Transcript for the 10th CDC Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Stakeholder Engagement and Communication (MECFS-SEC)

November 2, 2017

Coordinator: Standing by. At this time, all participants in a listen-only mode for today's duration. Today's conference call is being recorded. If you have any objections, you may disconnect. I will now turn the call over to your conference host, Dr. Dana Brimmer. Ma'am, you may begin.

Dana Brimmer: Thank you. Good afternoon everyone. My name is Dana Brimmer and I am a contractor working with the ME/CFS Program at the Centers for Disease Control and Prevention. On behalf of the program, I am pleased to welcome you to today's ME/CFS Stakeholder Engagement and Communication Conference Call, known as SEC. Our primary purpose here is to share information with a large number of people with interests in ME/CFS as part of our regular outreach and communication series. Before we get started I want to review how the SEC calls work.

Notification of calls will be sent by email, and information is also posted on the CDC ME/CFS website. There is no need to register or RSVP for the call. Simply dial the 800 number and use the participant code provided in the emails or found on the CDC website. Due to the large number of call participants we are unable to have call lines available in speak mode. Therefore, we will take questions via email using the ME/CFS SEC call email system. Note that this email address cannot respond to inquiries. Please note that -- due to time constraints -- CDC and the guest speakers will not be able to answer all questions. But the CDC ME/CFS program looks forward to reading them all.

Our guest panel presentation today is "Take Home Messages from the 2015 Institute of Medicine Report ME/CFS" by Drs. Lucinda Bateman, Ellen Clayton, and Peter Rowe. First we will hear from Dr. Elizabeth Unger, who will provide updates about the CDC's MECFS program. After Dr. Unger and our guest panels speak, we will answer questions submitted via email. I will first read the questions out loud and then our speakers will answer each one.

I now want to read a disclaimer. These calls are open to the public. Please exercise discretion on sensitive content and material as confidentiality during these calls or items submitted via email cannot be guaranteed. Today's call will be recorded by CDC and transcripts will be available at a later date on CDC's website. The views of non-CDC presenters expressed during this conference call are their own and do not necessarily represent the views of the US Department of Health and Human Services or the Centers for Disease Control and Prevention.

I would now like to ask Dr. Elizabeth Unger -- Chief of the Chronic Viral Diseases Branch at CDC -- to start the call. Welcome Dr. Unger.

Dr. Elizabeth Unger: Thank you Dana, and welcome to everyone on the call. So just adding on to what Dana has said, we initiated these calls to provide regular communication with the ME/CFS community about CDC's activities, and also to provide a forum to allow other experts external to CDC to share information on their work related to ME/CFS clinical care or research. Our program identifies a topic for each call and invites speakers based on their expertise and availability. Participating speakers prepare their talks independently and present their own views. They have all graciously volunteered their time, and we are so appreciative of their participation.

This tenth call is a bit unique as it was planned in response to recommendation in the 2015 Institute of Medicine's report on ME/CFS. This recommendation was to use one of CDC's calls to disseminate the report's findings. We are very fortunate that the chair and two members of the committee have agreed to participate today. Please use the SEC mailbox -- MECFSSEC@cdc.gov -- to suggest topics for future presentations. I'm now going to shift to give you an update on some of CDC's activities. I'm starting with our educational initiatives as dissemination of information about ME/CFS to the general public and health care providers remains a critical need.

Last year we began a process for broad stakeholder input into the educational materials to be developed. Specifically focusing on how the Institute of Medicine -- IOM -- how their recommendations should be communicated through the CDC's

website. In addition to small group phone calls, we held a face-to-face meeting with a broad range of stakeholders. The summary report from the round table meeting can be found on CDC's ME/CFS website under the Program tab. One of the strengths of the round table meeting was that it provided an opportunity for direct communication between stakeholders with different points of view. We hoped that involving medical professional groups will make it more likely that the medical societies will share ME/CFS information with their members. We used the comments gathered at the round table to revise the website. To match the timetable for CDC-wide changes to web page format, we divided a process for revising our web -- our ME/CFS web -- content into stages. We started with information for the general public that meets Plain Language Standards. These sections were posted this past summer.

The health care provider section of the website is nearing completion. CDC also plans to add a Voice of the Patient section which will feature stories of patients living with ME/CFS. We are hopeful that this new feature will increase awareness and understanding of the profound impact that ME/CFS has on individuals and their families.

