach out, and they figure
2 out all the different stakeholders and partners that
3 can bring something to the table.
4 And so I think that that is a particularly
5 good message for us to think about, partnerships with
6 academia, with the patient community and all of the
7 different kind of resources that we can use -- get from
8 them and give to them, and -- from the federal
9 government, from academia, from pharma, from
10 foundations. All of those things can -- if we can come
11 together, pool our resources, because it can't all come
12 from one place, obviously. Thank you.
13 DR. MAIER: I think the key message that I
14 heard yesterday and today is a very familiar one, and
15 I'll give you a hint. You remember when I first moved
16 up here to the DC Metro region and wanted to buy a
17 home, the voice of my real estate agent was "Location,
18 Location, Location." And, of course, she steered me to
19 a very expensive part of Rockville, but nonetheless, I
20 do love it.
21 But the message that I heard for the past day
22 and a half is measurement, measurement, measurement.

1 And as a psychologist, that is the key to making sure
2 that we have accurate representation of what happens,
3 whether it's in a clinical trial, whether it's in
4 clinical research, whether it's in any type of things
5 that are in a tissue bank.
6 Are the things that we're measuring
7 representative, truly representative, of what it is
8 that's going on with the patient, and then using those
9 accurate, valid, reliable measures to then devise
10 outcomes and use that to evaluate treatments.
11 And that is the message that I will take home
12 with all of my papers of all the different indications
13 that patients have articulated in the past two days
14 that I was not completely aware of, and I will admit
15 readily (ph) in the public forum my ignorance of what
16 you go through, and I appreciate your honesty in
17 sharing that with me. Thank you.
18 MR. MILLER: So for me as a patient, there's
19 a lot of messages that have come out over these two
20 days. And I'm going to preface this with I am having a
21 big of brain fog, so I'm just going to kind of like run
22 through what I have here.

1 First of all, I want to thank all the
2 patients for attending, because I do know what it is
3 like to try to attend a meeting like this, how much
4 energy you have to put out. One of the things that I
5 have heard the last couple of days, and I appreciate
6 it, coming from FDA representatives and other
7 clinicians here, is that they understand our
8 frustration and our pain. I think that they try to,
9 but I would rather ask them to say they would like to
10 understand our frustration and our pain.
11 And just for a quick example, on my flight
12 here, I set the arrangements up, and I sent them into
13 whoever the government travel agency was. And, you
14 know, it was a flight direct to -- from Reno to Denver.
15 Thirty minutes, I'm on the plane from Denver to here. I
16 got booked on a flight. I had to sit for three hours
17 in the airport in Denver.
18 It's those little things that, when a
19 representative says to me, "I understand your pain and
20 frustration," you're not quite there yet. I know
21 you're trying. And we, as a patient population, will
22 try to educate you the best that we can.

1 I'm very grateful and thankful to Dr.
2 Woodcock, Dr. Kweder for arranging this landmark
3 meeting. But I am just as grateful to a handful of
4 advocates and patients who pushed to get this meeting
5 today. So, like I said, brain fog, so I can't name you
6 guys, but thank you for getting this put together. And
7 I would ask the patients to applaud those advocates
8 that did this. Thank you.
9 So what I've heard the last couple days is
10 there's a crisis in the ME/CFS community. It has no
11 approved treatment options, and our government has to
12 take action now at this meeting to address this crisis.
13 We've heard from several key experts that there are
14 biological measures that correlate with patient
15 outcomes that should be used to demonstrate efficacy
16 for ME/CFS treatments, according to the experts. And
17 those measurements are natural killer cell numbers and
18 cell function.
19 Dr. Snell exercised, VO2 max stress test.
20 Cytokine levels. We heard Dr. Montoya talk about viral
21 load, viral activation, EBV, HHV-6, HSV, CMV,
22 Coxsackie, cognitive function tests similar to those

1 that they're proposing to do for Alzheimer's.
2 There are subsets of patients who may respond
3 differently to treatments. We've heard a number of
4 clinicians who have had positive results using
5 treatments that need wider availability and testing,
6 and FDA should take concrete measures to help to
7 facilitate clinical trials and clarify a pathway to
8 approvals.
9 And we've heard some of the drugs mentioned.
10 We've heard Ampligen. We've heard cidofovir, we've
11 heard Valcyte, we've heard Valtrex. FDA needs to
12 articulate a very clear special path to approval for
13 ME/CFS. FDA just established a special path for the
14 drug in early stages for Alzheimer's, recognizing the
15 unmet medical need, as there is with this illness. Also
16 recently, there was a drug actually approved called
17 Sirturo for TB that is receiving a special pathway for
18 approval, even though it kills five times more patients
19 on drugs than on placebo.
20 ME/CFS has a critical unmet need for 30
21 years. FDA must make clear to the drug development
22 companies that it will approve drugs for the indication

1 of ME/CFS, and the only way to correct the 30-year
2 deficit is for FDA to articulate a special path so the
3 drug companies will know FDA is willing to do so. It's
4 been said several times now, build it and they will
5 come. Fund it, and they will come.
6 Where we're talking about the next steps for
7 patients and for patient advocates and an advocacy
8 community, we need to build off of this meeting
9 together. We've been very united here. The patients
10 who have spoken have been very articulate. We've made
11 it a point not to just say, "I have brain fog." Well,
12 people have been very descriptive about what brain fog
13 is to them, and I think that's helped the clinicians
14 here, the researchers here, and I think that we have to
15 build off of that.
16 We need FDA to publish a list of measures
17 that will be accepted as objective outcome measures for
18 efficacy. FDA should recognize and articulate the
19 life-threatening and disabling nature of ME/CFS and
20 weighing the benefits of drugs against the risks, just
21 like it does for MS, HIV, and cancer, and all of those
22 drugs have serious side effects.

1 FDA needs to be willing to approve treatments
2 that work for a subset of ME/CFS patients with
3 selection critical so that treatments are not withheld
4 because of a heterogeneous patient population, which
5 has been repeated several times. FDA needs to allow
6 for the smaller clinical trials, which they've talked
7 about, to be able to demonstrate efficacy with
8 continuing studies after marketing so the path to
9 treatment is not another five to ten years away.
10 I'm 54. I've been doing this since I was 24.
11 I do not want to be sitting up here saying the same
12 thing when I'm 64. If FDA is not able to do -- I'm
13 sorry. We need FDA to publish those critical and
14 invite the drug companies to set up the clinical trials
15 for ME/CFS patients. And if FDA is not able to do that
16 from the input from this meeting and include immune
17 markers, then FDA should move quickly, within the next
18 two months, to convene our expert clinicians with the
19 most experience in ME/CFS clinical trials to help
20 create that set of selection criteria and outcome
21 measures.
22 And not least, FDA must pursue a path forward

1 for Ampligen, which is the only medication in the FDA
2 pipeline that could reach approval stages in less than
3 five years, and it clearly works for a subset of
4 patients. And if we can help 4 percent of our patient
5 population, we should do that. We do it with cancer
6 patients. It's done with several other indications,
7 and we should be able to do it for ME/CFS.
8 I'd request that CDC and that NIH work with
9 FDA and help to study the responders to Ampligen so
10 they can learn how and for whom it works. NIH did this
11 with the MS drug Zenapax and found an implicated a
12 unique cell in that disease. FDA needs to ask NIH to
13 conduct clinical trials in our illness, like they did
14 for AZT for AIDS. Open the door, just as they're
15 opening the door for Alzheimer's. I want the
16 Alzheimer's plan. We're willing to loosen the
17 restrictions.
18 I think we need very clear steps coming out
19 of this meeting from the FDA to be able to bring
20 treatment options to patients and their doctors on an
21 emergency timeline. This is a crisis. This is an
22 emergency. This is time for everybody to work together

1 and try to move forward. Thank you.
2 DR. MICHELE: I'll be very brief, but I
3 wanted to take this opportunity to say how impressed I
4 was with the patient testimony that we heard yesterday,
5 particularly in articulating the symptoms so very
6 clearly. And I think that that's just a huge help in
7 moving forward with outcome measures and helping guide
8 drug development to know what symptoms to take forward
9 into clinical trials.
10 So I found that remarkable, and I was, again,
11 utterly impressed with how articulately and clearly
12 that was described, how everyone stayed on topic and
13 just really did a tremendous job describing things
14 that, despite listening to CFSAC testimony for several
15 years now, I have not heard, so thank you for that.
16 MS. ROTH: I'd first like to echo some of the
17 comments that's already been said, but I do believe
18 that this is a great session and I think a session
19 that's allowed many of the stakeholders to come
20 together, and not one person, stakeholder or people can
21 solve this. We have to come together. That's very
22 clear. That's one key message that I've gotten out of

1 this.

2 And I think with that, guidance can be

3 generated if we come together and be creative about how

4 we might want to do that and what the regulatory

5 endpoints might be. It is essential for pharmaceutical

6 companies to understand what those endpoints are to

7 know kind of where to -- what is needed in the clinical

8 trials, and what is the threshold to meet substantial

9 evidence? So I think, out of the group that's here

10 today and the discussions, I think we have the right

11 framework to start those discussions and take off from

12 there.

13 I think the other thing that I learned

14 sitting here the last couple days is, although it's

15 called CFS and fatigue's a key component of it, it's

16 very complex, and there's many comorbid and also

17 concomitant positions associated with it, and that also

18 is something that I think, as we think about clinical

19 trials and so forth, something we've got to think

20 about. So I think the framework has been established

21 to build off of that, and I think we have a good

22 springboard to do that.

1 DR. CHOWDHURY: Thank you all, the panel
2 members, for this excellent discussion on this
3 question. This was very helpful for me and probably
4 for all of us here. Before moving on to the next
5 question, I just want to remind us and all of us that
6 we do finish at five o'clock, and the last 15 minutes
7 of the session is for audience question-and-answer
8 period, and we really want to keep it 15 minutes for
9 the audience participation here.
10 So with that in mind, I just want to bring up
11 you've got five more questions to go through, and we
12 want to give all those questions adequate amount of
13 importance, so we should time ourselves appropriately.
14 We took about 25 minutes or so discussing the first
15 question. I think it's important to get all the points
16 out, with the hope that the second and third questions
17 will go rather quickly.
18 So with that, I will pose my second question,
19 which is up on the screen, is what do you think are the
20 most important factors in facilitating drug development
21 in chronic fatigue syndrome and ME? Perhaps I can
22 start this time from the extreme end and then move down

1 here? Thank you.
2 MS. ROTH: I think there are several
3 questions I guess I would like to pose kind of to this
4 question back, which is what are the criteria by which
5 we need to have in place to register for a CSF (sic)
6 indication? And we've already talked about regulatory
7 path, but also then what might that look like? What
8 are the claims or indications that might be associated
9 with it? As we've heard over the last couple days,
10 those can be anything from signs and symptoms to
11 maintenance, and like one time I heard the word "cure."
12 So what is that going to look like, and what do we need
13 to make sure the clinical trials are set up to do?
14 The other pieces, the clinical heterogeneity
15 that we've been demonstrated on here with different
16 speakers, but what is going to be the framework? Is
17 there going to be an academic research organization
18 established? How are we going to be able to implement
19 the trials in such a way that we get the right patients
20 into those to get the endpoints that we need?
21 So I think -- I think the third piece is the
22 endpoints, which is where can we leverage maybe other

1 fatigue instruments we've used in other indications
2 which may be more secondary in nature, but may provide
3 a framework or proof of concept to allow us to know
4 that our drug may work in this syndrome as well. And I
5 think that's something else to think about, which was
6 hit on in the last session a little bit with some of
7 the PRO discussion.
8 DR. MICHELE: So I'd just like to bring out
9 two points here. The first one, I think several folks
10 have already commented on, which speaks to how much
11 it's resonated with all of us from Dr. Munos' talk
12 about the need for data. And I think in particular,
13 it's hard to get to clinical trials with drugs until we
14 have baseline data. And the good news is that we
15 already have a lot of that, but obviously the more you
16 have, the more rich the dataset is to build on for drug
17 trials. And in particular, I think longitudinal data
18 is important.
19 What I was so excited about that you folks
20 didn't get to hear is after my panel, we had a brief
21 sidebar conversation, and there are a number of
22 different databases already out there that I think give

1 us the opportunity to build on that. And I would just
2 really encourage establishing networks and bringing
3 many of those databases together. They may be
4 different. That's okay. We can look at things in a
5 variety of different perspectives.
6 I would also like to emphasize the excellence
7 in clinical trial design and the conduct of clinical
8 trials, which is so important. If you're going to see
9 something, it really has to have a lot of thought into
10 it ahead of time. And when you get to drug trials, I
11 mean, I think that's a place where FDA is certainly
12 very willing to help with those designs.
13 MR. MILLER: So for me, I've heard the word a
14 couple times, and I think it's willingness, willingness
15 from all the federal health agencies to work together
16 and figure out what the pathway is forward here to do
17 clinical trials. And, you know, I've heard it over the
18 last two days. It certainly appears that the
19 willingness is there, but, again, you know, I don't
20 want to leave this meeting today and, you know, have in
21 the back of my mind that we're going to be talking in,
22 whatever it is, a few weeks at CFSAC and not really

1 have some plan in place to be able to move forward.
2 Thank you.
3 DR. MAIER: So from my perspective, and the
4 perspective being, you know, NIH is a funder of
5 biomedical research, the basic research on mechanisms
6 and understanding of diseases and illnesses, up to
7 clinical trials of a limited nature, from my
8 perspective, it's important.
9 I know that we're here to talk about ME/CFS
10 and that it's a very debilitating illness, and I
11 understand that, but it's very important from a
12 research perspective to be willing to think outside of
13 ME/CFS, on the fringe.
14 All right? We're not not going to study
15 this. We're not -- it's not that we're going to abandon
16 this, but be just willing to accept new approaches, new
17 perspectives of individuals who are in other areas of
18 research who have techniques, they have ideas, they
19 have databases, they have other information that
20 they're willing to share with the ME/CFS researchers to
21 broaden out how we think about how we do research.
22 And that's very important to consider that

1 from the perspective that basic science research and
2 the limited clinical trials that NIH does fund, do
3 those all feed into what pharma will then take on as
4 Phase III clinical trials to move forward with drug
5 development.
6 DR. LEE: Most of what I was thinking about
7 has already been said. I just want to -- I'm a data
8 person, and I can't underscore enough the importance of
9 continuing not just gathering data, but developing the
10 data infrastructure. And something that I don't know
11 much about, but I think was something that we can't
12 lose sight of, was Suzanne Vernon's talk today on the
13 drug repurposing. That sounds to me like something
14 that has some promise in the shorter term, to find more
15 useful therapies, perhaps drugs that are already
16 approved, but then could be either -- should I say off-
17 label? Can I say that?
18 MALE SPEAKER: Yeah.
19 DR. LEE: Off-label or could -- they could
20 come in -- they could come in for other -- for other
21 uses and get it on-label. So just to mention that we
22 shouldn't forget the sort of work that we saw

1 demonstrated today in Suzanne's talk.
2 DR. KLIMAS: So I think the most important
3 facilitating factors right now have to do with
4 organizational infrastructure and if there are avenues
5 to develop the infrastructure that's necessary to
6 really put together a functioning clinical trials
7 group. I can't underscore enough -- one thing you
8 heard earlier from Dr. Munos was that things are
9 cheaper. Things are cheaper. We have the assessment
10 platforms, you know, on these Web-based platforms now.
11 We're experienced at using them. They definitely
12 brought way -- bring down the cost of doing work. And
13 it's very reasonable to think about putting together a
14 series of targeted treatments of Phase I/II trials or
15 two Phase II, but I/II, probably, to get this on the
16 ground.
17 In terms of subgrouping, I think that's the
18 other big thing that we talk about a lot, and you
19 raised some trepidation about the heterogeneity of the
20 group. I think, actually, subgrouping can be a
21 strength, because it helps us pick out the best
22 population to target that particular approach, and not