CDC just awarded a contract to McKing Associates to extend this stakeholder engagement process. McKing facilitated the prior successful round table meeting. The next initiative will focus on identifying educational materials beyond our website that will be most useful to health care providers.

We are coordinating a Continuing Education event to be held in Atlanta at the Savannah College of Art and Design Theater on the evening of November 30. This will feature the award-winning documentary film “Unrest” followed by a panel presentation including speakers from the CDC, a national clinical expert on ME/CFS -- Dr. Nancy Klimas -- and the documentary's director, producer Ms. Jennifer Brea. This has been tailored for health care, public health, and other professionals and students but is open to all. CDC will be offering Continuing Education credits to participants.

We're building on our prior collaboration with WebMD Medscape to develop a Continuing Medical Education -- CME -- activity called a Spotlight. Clinical information on how to asses ME/CFS using the recommendations of the IOM report will be presented using a moderated panel discussion between health care providers. The ME/CFS Spotlight will be recorded and hosted on the Medscape website with CME credit available for one year. Medscape has a nationwide distribution to health care professionals, so it is an ideal platform to teach health care providers about using the IOM ME/CFS guidance. Our program's two prior Medscape CME events were very successful. In combination over 9000 learners earned credits. The new CME course should be available by Spring 2018.

Shifting now to updates on the Multi-Site Clinical Assessment of MECFS Study, referred to as MCAM. This study continues to be a major focus of our group, but in the interest of time I'm only going to touch on a few items. As a very quick review, the study is designed to use a standardized approach for collecting information on patients in the clinical practices of clinicians with ME/CFS experts. A synopsis of the MCAM study can be found on CDC's ME/CFS website under the Program tab. In December we will hold our seventh meeting of the collaborating clinicians and study coordinators on CDC's campus. While progress has been very good, the MCAM study clinics have had difficulties enrolling children and adolescents with ME/CFS as well as persons diagnosed with other illnesses who serve as comparison groups to ME/CFS. To address these gaps, CDC announced two contract solicitations last summer. These were recently awarded to Eagle Global Scientific -- EGS. We will share more details once EGS sets up their contracts with additional clinics. Enrollment through these contracts will increase the sample size and power to examine the similarities and differences between ME/CFS and ill comparison groups and to provide much-needed data on pediatric ME/CFS.

Data dissemination and presentations also help raise awareness and educate. Dr. Lilly Chu initiated and coordinated a special epidemiology session at the upcoming American Public Health Association -- APHA -- annual meeting, which is entitled “ME/CFS Fact, Fiction, Findings.” This conference will be held Monday, November 6. Dr. Chu will be the moderator and will contribute a presentation. The session includes three additional speakers, Drs. Jose Montoya, Louise Nacul, and myself. I'm very excited that CDC was invited to participate in this session and I'm glad that I'll be able to share CDC's information at this prestigious APHA conference.

CDC's ME/CFS program has consistently sought to present CDC's work at the annual APHA conference, as it provides an opportunity to educate the public health community about MECFS. This year -- in addition to the talk at the special session -- we're presenting two abstracts. One is an oral presentation examining the relationship between allostatic load -- a measure of physiologic stress -- and ME/CFS. The other is a poster tackling the analytical challenges relating to integrated medication information in studies of ME/CFS, using a novel method known as tensor factorization.

CDC continues to be involved in other partnerships. We've been actively collaborating with other Health and Human Services agencies to ensure each agency's activities provide the greatest benefit to the American public. With the National Institute of Neurologic Disorders and Stroke -- NINDS -- at the National Institutes of Health we are co-sponsoring the ME/CFS Common Data Elements Project. Common Data Elements -- referred to as CDEs -- are not a database. They are standards to enable information to be consistently captured and organized across ME/CFS studies. The ME/CFS CDE project involves almost 60 members of the international ME/CFS community. Persons with ME/CFS have played extremely active and critical roles in this process. The work groups also include clinicians and researchers with expertise in the varying domains of ME/CFS. Emmes Corporation has been facilitating the process. The working group recommendations for case report forms, instruments, details of the CDEs and guideline documents will be posted on the NINDS website. The period for public comment is expected to be December 2017 through January 2018. After the comments are incorporated version 1.0 of the ME/CFS CDEs will be available. As noted by the version number, CDEs are intended to be living documents, revised as progress is made.