1 generalize, but go ahead and -- for instance, if we're
2 using biological response modifiers for people with
3 proinflammatory cytokine cascades, well, let's use
4 cytokines to define the population, or receptors or
5 something, but there are certainly ways to do that.
6 And we have, I think, very reasonable
7 strategies to target therapies on targeted groups and
8 do it now. There's really no reason at this point to
9 delay any further. I think we can beat this what are
10 our variables to death, but we can go to the FDA with
11 our list of variables, which I would argue strongly
12 should be functional, rather than symptom.
13 But we have good, reliable, validated, well-
14 published, compared across each other, variables
15 already, in addition to these lovely datasets that we
16 have in hand to further test those variables. So I
17 think that we're ready to go.
18 DR. DIMITRAKOFF: The keyword for me that --
19 listening to everyone else that spoke on this question
20 and throughout the meeting is collaboration. And I
21 think, if you just read the question, what do you think
22 are the most important factors in facilitating drug

1 development, I think it's just collaboration and
2 working together.
3 And I also want to emphasize the importance
4 of something that Susan Maier mentioned, the importance
5 of working together with other researchers and people
6 in similar or related fields. I could just give you a
7 very simple and brief example.
8 So when I was trying to work on a biomarker
9 for chronic pelvic pain syndrome, or interstitial
10 cystitis is one of the forms, it's more popular in
11 females, so I went and spoke to a very famous
12 neuroscientist at Harvard Medical School, who is
13 actually now a head of the one of the departments, and
14 mentioned to him that I'm trying to look at an animal
15 model or a mouse, just because that's what initially a
16 drug company wants or is interested in.
17 He said, "Well, Jordan, why are you bothering
18 me with this disease? It's a cystitis thing. It's
19 just an inflammation. Just put some bacteria in the
20 bladder of a mouse, and then you get your model." I
21 said, "No, no, it's not actually that simple. People
22 with this disease actually have chronic pain. We

1 assume it's an inflammation, but we don't actually know
2 what's going on, and it's a very heterogeneous
3 disease."
4 And he said, "Well, that sounds very
5 interesting. You know, we actually have a mouse. We
6 have knocked out the gene, and we're working on another
7 disease, obsessive-compulsive disease, but we knocked
8 out this gene, and, you know, these mice have this most
9 weird behavior. They keep picking at their, you know,
10 inguinal area, and they pick to the extent where they
11 create wounds. But it's such a targeted behavior, and
12 it's happening in the pelvic area."
13 He said, "Well, maybe that's what you're
14 looking for." I said, "Well, it's an extremely
15 interesting thing." And then he showed me the pictures
16 of those mice, which actually they can't stand. So
17 they have that pain in the pelvic area to the extent
18 where they cannot use their hind paws, and they just
19 walk on their front paws. It's a most impressive
20 picture.
21 But I do think that that was actually a very
22 interesting discussion, and I do think that -- I don't

1 think -- I don't -- I'm not an expert in this field. I
2 don't think there is a mouse that's representative of
3 the chronic fatigue syndrome phenotype. And I'm not
4 trying to move that discussion in that direction, but
5 all I'm saying is that you can actually learn a lot
6 from talking to people in other fields, and we can
7 learn from each other and probably help the field in a
8 way which you cannot even imagine.
9 DR. CHU: Well, it was gratifying to me to
10 hear people at the table talked about how they were
11 learning from patients about the symptoms of CFS that
12 maybe they didn't understand as much previously. And I
13 want to thank everyone in the audience from the pharma
14 industry, as well as those out in the Internet land,
15 hearing about these symptoms.
16 I think a big piece of facilitating drug
17 development is to educate clinicians and researchers
18 about CFS/ME, in particular -- not so much people in
19 this audience or listening to this webcast, but Dr.
20 Unger did a survey back in 2011, presented it in
21 abstract at the IA CFS/ME Conference, showing that 85
22 percent of physicians think that this disease is either

1 psychiatric or a mixture of medical and psychiatric.
2 It really needs to be emphasized out there to
3 clinicians and researchers that this is a medical
4 illness. Certainly there are people with comorbid
5 psychological or psychiatric disorders, and those
6 should be treated, because there are effective
7 treatments for that, but those treatments -- those
8 psychiatric and psychological treatments are not going
9 to really help people recover from this illness. It
10 may help them cope, but it's not going to help them
11 recover.
12 Secondly, I'm always concerned about this old
13 statement in public relations, where if you say
14 something enough times, it becomes true, even if it
15 isn't. And we've heard so many times, not just here,
16 but outside, that there are no biomarkers for CFS, and
17 as people have brought up at this table, there are
18 biomarkers. Not every CFS patient has them, but there
19 are biomarkers that a lot of patients have, and we need
20 to work with that with what we have currently. So
21 that's my point.
22 And, oh, yeah, last point about working with

1 people outside the field, CFS is not the only disease
2 that has a lot of heterogeneity and not the only
3 disease where if you're conducting a clinical trial,
4 there are people with multiple other comorbidities.
5 It's not some unique, little disease off on its own
6 little corner. We can use lessons from those other
7 trials and apply those to CFS.
8 DR. MANGAN: Thank you. Now, the third
9 question for the panel that we'd like to pose is we
10 heard this afternoon about trial design elements to
11 ensure success from Panel 3 about clinical trial
12 design elements. And one of the most important
13 ones to ensure that drug development programs are
14 created, then, for CFS and ME. And I might want to
15 just direct this to Nancy Klimas for her comments.
16 DR. KLIMAS: It just -- the numbers just jump
17 right into me. Yeah, sample size, we're measuring --
18 we're measuring things that have the ability to change
19 with improvement in a way that you can track and have
20 reliable data.
21 And this is really important, the length of
22 the trial itself. To date, almost every study that I

1 have seen that even hinted at efficacy didn't see the
2 response for -- until the fourth month, and so
3 designing little ten-week trials or four-week trials
4 may not be enough.
5 Now, our group is doing something unique, and
6 it's pretty cool. We're using the exercise challenge
7 to induce a relapse, and we're measuring a lot of
8 things over the course of this exercise challenge,
9 genomics and cytokines and all the -- everything under
10 the sun, and we're modeling illness and therapeutic
11 intervention points.
12 Our intention in Phase I is to do that
13 challenge upfront, intervene with our targeted drugs,
14 and then do that challenge again and see if it really
15 did change the homeostatic model of the illness. So
16 that's kind of cool and unique, is to be able to say
17 let's use computational biology tools, which are pretty
18 exciting, and see whether or not the intervention not
19 only works or has the hint of efficacy here, but also
20 if it teaches us more about the dynamic of the illness.
21 And I would argue that that would be my perfect Phase I
22 study.

1 DR. CHOWDHURY: Anybody else would like to
2 comment on that question? Terri Michele?
3 DR. MICHELE: Yes, I'd just like to bring up
4 one thing that hasn't been mentioned very much today
5 that I think is critical that we don't forget. We
6 have, very appropriately so, spent a great deal of time
7 over the last day and a half talking about measures of
8 efficacy, but I'd like us not to forget that also as
9 we're designing our clinical trials, you also have to
10 design in upfront measures of safety, because measuring
11 efficacy is only half of the equation.
12 We need to be able to balance risk and
13 benefit, and we need to understand clearly what those
14 risks are. Even for drugs that are being repurposed
15 and perhaps have a side effect profile that's well-
16 known in other diseases, it may be different in chronic
17 fatigue syndrome, and we have to build those into our
18 trial so that we're carefully assessing them upfront;
19 otherwise we really can't collect them, particularly in
20 a disease like this, where there are so many
21 heterogeneous symptoms, it's hard to know what's an
22 adverse event and what's baseline status.