CDC is preparing to participate in the Food and Drug Administration's qualification process for ME/CFS outcome. We have had calls -- with representatives from FDA's Drug Development Tool Qualification Program and the American Institutes for Research focusing -- on how data from our MCAM study could be used to streamline the identification of fatigue measures for ME/CFS. The goal is to define acceptable outcome assessments that measure a patient's symptom or ability to function to determine whether or not a drug has been demonstrated to provide benefit. FDA recognizes this as a critical need for ME/CFS clinical drug trials. We are currently preparing documents to formalize this collaboration.

This is the end of CDC's updates for today. Thank you for your attention and participation. At this point I would like to turn the call over to Dr. Dana Brimmer so she can introduce our speakers.

Dana Brimmer: Thank you Dr. Unger. I'd now like to introduce our guest speakers. Dr. Lucinda Bateman is founder and medical director of the Bateman Horne Center in Salt Lake City, Utah.

Dr. Ellen Clayton is the Craig-Weaver Professor of Pediatrics at Vanderbilt University Medical Center, and Professor of Law at Vanderbilt University School of Law in Nashville, Tennessee. She is also a co-founder of the Center for Bio-Medical Ethics in Society.

Dr. Peter Rowe is a Professor of Pediatrics at Johns Hopkins Children's Center at Johns Hopkins University and the Director of the Children's Center Chronic Fatigue Clinic.

All three served on a 15-member panel for the Institute of Medicine -- the IOM -- which produced a consensus report titled Beyond Myalgic Encephalomyelitis Chronic Fatigue Syndrome, Redefining an Illness. We welcome you all today, and we'll start with Dr. Bateman.

Dr. Lucinda Bateman: Thank you very, very much. I appreciate the opportunity to participate in the call and to comment on the report by the Institute of Medicine. It was a pleasure to serve on the committee. And I still love the clinical diagnostic criteria recommended by the IOM report and have used them very effectively to teach medical providers how to recognize MECFS.

I think I'd like to start by commenting on some disappointing aspects to me of how the IOM was received, including backlash from recommending a new name and misconceptions or misunderstandings about how to apply the clinical diagnostic criteria. The core criteria proposed by the IOM to make a diagnosis of ME/CFS were fairly simple. One, a

substantial reduction in functional capacity manifest as fatigue. Second, the presence of post-exertional malaise. Third, unrefreshing sleep and then either cognitive impairment and or orthostatic intolerance.

Now one of the - and then in addition -- and those are outlined very well in Chapter Four -- and the core diagnostic criteria must be moderate to severe and present more than 50% of the time to meet these criteria. Then a number of other symptoms were validated in Chapter Five as other manifestations of illness, including pain, infections that act as triggers, gastrointestinal or urinary symptoms, sore or scratchy throat, painful lymph nodes, and sensitivity to stimuli.

So one of the disappointments that happened after the release of the report is that critics said that there were no exclusionary conditions required to make a diagnosis of ME/CFS in these criteria. And that the patients identified would have too many other illnesses and create an even more heterogeneous group. Or that the IOM criteria haven't been applied to real patients or in comparison to healthy controls.

So I wanted to bring out a couple of aspects of the report -- including recommendation number one in the report -- and that is that physicians should diagnose ME/CFS if the diagnostic criteria are met following an appropriate history, physical exam, and medical workup. And the doctors - that's the recommendation. But it - there's additional information that doctors should not be afraid to make the diagnosis as a working hypothesis early and then use the first six months to take care of the patient, do the appropriate work up, and then be in a position to make the diagnosis if the symptoms are persistent after six months.

One of the things most commonly missed is -- in interpreting the core diagnostic criteria -- not applying the severity and frequency criteria. Now these came from strong evidence in the report. Lot - much of this from publications by Dr. Leonard Jason. And -- in a 2013 paper -- Dr. Jason evaluated the symptoms of 2036 MECFS patients and 86 healthy controls who had completed the DePaul symptom questionnaire. These were patients from the SolveCFS BioBank. These patients had been evaluated, diagnosed by expert physicians using - the entry criteria were either Fukuda or Canadian criteria. And this study showed that if you apply these criteria of frequency of severity across all the DePaul questionnaire you can separate out patients with ME/CFS from healthy controls. And this is quite important because -- although the report does mention frequency and severity -- but it's not always emphasized when people are talking about the report or applying the report. And the same is true with the need for physicians to do an appropriate medical workup and diagnose other conditions if they're present in the patient. Another comment I'd like to make is these criteria cannot be applied retrospectively to an existing data set. They are clinical criteria that require a physician to interview the patient, examine the patient, evaluate the patient with a differential diagnosis and apply these criteria.