1 DR. CHOWDHURY: Thank you for that comment.
2 Anybody else from the panel who would like to add
3 anything to what has now been stated on that question,
4 Question Number 3?
5 DR. CHU: I just have two resources that
6 might be interesting to pharmaceutical companies. One
7 is a article by Kirstie Haywood, last name H-A-Y-W-O-O-
8 D, and it's a paper on the quality and acceptability of
9 patient-reported outcome measures used in CFS and ME
10 and its systematic review.
11 And their conclusion was one of the better
12 measures is the SF-36, Version 1, but she reviews all
13 these different measures that might be of interest.
14 Another article on cognitive measures is from
15 Australia, and it's by -- first author, last name is
16 Cockshell, C-O-C-K-S-H-E-L-L, and that might also be of
17 interest for pharmaceutical companies. I don't have
18 the title of that article, unfortunately, with me.
19 DR. CHOWDHURY: Thank you very much. If
20 anybody else wants to make any comment on this
21 question? If not, then I'll move on to Question Number
22 4. And the Question Number 4, which is up here, is

1 what are the most important barriers of conducting
2 research in CFS and ME, and what can be done to
3 overcome them?
4 And the point here is this meeting being a
5 patient-focused sort of development is what can we, as
6 a group here, can do to overcome the barriers, not
7 necessarily listing all the barriers, which we have
8 discussed here quite extensively.
9 So with that introduction, I'll just throw it
10 open to the panel members here. Anybody who would like
11 to take it on, then start some comments, and others can
12 add on to that.
13 DR. MICHELE: I'll perhaps start --
14 DR. CHOWDHURY: Thank you.
15 DR. MICHELE: -- if you don't mind. Just to
16 very clearly put it on the table, from the FDA
17 perspective and a regulatory perspective, we don't
18 perceive any barriers. That's not to say that there
19 aren't barriers in other arenas, but regulatory-wise,
20 I'm very pleased to say that, you know, we've heard
21 this from multiple people.
22 We heard from our Panel 3 members. Dr. Rowe

1 outlined it so very nicely, that we have outcome
2 measures. We also heard it on Panel 2. Dr. Bateman
3 said any of these symptoms could be used. We heard a
4 number of different measures that could be used, and so
5 we have outcome measures that could be used. We have
6 definitions that could be used, and they may not always
7 agree, but that's okay.
8 We can have different clinical trials were
9 tailored to the drug, tailored to the symptom that you
10 want to measure. You may design your
11 inclusion/exclusion criteria slightly differently to
12 precisely define the patient population that's most
13 likely to benefit, and that gets back to the enrichment
14 designs that you heard about from Dr. Rowe. So
15 regulatory-wise, I think we're ready to go, and FDA is
16 certainly very open to hearing about trials in this
17 area.
18 DR. CHOWDHURY: Thank you, Dr. Michele. And
19 I think some others speakers earlier said that we
20 cannot hold the perfect to be an enemy of drug
21 development, and for chronic fatigue syndrome, the
22 perfect will come sometime, but I think the time, as

1 Dr. Michele mentioned, is already ripe to enroll
2 patients in new trials, not necessarily for cure, but
3 at least to make some headway.
4 So with that, anybody else from the panel
5 here would like to add their thoughts or words on this
6 question?
7 DR. DIMITRAKOFF: Yes. Can I
8 DR. CHOWDHURY: Please.
9 DR. DIMITRAKOFF: I think that we've
10 discussed this on several occasions. We actually had a
11 brief discussion over lunch again with Nancy Klimas and
12 Susan Maier and just the table where we were having
13 lunch, but I think one of the barriers that has
14 consistently been pointed out is that -- well, there
15 were two of them, actually, so one of them is the lack
16 of new investigators coming into the field and of
17 people that are actually interested in doing additional
18 research on ME/CFS. And on the other hand, we have
19 consistently heard, at least at CFSAC meetings, about
20 the limited availability of funds or funding.
21 So some people point out that there's
22 actually not that many investigators; on the other

1 hand, it's being pointed out that there isn't that much
2 availability of funds. In all honesty, I think Susan
3 Maier can actually speak better to that from the
4 perspective of available request for applications and
5 other funding resources from the NIH.
6 But the one theme that's consistent is that
7 we actually need a concerted effort. We probably need
8 all the different clinical centers to come together and
9 probably do a large, mega trial. And it might be
10 interesting to have a discussion. There are obviously
11 different mechanisms under which this can be done at
12 the NIH level, which seems to be an interesting way of
13 doing that, but I just wanted to mention -- so, for
14 example, there is a network that I'm familiar with, the
15 MAPP Network, or the Multidisciplinary Approach to
16 Pelvic Pain, which actually has $40 million in funding
17 over five years.
18 And the way this network actually came
19 together was that there were requests for applications,
20 there was money set aside that was dedicated to this
21 network, and then the requirement for submitting an
22 application was that every site that was submitting an

1 application must have a clinician recording patients,
2 an expert in the disease, an epidemiologist who knows
3 the epidemiologic aspects, and then a loosely defined
4 basic scientific component, but mostly something that
5 has to do with biomarker discovery or validation,
6 including imaging in that respect.
7 So I think -- I personally think that the
8 field of ME/CFS needs something like that. I think
9 that the field needs a MAPP Network. I don't know how
10 that can be done, or I don't know the specific
11 mechanism that this can be done.
12 One possibility we just mentioned over lunch
13 is something that I'm vaguely familiar with, that the
14 NIH actually has a funding mechanism and a cooperative
15 agreement where interested investigators in clinical
16 trials can work with the NIH over a period of one to
17 two years in putting together a team, designing a
18 clinical trial, bringing people from different sites
19 together, working on a specific theme.
20 And this is under one of the mechanisms which
21 are called a U34 grant, I think. I'm not an expert in
22 that field, but -- and then following those initial one

1 or two years, when you actually design the trial, put
2 together the team of multiple sites, get the manpower
3 to do that, there's an additional funding period of
4 five years, where you actually do the real trial.
5 And I personally think that, just listening
6 to what everyone has been saying, that might be a very
7 good way for the field to move forward, going with what
8 Nancy Klimas was saying, that the people are there, the
9 sites are there. We heard from a lot of experts in the
10 field that they're recruiting patients. There's
11 interest in testing different medications. Maybe
12 that's the way to do it.
13 DR. CHOWDHURY: Thank you very much. This is
14 a great comment. And, actually, what you mentioned
15 here makes very good sense. There are other disease
16 areas also where such network has been launched, and in
17 the pulmonary area, we are very familiar with -- of
18 launching, actually, a network with NIH on chronic
19 obstructive pulmonary diseases to study natural history
20 going on for five years with, actually, public and
21 private funding, meaning government, NIH, and also
22 industry coming in.

1 And these are for studying the natural
2 history of the disease, understanding the disease that
3 will lead to future drug development, just to make a
4 point. I mean, those are not necessarily for
5 (inaudible) clinical trials before the drug can come to
6 the market. They're more to understand the disease.
7 With that comment, I'll ask Dr. Maier to
8 respond if she has anything very briefly and then pass
9 it to the next question.
10 DR. MAIER: Thank you, Jordan.
11 DR. DIMITRAKOFF: Sorry, I didn't mean to put
12 you on the spot. I mean, you can say something brief
13 or not.
14 DR. MAIER: Okay. I can be really brief. I
15 wrote down an answer to this question, and the first
16 thing I wrote down was money. Money is an issue. I'll
17 be honest about that. It's an issue for everyone in
18 the federal government. It's an issue for all of us.
19 And so I cannot make excuses about the money issue.
20 The -- really, what drives the research at
21 NIH is well-conceived ideas, good science, and well-
22 written proposals, and if you write those and you

1 submit proposals and they go through peer review, we
2 can fund it, but we can't fund research without a
3 proposal, even if it's a request for applications.
4 And I'll give an example. Requests for
5 applications, as Jordan stated, is a mechanism by which
6 NIH says we're going to set aside X million dollars for
7 this particular activity. Submit your proposals. There
8 are guidelines, et cetera.
9 So let's say $6 million was set aside for
10 specific activity. Proposals come in, they're reviewed
11 for the science, for technical merit. If there aren't
12 enough proposals to fund at the $6 million mark, NIH
13 doesn't spend $6 million on that activity. They could
14 only fund the science that is reviewed by peers to be
15 scientifically acceptable.
16 So an RFA or a Request for Applications that
17 has a set-aside to it is helpful, but it's not the be
18 all, end all of spending money at NIH. We have to have
19 proposals. They have to be well-conceived. They have
20 to be well-designed, whether they're clinical research,
21 or whether it's a clinical trial, and they have to pass
22 the scientific muster. And if you submit them and they

1 go for peer review and score well, we can fund them.
2 DR. CHOWDHURY: Thank you for that comment.
3 I think it sort of resonates also with the FDA. We
4 approve drug, but to approve drug, we have to have an
5 application to approve a drug. We cannot approve a
6 drug which is not there.
7 DR. MAIER: Right.
8 DR. CHOWDHURY: And I think this is also sort
9 of a pitch in some ways to the patient's group,
10 physician's group, interested in the disease is for
11 them to take initiative, put a fund and granting
12 applications together for NIH and others to review and
13 hopefully fund it, and I'm assuming this will lead some
14 interest, what you're saying here, for the people here
15 to take some initiative in putting it all together.
16 DR. DIMITRAKOFF: I wasn't advocating for
17 Susan to write the check today, by the way.
18 DR. MAIER: Not under sequester. Wait for my
19 furlough (inaudible).
20 DR. MANGAN: So now that we put NIH on the
21 spot, let's ask the question, Question Number 5,
22 please, on the slides. For -- you know, based on your