I would be cautious interpreting papers that have applied the IOM criteria to an existing data set rather than in the study of evaluating a patient in a medical setting. Some of the other criticisms were that the IOM criteria left out too many symptoms that were part of the Canadian criteria. And my contention is that those symptoms are very well laid out in Chapter Five. Chapter Four has the core criteria, which are - need to be present - which have been shown to be present in almost all patients based on doctor -- sorry -- on Jason's paper. But that Chapter Five lays out the evidence and support for the other major symptom - the other minor symptoms and - that are present often but not at every stage of illness or in every patient. There - I think there's been some criticism that pain was not included in the core criteria. But there is a very good section in the IOM report -- in Chapter Five -- that describes pain as a very important, common symptom. But highly variable in presence, nature, and severity.

And the report says we can lean on a substantial evidence base in diagnostic criteria in the fibromyalgia literature. And that indeed most of the good pain research comes from this fibromyalgia literature. And making a diagnosis of fibromyalgia -- as we often due to describe the presence of wide-spread pain, (central) sensitivity in patients with ME/CFS -- is very descriptive in combination with the ME/CFS criteria. And honestly most of the literature in either the ME/CFS or fibromyalgia publications do not rigorously evaluate for the other. And this is explained in the report. And there's significant overlap. So I feel like those were some areas of the report that maybe weren't clear as the report was released and then have been passed over and not really understood by those receiving the report.

I think the strengths of the report are that it is an evidence-based report based on research in ME/CFS patients by ME/CFS researchers and clinicians. I think that - and the report is designed for practicing primary care providers and clinicians to help them recognize the most devastating and constant features of the illness. And to take better care of ME/CFS patients in the early stages of illness. And to be able to recognize the chronic symptoms that develop in their patients. One of the major limitations of the report -- I think, it's not the fault of the report -- but as might be expected in an expanding scientific field -- such as the research in ME/CFS -- some aspects of the report become outdated. And even by the time the report was published -- in February of 2015 -- a lot of advances had happened. We should keep in mind that the literature review for the report ended in the middle of 2014. So most of the scientific research presented at the 2014 IACFS ME Scientific Meeting and at the Stanford Symposium in 2014 had not reached publication, so they couldn't be included in the IOM report. And that conference provided exciting new focus on data, especially in support of ME/CFS as a neuro-immune illness. And that's one reason why the IOM report was not able to include those scientific advances. And why we were unable to include these features in the new name that was recommended.

I will point out though that the diagnostic criteria include symptoms -- sleep, cognitive impairment, orthostatic intolerance, pain -- these are all aspects of illness regulated by the central nervous system and the peripheral nervous system. So the symptoms are captured by the diagnostic criteria. And I'm sure -- if the report is revisited -- that those will be some of the important things that will be part of the update. So I think that's what I'd like to address in my portion. And I'm happy to also answer questions in the Q and A. Thank you for the opportunity to talk today.I think I'll turn it over to (Peter).

Dr. Peter Rowe: Great. Well thank you very much and thanks to everybody for joining. I share a lot of Cindy's views of the overall report. And I thought what I would do today is discuss two of the areas that I was more involved in. One was the chapter on -- or the section on -- orthostatic intolerance and autonomic dysfunction. And the other on pediatric ME/CFS. And so I just want to hit the main highlights of those sections for those who didn't get a chance to read them or haven't had the opportunity to review them recently.

Orthostatic intolerance -- as many people on this call will know -- is defined as a group of clinical conditions where symptoms worsen with assuming and maintaining an upright posture. And usually improve -- although aren't necessarily abolished by -- lying back down. And the main symptoms in orthostatic intolerance are thought to be due to two main factors. One is a lack of adequate blood flow to the brain. And that can lead to light-headedness, near fainting, fainting, impaired concentration, headaches, and even visual changes with blurring and dimming of the vision. And then the second mechanism is an - a compensatory response by the nervous system of an overactive sympathetic nervous activation. And then the symptoms that can occur with that include intolerance of low-impact exercise, nausea, abdominal pain, pallor, and shortness of breath even as an orthostatic symptom.