1 experience and so forth in the various different
2 agencies and different viewpoints in looking at this
3 conference, how can we leverage your experience or your
4 agency's experience in moving drug development forward?
5 And we're looking right now at the FDA, for example.
6 Theresa?
7 DR. MICHELE: All right. So I think this
8 workshop is a big step for us, and one of the things
9 that's important that we at FDA can do is, as you heard
10 from Badrul, we can't approve a drug if we don't have
11 an application for it, so how can we stimulate the
12 field to get more applications? And one of the ways
13 that we can do that is by expressing FDA's willingness
14 to work with companies and investigators on drugs for
15 CFS.
16 You know, I think that the most important
17 thing we can do is continue to be good ombudsmen
18 wherever we are, to say, you know, "CFS, we consider it
19 to be a serious disease." That should send a very
20 strong message out there to pharma that, hey, this may
21 be a financial opportunity here. And that's -- money
22 makes the world go 'round. That's how it works, so

1 that's, I think, from an FDA perspective, how we can
2 leverage our experience.
3 The other way we can leverage our experience
4 is when people do come in with clinical trials is we
5 can continue to work with sponsors to help them with
6 those trials. We have a vast knowledge base of
7 clinical trial design that, while much of it has not
8 been in chronic fatigue syndrome because we haven't
9 seen very many trials in chronic fatigue syndrome,
10 lessons learned from other diseases are directly
11 applicable here.
12 And I was struck by Dr. Rowe's talk and how
13 beautifully he laid out issues with clinical trials. We
14 could take that talk and apply it equally to many other
15 disease areas that we do have a lot of experience with.
16 So I think that we can help you with that, and our
17 division has its doors wide open for applications for
18 chronic fatigue syndrome.
19 DR. MANGAN: Jody, how are we --
20 DR. MAIER: Can I -- oh, I'm --
21 DR. MANGAN: I'm sorry.
22 DR. MAIER: Can I jump

1 DR. MANGAN: Uh-huh.
2 DR. MAIER: Talk to us. Honestly, talk to
3 us. Don't be afraid to call if -- we're talking -- I'm
4 talking from the research perspective. Call me, email
5 me. If I don't have the answer, I will put you in
6 touch with someone who will provide you with an answer.
7 But if I don't know what you're thinking as a
8 pharma, if I don't know what you're thinking as an
9 advocacy group, if I don't know what the researchers
10 are thinking, call. Just talk to us and let us help
11 you with the -- I can't write your proposals for you,
12 but I can provide technical assistance that will
13 enhance the proposals that come in. And once those
14 proposals come in, they get reviewed, and then we can
15 fund them.
16 DR. MANGAN: Good. And, Jody, how are we
17 going to get the pharmaceutical companies and the
18 biotech companies excited?
19 MS. ROTH: Well, I think today is a -- in
20 this workshop is a good start. You know, I don't know
21 if this was an indication that was on folks' radar
22 screen much before this, so I think this is one way to

1 do it. I think the other way is understanding what
2 endpoints it's going to take for registration. And I
3 understand we've put some forward at this conference,
4 which has been great, but will they be of enough
5 evidence for, you know, a benefit risk and also for
6 substantial evidence?
7 I think one thing that struck me is the
8 discussion on the PROs, is how can we leverage our PRO
9 consortium that we have, and how can we maybe, as a
10 pharmaceutical industry, come together to say -- with
11 the FDA and these consortiums to say, "What is it that
12 we need to measure this with?" And I think that would
13 really help, to understand kind of what that endpoint
14 is.
15 And I think -- I really do believe that today
16 is a big -- and the last two days have been a big
17 stride in that, and I think the idea that we could
18 actually maybe work together for guidance is going to
19 be another big thing, is to help us understand what's
20 that regulatory hurdle so that we can assess what that
21 probability of success is for really the commercial
22 investigator that's made for a lot of these

1 indications.

2 DR. MANGAN: Thank you. And Nancy Lee, as

3 far as the HHS goes

4 DR. LEE: Right. And I'm going to sort of

5 talk out of turn and speak for one of the agencies that

6 I don't directly represent, because I'm not in the

7 agency, but I'm going to talk a little bit about what I

8 know, which is epidemiology. A little bit earlier, I

9 said we need to have the data infrastructure, and the

10 work that CDC is doing is really about developing that.

11 So as a concrete example, Beth showed some

12 wonderful slides that showed the distribution of the

13 various symptomatology. So now we have -- I mean, and

14 that's not a representative sample of all of the people

15 with CFS we know, but it's a start. And if you can use

16 that information, and you pick whichever of those

17 symptoms you're going to kind of think about, then when

18 you do your sample size calculations, you're going to

19 have a better idea of really how many people you need

20 to -- how many patients you need to have in your study.

21 I was saying to Susan while ago I don't know

22 how -- they must not have had a statistician or an

1 epidemiologist on some of those early trials, where
2 they had 15 people in each trial, because there's no
3 way. I don't know how they even thought they would get
4 anything out of that, knowing that these are sort of
5 the prevalence of the symptoms and the likelihood of
6 response.
7 So you -- so having the data to really help
8 us figure out the best way to decide trials, to decide
9 sort of how to move on the trials, is really important.
10 CDC is doing some very important stuff in that, and I
11 know that they're planning on getting some -- in the
12 next phase of this study that Beth talked about today,
13 they're going to be doing some blood work, et cetera.
14 And so that's what I want to say.
15 DR. MANGAN: Thanks.
16 MR. MILLER: Excuse me, Dr. Mangan.
17 DR. MANGAN: Uh-huh?
18 MR. MILLER: May I?
19 DR. MANGAN: Yeah. Okay. We're going to put
20 you next here. Okay? Go ahead, Robert.
21 MR. MILLER: Thank you. So I just -- I
22 wanted to respond to what Dr. Maier was saying earlier

1 about, you know, submitting grants and getting them
2 funded. And I'm going to kind of just take this and
3 throw this to Dr. Klimas, because I think yesterday,
4 you were talking about how many applications that
5 you've put in and what the response is. And so I would
6 ask you to reiterate that.
7 DR. KLIMAS: Thanks. I don't know if this
8 makes me look bright or dull, but, yeah, we --
9 DR. MAIER: No, you're bright. Don't worry.
10 DR. KLIMAS: We have about an 8 to 1 ratio
11 for funding. We write 8, and we get 1 funded. And I
12 think I've only once in my life been funded the first
13 time I submitted something. It's always on the second.
14 And you can't go three times anymore, so the second
15 round.
16 But since I got the mic, I'm going to take
17 the academia perspective that's up there and say that I
18 think the best way for drug development to leap forward
19 right now -- I'm going to be bold and crazy and say
20 right out front, we need philanthropic support. You
21 can cut two years off.
22 If I have to go in for Phase I, I'll have an

1 excellent study. I've submitted it three times to
2 three different agencies. I've had it turned down
3 three times. I should have had it in play two years
4 ago coming right out of our computational modeling
5 work. And we could say, "Was it well-written?" And if
6 people didn't understand it or whatever, there's good
7 reasons why it might have been accepted. But in the
8 end, I could have already done the Phase I study while
9 I waited around to try to find the funds to do that
10 study, and it wouldn't have cost that much.
11 So it's very, very frustrating, and then you
12 all want us to be so much quicker at getting you your
13 through Phase III, times two, get the label on,
14 clinical trials work so that you can have your drugs.
15 I'm struggling to give you your Phase I/II work that
16 would lead to the Phase II, II/III, III work that would
17 eventually end up with a label on the drug.
18 And there are a lot of different
19 opportunities of things to study, a lot. It's not that
20 we don't have good ideas and good science to go behind
21 those ideas. What we don't have is your time to waste.
22 And if there's something that we could do that would

1 just knock two years off the time clock, it would be
2 starting from foundation or philanthropic support to do
3 that work.
4 Now, I know my institute, we're working very
5 hard. We have a Translational Medicine Unit, and it's
6 our number one fundraising thing that we're doing is
7 let's fund this Translational Unit. Let's get some
8 clinical trials on the ground. Let's get it going.
9 Let's get it going. And it's very exciting, and it's
10 definitely what we should be doing right now. And
11 we'll still knock at the right doors, all the other
12 doors.
13 I've got nine grants on the board right now
14 that we're going to be submitting between now and next
15 Christmas. We're all working very, very, very hard on
16 your behalf, but, yeah, maybe one of them will get
17 funded. That would be cool.
18 DR. CHOWDHURY: Thank you again for the panel
19 for this discussion on Question 5.
20 DR. CHU: Can I say something?
21 DR. CHOWDHURY: Dr. Chu?
22 DR. CHU: Yeah. I have three points. Point

1 number one, the survey that I did earlier, I wasn't
2 able to present the results, so if anyone wants a page,
3 and it has to do with the epidemiology of CFS, you're
4 welcome to email me at lilyxchu@gmail.com. So that's
5 point number one.
6 Point number two, as an IA CFS board member,
7 I want to invite everyone who's interested in learning
8 more about CFS to join our organization or to attend
9 our scientific meeting to be held in San Francisco next
10 March.
11 We also publish a peer-reviewed journal about
12 fatigue, CFS/ME, fibromyalgia, and a quarterly
13 newsletters. We're open to accepting different types
14 of articles, and on the other side, we can also help
15 disseminate information to our clinician and research
16 members about, for example, funding or collaborative
17 opportunities. That email address for the organization
18 is www.iacfsme.org.
19 And, finally, as a patient, I want
20 pharmaceutical companies and other people to understand
21 that patient groups are enthusiastic and willing to
22 work with anyone to advance progress on this illness.

1 For example, if you need help with recruiting patients
2 to a trial, there are many organizations that work
3 together now, patient organizations, and one of them is
4 the National Advocacy Alliance for ME, which consists
5 of many state groups across the country. Their Web
6 page is www.naame.org. Thank you.
7 DR. CHOWDHURY: Thank you very much, and in
8 about two or three minutes, we'll be going to the next
9 phase, which is taking questions from the audience. And
10 before that, I'll put up Question 6 here and very
11 briefly ask the panel members who are interested to
12 comment or give your opinion on that. And, again, be
13 cognizant about time, about two or three minutes on
14 this.
15 And the highlight of the question is next
16 steps forward. With that, I'll turn it over to anybody
17 who would like to speak. Please.
18 DR. KLIMAS: I would like -- it's the obvious
19 thing, that we need to have a small meeting with the
20 experts in the FDA to talk about these outcome
21 variables and really nail some outcome variable stuff
22 down. That would be very, very helpful, and I would

1 volunteer to come back to D.C. and do that with anyone
2 else that wants to do that.
3 DR. CHOWDHURY: Anybody else from the panel
4 here wants to comment on this?
5 MS. ROTH: I think I've kind of already
6 stated this, but I do think the -- just to build on
7 that, I think that, going into a guidance or some
8 regulatory precedent of what we need to do to devise
9 trials is going to be essential to move this forward so
10 that we can understand kind of what that is overall and
11 what's needed for that.
12 DR. CHOWDHURY: Please.
13 DR. MICHELE: Thank you. Sorry.
14 DR. CHOWDHURY: Go ahead. Go ahead. You go.
15 DR. MICHELE: So as my colleague from Lilly
16 so nicely put, guidance for industry is definitely, I
17 think, an important next step. It's something that we
18 here at FDA are already thinking about. I suspect that
19 we'll be able to gather a lot of the information that
20 we have heard here at this meeting and begin to
21 formulate that, and we'll need to continue to gather
22 some additional information as we move forward.

1 And there are a variety of sources to look
2 for that, including information that the CDC and the
3 NIH are currently developing. So I think we have a lot
4 of resources in that area, and we hope to be working on
5 that definitely over the next months to a year or so.
6 It takes a long time for a guidance from FDA, just the
7 logistics of getting it through the system. So don't
8 look for it next month, but it's definitely something
9 that we are very well aware of. And people sitting
10 next to me can see that I already have that circled on
11 my paper. That was written there before we came up. So
12 thank you for that.
13 DR. CHOWDHURY: Thank you. Anybody else
14 would like to make a brief comment?
15 DR. DIMITRAKOFF: I just wanted to make two
16 comments that are very brief, actually. So I'll
17 volunteer to come back as well, and I don't have to be
18 paid for that, as Nancy Klimas was saying, if the FDA
19 actually has a small meeting with -- just articulating
20 the specific endpoints.
21 Another thing that I wanted to make -- to
22 bring is that we -- during one of the conference calls,

1 we actually brought this point, is that might actually
2 be helpful if a peer-reviewed paper comes out of this
3 discussion, just to inform the medical community about
4 the progress that has been made over the past two days
5 so that, actually, the community at large has some
6 better idea about the field moving forward, so it would
7 be a good idea if we can work on this together as a
8 group or with -- if other people are interested in
9 doing that.
10 DR. CHOWDHURY: Dr. Chu, please go ahead.
11 DR. CHU: Adding to Jordan's point, this is -
12 - publishing in a peer-reviewed journal would also be
13 an excellent way to recruit new investigators and
14 people from other fields that might not have realized
15 that their fields overlap with CFS. Audience Question
16 and Answer period
17 DR. CHOWDHURY: I would like to move on to
18 the next set, which is questions from the audience, and
19 before I do that, I just wanted to make sure -- anybody
20 else from the panel here wants to make any comment? Now
21 -- okay. The audience, you're listening carefully,
22 writing very important, interesting questions. We do

1 want to give these questions due time and discussions.
2 So with that, I'll put up three questions
3 together and try to answer it myself or pass them on to
4 the panel. First is other clinical FDA trials approved
5 for CFS, why exactly for Ampligen was not approved, and
6 does FDA have a working group to write industry
7 guidelines?
8 The guidance question, Dr. Michele just sort
9 of answered, and for the other questions, for the
10 Ampligen, there was an open public meeting, and many
11 materials are up there on the website. And why exactly
12 Ampligen was approved, just as a point of the process,
13 FDA takes a decision, writes a letter to the company,
14 and that is confidential for the company if they want
15 to hold onto it. If they wish to make it public, they
16 can make it public. We from the FDA cannot.
17 So I think the materials are up there on the
18 Web, and one can, again, review that. And there are
19 other clinical FDA trials approved for chronic fatigue
20 syndrome, and as Dr. Michele earlier mentioned, there
21 are, but there are not too many.
22 With that, I'll turn to Dr. Michele. Do you

1 want to add anything on these questions? And, again,
2 the questions were do we have a working group and a
3 guidance-writing activity?
4 DR. MICHELE: No, I think you covered it
5 beautifully. Thank you.
6 DR. CHOWDHURY: Okay.
7 MR. MILLER: I wanted to ask Dr. Chowdhury,
8 you said there were other clinical trials. Can you
9 tell me what those are, specific to chronic fatigue
10 syndrome?
11 DR. CHOWDHURY: I think Dr. Michele is --
12 might want to respond to that.
13 DR. MICHELE: Right. So Dr. Kweder had this
14 in her presentation at the CFSAC, and I'd encourage you
15 to take a look at those slides, which are up on the Web
16 at the CFSAC website. And Nancy Lee probably knows the
17 URL off the top of her head. But if you --
18 DR. LEE: Just Google CFSAC.
19 DR. MICHELE: Exactly. That's how I get
20 there.
21 DR. LEE: Yeah, always.
22 DR. MICHELE: And it outlines exactly the

1 number of trials, which isn't a lot, and the number of
2 active INDs, which is a handful.
3 DR. MANGAN: Okay. And Jody Roth, the
4 question comes in here, it says, "Can you comment on
5 how investing and repurposing of currently available
6 drugs for CFS can be financially worthwhile investment
7 for a pharma company?"
8 MS. ROTH: Well, first of all, I think
9 there's some fundamental principles that a
10 pharmaceutical company kind of uses when they look --
11 we continually want to look for opportunities for that
12 drug to be used once we establish it for its initial
13 indication, and that helps many different patients. So
14 we are looking for what we call NILEX or line
15 extensions basically to add on to that drug.
16 I think the items that factor into that are
17 no different than the initial indication, which is what
18 is your regulatory pathway, what is your endpoints, and
19 what's your likelihood of success to be successful in
20 that indication, based on what you've already
21 demonstrated in your other areas?
22 So you build with your safety, as was alluded