So there is immediately a recognition of a huge overlap in the symptoms between ME/CFS and forms of orthostatic intolerance. The most common forms that the committee recognized were postural tachycardia syndrome -- or POTS -- neurally-mediated hypotension -- which is synonymous more or less with neurocardiogenic syncope or vasovagal syncope -- but not all the patients developed actual loss of consciousness. And then low orthostatic intolerance can be part of the picture in some individuals where they don't really have any heart rate or blood pressure changes, but they nonetheless have a great deal of symptom provocation with upright posture.

We looked at a number of papers on a variety of topics. One was the prevalence of orthostatic and autonomic symptoms. The prevalence of abnormal heart rate and blood pressure responses. And then papers on a variety of other autonomic measures. One of the things that struck us as we read these -- read through the literature and critiqued it -- was that there was a lot of methodologic variability. The studies varied widely on a number of things. One was patient characteristics that included things like the age of the person, how long they've had the ME/CFS. And I think we all recognize that patients studied in the first six to twelve months after the onset of illness will be very different that those who've had it for seven or eight years.

The severity of the illness varied a lot. The case definition that was used varied. And then some patients were selected based purely on whether they already report autonomic symptoms. There was a lot of variability in the way they

were prepared for the orthostatic challenge test. So for example were they allowed to remain on their medications even if those medications affected the autonomic nervous system? What was their prior sodium intake? How long did they fast beforehand? And that can affect the response or the results of the test. The type of testing that was done. So people could have either a free-standing test, they could have what we call a passive standing test -- where they leaned against the wall -- and then also a formal tilt table test where the table lifted them upright. And so there were a lot of - there was a lot of variability in the type of testing used. And then whether it was done at - in the morning or the afternoon. It's been shown that tests in the morning are more likely to identify orthostatic intolerance. The room temperature wasn't always described. And the degree of movement that the patient was allowed to have during the tilt test also wasn't described. Even the duration of the test varied tremendously between these studies. And so there was a lot of difference in the way these tests were conducted that led to tremendous variability in the responses.

Even with that, what we found was that there were 14 studies that looked at prolonged orthostatic testing. That was testing was longer than 10 minutes. And in those, the main result was that only two of those 14 studies failed to identify an increased prevalence of either POTS or neurally-mediated hypotension. So -- even with all the variability when those studies were combined -- the median proportion who had orthostatic intolerance was 37% in the ME/CFS group and only 7.5% in the health controls. So it was - the orthostatic intolerance is much more likely to be present in people with ME/CFS. The range of abnormalities in the 14 studies was from zero -- which was very much an outlier prevalence -- all the way up to 96%. And this was in adults.

When we looked at the studies that were done that last less than 10 minutes, same kind of methodologic problems were present in those studies. But even with that the POTS prevalence was 27% in those with ME/CFS versus just 4.2% in the healthy controls. And again, the range of orthostatic hemodynamic abnormalities was quite wide, from 14 to 67% in the ME/CFS population.

Hitting on a couple of other areas where there weren't quite as - there wasn't quite as much data, there were several studies that looked at symptoms that occurred during standing or tilt testing. And between 55 and 100% of those with the illness reported that they had provocation of fatigue and light headedness during upright challenge. Heart rate variability is often used to look at which arm of the autonomic nervous system is most active. And those measures consistently show that ME/CFS is associated with an enhanced sympathetic nervous system tone. Blood volume studies. There weren't many of those but they showed approximately a 10 to 15% reduction in blood volume in people with ME/CFS versus healthy individuals.

And there were three studies looking at what's called end-tidal CO2 measurements. These - this is the exhaled carbon dioxide. And those started off equal when patients were supine -- suggesting that they were not hyperventilating at base line -- but by the end of the tilt testing the end-tidal CO2 was lower in those with ME/CFS. And it's thought by some that this is because the lack of blood flow to the brain triggers an increased depth and rate of respiration.

So the end result of that literature summary was that we felt that up the - there was sufficient evidence indicating a high prevalence of orthostatic intolerance in ME/CFS as measured by objective heart rate and blood pressure abnormalities during standing or head-up tilt testing. Or by patient-reported exacerbation of orthostatic symptoms with standing in day to day life. These findings indicate that orthostatic intolerance is a common and clinically important finding in ME/CFS. And it was the strength of that evidence that led to the criterion that orthostatic intolerance could be a defining feature of the illness.

This stands in direct contrast to some of the other national guidelines that are available in other countries. Particularly the NICE guidelines in England which don't even mention orthostatic intolerance either as something to look for in those with ME/CFS or as part of the differential diagnosis in evaluating patients. So our expectation would be that -- as those guidelines are revised -- they will be looking at the same data that the IOM committee was and it would almost seem mandatory that they include that in the NICE guidelines.

Switching over to pediatric section. One of the primary problems with the pediatric literature is the paucity of the studies and the lack of replication of - in many areas. There is an equally wide variability in the evidence about prevalence estimates for ME/CFS in children, partly because the studies use different case definitions. They might use self-reported symptoms rather than a physician diagnosis. They might have community-based origins versus tertiary care. And we reported that one other newer problem in the epidemiology of ME/CFS is that many physicians prefer to diagnose something like POTS based on the heart rate numbers rather than the diagnosis of ME/CFS. And so -- if there are a lot of physicians doing that -- then the prevalence of ME/CFS would be under reported. That probably needs further study.

Among the observations that I think are very commonly understood with pediatric ME/CFS is that the illness is less common under the age of 10. It's not that it doesn't occur, it's been reported down to I think, about age 2. But it's much more common after the age of 10 and during the pubertal growth spurt. We know from the literature that females are more commonly affected in a ratio of between two to one or six to one female to male in the various pediatric studies. There's clear evidence of the impact of the illness on education. School attendance is significantly reduced. And in one Dutch study 90% of the Dutch ME/CFS patients had what they termed considerable school absence. We know from studies in England that ME/CFS is the primary cause of prolonged school absence. So it has a major effect on educational attainment.

When we looked at studies on post-exertion malaise that's reported in various countries that have studied pediatric ME/CFS as being fairly common. Seventy-one percent in an Australian study, 80% in a Dutch study, and 97% in a British study. But there has been very little formal study of that phenomenon. And none of the two-day consecutive - consecutive two-day cardiopulmonary exercise tests that have been done in adults. I'm not sure those would be well tolerated by children, but just to point out that they haven't been done.

Then if we look at orthostatic intolerance in children, this is where the data become much more consistent. There have five studies with controls, all of them showing numerically higher proportions of ME/CFS patients who have orthostatic intolerance primarily POTS and NMH. There have been a number of heart rate variability studies all showing what the adult studies show, which is mainly a sympathetic predominance of heart rate control. There have been some studies of open treatment of orthostatic intolerance which show improvement in ME/CFS symptoms.

There have been some - a few studies of cognitive dysfunction. The baseline neuro-psych testing that's done is usually similar between ME/CFS patients and healthy controls. But there was at least - there were at least two studies showing that if you combine both the cognitive test and an orthostatic challenge, then neurocognitive symptoms emerge quite promptly.

With regard to infectious onset, it's well known and well established that ME/CFS can follow EBV infection or other forms of infectious Mono. And one of the large studies -- by Katz and colleagues -- showed that at 6, 12, and 24 months after infectious Mono, 13% met the ME/CFS criteria -- that was at six months -- 7% at 12 months, and 4% still met criteria 24 months. In larger studies that have looked for other etiologic agents -- one by Soheim and colleagues in Norway in 2014 -- looked for a wide variety of organisms and did not find many differences between the patients with ME/CFS and healthy controls with regard to seropositivity.

With regard to immune impairment, there have not been very many studies. There are only five studies that were germane to that topic. And most had single observations of abnormalities that no one else has replicated. That doesn't mean that they can't be replicated, it's just that that work has not been done. The one study by Kathleen Rowe, Kathy Rowe, in Australia -- no relation to me - was interesting in that she conducted a trial that was done in 1997 in 71 Australian adolescents with the illness who received immunoglobulin intravenously once a month for three months. And there was a significant improvement in overall function at the six month follow up. And the ones who had received the IVIG they had - half of those -- the patients -- in that study had abnormal cell-mediated immunity. And the committee felt that this was the kind of important study that desperately needed to be replicated given those changes. Thus far -- 20 years later now -- nobody else has done an IVIG study or has been funded to do it.