1 to already, but the safety may be different than CSF
2 (sic), so how do you establish the safety and the
3 efficacy in that new indication?
4 So it's a -- you build a commercial case as
5 well as a risk-benefit case and kind of build that
6 forward to say is that an indication that is worthy of
7 investing? Is it going to serve patients, and is this
8 particular drug -- do we have proof of evidence that
9 it's going to work in this population, which is another
10 one of the key attributes.
11 DR. MANGAN: Thank you. A question's coming
12 in here, which I just love here, because I don't work
13 for the NIH anymore, and I can actually ask this
14 question. It says, "Is anybody lobbying Congress to
15 set aside money for CFS research?" Lily can -- there's
16 not too many people up here that can answer that. Go
17 ahead.
18 DR. CHU: Well, I've been trying to lobby
19 Congress to set aside money for CFS research, and it's
20 not easy. I mean, I think the legislative aides that
21 I've talked to and some of the Congress people, they're
22 interested, but my problem is I don't have the energy

1 to do it, to follow up, and that's my biggest issue.
2 I've tried getting more people interested in
3 doing this, but it's hard, just because I have really
4 very little energy to coordinate. So I'm hoping that
5 people will take this up or work together.
6 DR. KLIMAS: So when you lobby Congress, the
7 most obvious pot of money that would then go into is
8 the DOD pot that's administered through the Office of
9 Congressionally Mandated Research. CFIDS Association
10 and others successfully lobbied Congress and put aside
11 some money into that pot last year. I don't believe
12 it's in the pot again this year. I think it was not.
13 So, however, as a Gulf War illness
14 investigator, I can tell you that the DOD is a
15 wonderful place. The Office of Congressionally
16 Mandated Research has a very professional, outstanding
17 group of people trying to push their -- those protocols
18 forward. They take it very seriously. They do an
19 excellent job.
20 They have -- they have basic science, Phase
21 I, Phase II, Phase III. I'm in a Gulf War illness
22 consortium that was just awarded a $4 million, $1

1 million a year consortium after a planning year. Does
2 this sound familiar? And we were successful.
3 And, actually, the second consortium I put my
4 toe in also was successful. They funded two $4 million
5 consortiums last year. This year, they have $25
6 million for Gulf War illness. Last year they had $19
7 million. The VA has $19 million this year for Gulf War
8 illness. Does it sound kind of cool to those of you
9 that are thinking, "Wow, if my field had
10 And it's really true. I mean, when you think
11 about that, they're spending, you know, maybe $40
12 million a year on Gulf War illness, which affects a
13 quarter of a million veterans who went to the first
14 Gulf War, came back ill. It's a very terrible illness,
15 feels just like chronic fatigue syndrome, and is very
16 different at the biologic level and very overlapping in
17 other areas. So it's a fascinating illness to be
18 studying side by side with chronic fatigue syndrome and
19 gives us, I think, some very sophisticated and very
20 well-funded ways to better approach these illnesses.
21 DR. CHOWDHURY: Thank you.
22 DR. KLIMAS: My personal approach has been to

1 put chronic fatigue in as a comparator group for many
2 years.
3 DR. CHOWDHURY: Thank you. Be very brief. I
4 have two more questions to go through. Please. Please,
5 yes, one.
6 DR. LEE: Just a quick cite (ph), because I
7 have heard about this alternative source of federal
8 funding, and my understanding is their process is very,
9 very inclusive of patients, maybe more so --
10 DR. KLIMAS: Very much so at the review
11 level.
12 DR. LEE: They are much -- very, very
13 inclusive of patients, and so -- and they're very --
14 well, they get their response -- they make their
15 decisions based on the input of the advocates that get
16 to Congress and convince them. Is that fair to say?
17 DR. CHOWDHURY: Mr. Miller, you want to say
18 something?
19 MR. MILLER: Yes.
20 DR. CHOWDHURY: Yes. Please, go ahead.
21 MR. MILLER: I want to echo what Lily said.
22 I spent quite a bit of time going up on the Hill, and

1 it's very difficult, because, you know, you get a
2 meeting set up at one place, and you've got one 30
3 minutes later, but it's in a whole 'nother building.
4 And so it takes a lot of time, takes a lot of energy,
5 but it's certainly worth doing.
6 And I would ask, you know, patients that are
7 watching, patients that are sitting in the audience,
8 you don't necessarily have to go to the Hill to lobby.
9 You can write your senators, you can write your
10 congressmen, and they will respond. I have several
11 letters --
12 DR. CHU: You can go to the local office as
13 well.
14 MR. MILLER: Yes. Thank you.
15 DR. CHOWDHURY: Thank you. I think -- again,
16 I think we have discussed this question. I have got
17 two more questions to briefly go through, and these are
18 somewhat long questions. The first one is directed to
19 Dr. Michele, and this is on a safety evaluation,
20 specifically serious adverse events. I'll read the
21 question (inaudible) Dr. Michele to respond to the
22 question.

1 "SAEs, or serious adverse events, all
2 hospital admissions are considered SAEs since 2010,
3 although not drug-related, nor serious. This
4 complicates safety evaluations of an IND with non-drug-
5 related adverse events. Can FDA review this and sort
6 of clarify?"
7 So I think the question here is hospital
8 admissions being considered serious drug-related versus
9 not drug-related, if you can respond, please.
10 DR. MICHELE: Right. So the definition of a
11 serious adverse event is well-codified in the guidance
12 documents, and it's also in the Code of Federal
13 Regulations, so we don't really have much leeway to
14 change that, but what we do do in clinical trials is
15 that's the beauty of a comparator group is that you
16 have your drug-treated patients, you have your patients
17 who are not being treated with that drug, and you look
18 at the serious adverse events that occurred in both
19 groups, and you compare them.
20 That's also why it's so critically important
21 in a heterogeneous disease like this to have a large
22 enough database so that you can sort these things out.

1 If you're talking about one or two events, it's hard to
2 know what they really mean, but if you have a large
3 enough database, then you can see adverse events that
4 occur more frequently in your treatment group.
5 DR. CHOWDHURY: Thank you. And the last
6 question for the day -- I'll read the question and try
7 to answer it myself and then pass it on to the panel,
8 if anybody wants to respond. And the question is on
9 biomarkers. It says that "We have biomarkers. Why
10 does FDA continue to insist we have none? What needs
11 to be done to validate NK cell functions, immune
12 markers, and viral titers as biomarkers?"
13 So let me try to respond to this, as one way
14 of looking at it, is it really necessary to have a
15 biomarker to have a drug approved? The answer is no.
16 If one shows benefit on a clinically meaningful
17 endpoint to your patients, one does not need a
18 biomarker. And how does one validate a biomarker? It
19 becomes very complicated. I mean, biomarkers,
20 laboratory measures, physical functions, and others
21 which we have heard earlier, it gets validated and
22 evaluated and becomes at some point surrogate markers.

1 Then surrogate becomes a reflection of the actual
2 clinically meaningful endpoint, and then at some point
3 even the surrogate may be considered to be real
4 outcome, as one mentioned about cholesterol.
5 So the point here that I would respond
6 that I think for chronic fatigue syndrome, there is no
7 upfront need for drug approval process for an IND study
8 and drug evaluation and research to develop a
9 biomarker. So, again, that's my comment on this
10 question. I will look to the panel, for instance
11 anybody wants to respond. I see one hand's up. Please
12
13 DR. KLIMAS: So as we enter into the era of
14 clinical trials, now is our chance to test our
15 biomarkers, but as you heard before, the primary
16 outcome variable might be something like function, and
17 your secondary outcome variable might be a series of
18 biomarkers that you'd like to test against that primary
19 to see if it's going to be a decent surrogate or not.
20 So in your early trials, you can throw in some extra
21 variables if you would that are biomarkers, and then
22 you're collecting this data, this validation dataset.

1 So when you heard that HIV work, I was a part
2 of that very first AZT trial. I was there, and the
3 second and the third. The -- you know, death was the -
4 - was the primary, and then -- and we had CD4 count
5 initially as our secondary. And then eventually we had
6 viral load as our secondary, which turned into our
7 primary, and we could approve drugs way, way faster
8 because we were able to prove that something actually
9 did predict death.
10 So what we need is something that will
11 predict function or some other variable that's very
12 important, but I would argue function in chronic
13 fatigue syndrome. And, yes, I do think we have the data
14 to support that there are biomarkers in our hands right
15 now that predict function. In fact, we've been
16 publishing them and presenting them, and you've heard
17 them. We don't have to go over them.
18 But they need now to be attached into
19 clinical trials as secondary outcome variables, and
20 then I think we could be -- make a compelling case for
21 drug development, for drug trials, which is a little
22 different than what will your insurance company pay

1 for, but for drug trials, that these things are
2 actually useful and could become surrogates.
3 DR. CHOWDHURY: Anybody else wants to comment
4 on this?
5 DR. KLIMAS: Yeah, that's a good point. You
6 could say that.
7 DR. LEE: Well, I can't give you -- she's
8 been helping me with this, but fibromyalgia has drugs
9 approved for it, and there are no biomarkers, and it
10 was approved basically on the functional -- on the
11 clinical outcome.
12 DR. KLIMAS: Pain, yeah.
13 DR. LEE: Right. So -- and that's a drug --
14 or that's a condition that has a lot of overlap with
15 ME/CFS.
16 DR. KLIMAS: Yeah. I'd like to comment,
17 though, that I think biomarkers are really important,
18 and this is a little different, but I think they're
19 very important for like inclusion criteria and
20 selecting subgroups, because even as Dr. Unger pointed
21 out, in their studies so far, you know, you could have
22 clinical phenotypes, but it may be very difficult as a

1 way to distinguish different groups, though, in my
2 opinion, I think the orthostatic intolerance subgroup
3 might be a very interesting one to explore.
4 MS. ROTH: Dr. Chowdhury --
5 DR. CHOWDHURY: Thank you very much -- yes,
6 please.
7 MS. ROTH: Can I just add -- I mean, I think
8 biomarkers are very important, and I still would come
9 back to the regulatory endpoint is sometimes more
10 informative, and fibromyalgia's a great example. I
11 think that biomarkers have their own set of hurdles to
12 get in and label and so forth, but I think both need to
13 be studied in this, based on where we're at with this
14 condition.
15 But the regulatory endpoints of what is going
16 to be meaningful in a label is kind of what -- what
17 I've taken out of this is going to be the utmost
18 importance to move a drug through most expeditially
19 (sic) for the patients, so
20 DR. CHOWDHURY: Anybody else has any comments
21 on this question or any other questions?
22 DR. KLIMAS: Just one historically relevant

1 point. AZT was approved with the requirement that you
2 had to have a CD4 count less than 200 to be allowed to
3 have the drug, and CD4 count had not been approved as a
4 biomarker for anything. So we were using a research-
5 only biomarker for about a year before they got the
6 biomarker labels under the thing that we had to do in
7 order to get to the drug. So sometimes you just move
8 on forward.
9 DR. CHOWDHURY: Thank you very much for this
10 comment, and, again, thanks to the panel for a very
11 interesting, exciting discussion here. Thanks to the
12 audience staying engaged, putting together a lot of
13 interesting, thoughtful questions. We really
14 appreciate it. And before I pass it on to Dr. Kweder,
15 just one small announcement I have to make is Mary
16 Leuchars, she's been asked to meet somebody in the
17 desk, which is just outside the desk here.
18 With that, I'll ask Dr. Kweder to give some
19 closing comments. Thank you. Closing Remarks
20 DR. KWEDER: Well, again, I really want to
21 thank this final panel. I think you did a really
22 wonderful job of pulling together a lot of the points

1 that have been made over the past two days, really,
2 including, you know, going back to yesterday with the
3 real, you know, very focused patient discussions and
4 then bridging us to clinical research and, you know,
5 sort of the bigger picture of developing products to --
6 that can be helpful in this serious disease. So,
7 really, thank you very much. It was really a great
8 job.
9 And I know -- I also wanted to thank all of
10 you in the audience who have persisted, but probably
11 need to stretch right about now. This meeting has
12 really, I would say, far -- it has met and exceeded our
13 expectations, and a lot of the reason for that is
14 because you have been here. You have engaged. You've
15 asked really good questions. And you have rolled up
16 your sleeves and shown up. I always tell my kids,
17 "Showing up is half a life." And you've shown up, and
18 for many of you, you've shown up in the face of great
19 difficulty. And I personally, and I know all of us at
20 FDA who've been working on this meeting, appreciate
21 that greatly. We have -- we have started on an
22 important path together.

1 There has been -- and I'm really excited to
2 see all of -- was very excited to see how much work
3 there -- and energy and passion already exists in this
4 field by clinicians, by investigators, most of whom are
5 working a lot on their own and don't have a lot of
6 opportunities to come together. And if I heard one
7 thing in this meeting, it is the importance of
8 collaboration.
9 And I would urge everyone who has an interest
10 in this field to take that message to heart and to take
11 another message to heart. What will make a difference
12 is personal leadership, personal leadership, not the
13 leadership of this group, that group, the government,
14 DOD, whoever it might be, but the sense of personal
15 leadership among people who have a passion for this,
16 who are willing to roll up their sleeves and say, "What
17 can I do? Who can I collaborate with so that we can
18 get something productive done? Who can I listen to who
19 might approach this from a way that is a little
20 different than I've been thinking about this, who maybe
21 I've had some conflicts with in the past about the best
22 way? How can we come together and find our common

1 ground and really make some progress?"
2 I can tell you from the comments that I heard
3 on this last panel that it seems to me that most people
4 here at this table are expressing a willingness to do
5 that, and I want to challenge you all to bring that to
6 fruition, and I want to challenge those of you in the
7 audience to work with us all collectively to make that
8 happen.
9 Two other things. First, you'll -- this
10 meeting in its entirety, yesterday and today, has been
11 videotaped. People have been watching it on their
12 computers at home, and those of you who are with us
13 remotely, I want to thank you for sticking it out.
14 For those of you who want a refresher, this -
15 - the whole thing is going to be available on the FDA
16 Internet site so that you can watch sections that you
17 want -- that you want to review again, and you'll be
18 able to watch them with the slides up close, because
19 the slides are going to be posted on FDA's website as
20 well, and we'll make sure that they're easy to find.
21 I also want to thank the people in the room
22 who have not been participating in asking questions and

1 who've not been sitting up here at the table. So I
2 particularly want to see the people who are in the back
3 who have been really doing a lot of the legwork.
4 And in particular, I'd like to see Mary Gross
5 who's over in the corner. Mary Gross has been our
6 absolute taskmaster inside the FDA, making us come to
7 meetings, making us send the slides, making these
8 people send the slides, and really keeping us on track.
9 And Randi Clark, where is Randi? She's
10 hiding, right? There's Randi. Stand up, Randi. Randi
11 is just like one of the most positive forces we know.
12 She helps get things done, and always with a smile. She
13 has great ideas, and we're like, "Wow, Randi, we didn't
14 know you were -- that you were going to contribute
15 that." She's just overall wonderful.
16 And these are the kind of people at FDA --
17 and I can't -- there are many, many others. People in
18 our Office of Special Health Issues people like
19 Richard Klein and David Banks and our special --
20 our patient outreach groups, our policy
21 folks, who have been very involved, but you haven't
22 seen them.

1 And when we put this kind of meeting
2 together, it's people from across our center who really
3 do come together and put their heads together and take
4 -- they take their work very seriously. To them, this
5 is public health, and that's why they come to work
6 every day. And it's because of things like this they
7 wake up in the morning and they say, "I am going to
8 make a difference." And so we hope that we can all
9 continue collectively to make a difference.
10 I want to thank you again for your
11 inquisitiveness, your commitment, your willingness to
12 ask questions, your willingness to challenge each
13 other, and wish you safe travels and a wonderful,
14 rejuvenating weekend. Thank you very much.
15 (Whereupon, at 4:58 p.m., the meeting was
16 adjourned.)
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