With regard to the endocrine abnormalities, several studies find a statistically significant lower cortisol level in adolescents with ME/CFS than controls. But those cortisol levels are still usually within the normal range. So it's unclear whether this is a primary problem or related to sleep cycle abnormalities -- as has been suggested in some adult studies -- or is due to some other aspect of being chronically ill.

So those are the main highlights from the pediatric chapter. And the conclusion was that there was sufficient evidence that orthostatic intolerance and autonomic dysfunction are common in pediatric ME/CFS. That neurocognitive abnormalities emerge when pediatric ME/CFS patients are tested under conditions of orthostatic stress or distraction. And that there's a high prevalence of profound fatigue, unrefreshing sleep, and post-exertional exacerbation of symptoms in these patients. There's also sufficient evidence that pediatric ME/CFS can follow acute infectious mononucleosis and EBV.

So those were some of the highlights from those two chapters. And I'll stop there and -- along with Cindy and Dr. Clayton -- take questions.

Dana Brimmer: And Dr. Clayton, have you been able to join us yet?

Dr. Ellen Clayton: I was on and then I was off and now I'm back. But I'll just say a few words. So I think the main message that I would want to say is that it was really -- I think -- a sobering experience to learn more about this disease. To learn about its complexity. And to learn about the suffering that people who are affected with this disease have. And it's also been I think heartening to see a number of the discoveries that have been made since we conducted our study. And, you know, and in some of the increased funding that is now available. On the other hand, I would say that something that saddens me greatly is that I probably get about an email a week from someone wanting a referral to somebody who takes care of patients with this disorder.

And frankly it's - if they're lucky enough to live in Utah or Maryland or a few other places where our committee members live, you know, I feel very comfortable knowing that I can make a referral that, you know, that is going to help them get the care that they need. But it is striking the amount of resistance there is to taking care - to providing care for these patients. And I don't know when that's going to get fixed. I hope it gets fixed soon. But it is really quite striking. So I think that's actually really probably the main thing that I would want to say. I think it's exciting to hear about the progress but there sure is a lot more work that needs to be done and a lot more acceptance of this disease in the larger community.

Dana Brimmer: Okay, thank you. We now have some questions for our speakers. And I have the same question for all three speakers. And Dr. Clayton why don't we start with you. In hindsight, what do you -- Dr. Clayton -- wish the IOM report had said differently? Or are there things -- looking back -- you would change now?

Dr. Ellen Clayton: You know -- truthfully if there was any one thing -- I - we were asked to come up with a new name for the disorder. And although I think the name we proposed was -- I think -- appropriate in terms of describing I think more accurately exactly what's involved with this disease, I think that that ultimately probably was a bit of a distraction. I think that we did I think the very best that we could with the information that was available at the time. And I actually am very proud of what we pulled off.

Dana Brimmer: Thank you. Dr. Bateman?

Dr. Lucinda Bateman: I think in hindsight similar for me. The main things I might have done differently on the committee, one is more emphasis on correctly applying these clinical diagnostic criteria -- both the core and the required aspects -- and you know, with the severity and frequency. And much less on recommending a new name. Which the - you know, we were commissioned to assess whether a new name was appropriate. But it was deeply disappointing to me that the release of the report and the content was overshadowed and undermined by the controversy over this. And I understand where it came from, because an earlier overlapping effort of the ME/CFS community -- including myself -- to abandon the term Chronic Fatigue Syndrome and accept ME or ME/CFS as the terminology. And it was just - it was unfortunate there was opposition to the IOM project before it even got started. And that undermined and biased evaluation of the results.

So I think we might have framed it a little bit differently to downplay the suggestions about the name and really emphasize more. I also think less emphasis on the diagnostic algorithm, it's just a diagram. And more emphasis on people reading the content and Chapters Four and Five and really understanding how these diagnostic criteria evolved and why we think they're strong.

Dana Brimmer: And Dr. Rowe?

Dr. Peter Rowe: Yes, well stated. I couldn't agree more. I still remember reading the blog on the New York Times the day that the report was released. So clearly people wouldn't have had a chance to read it. But there was something like 250 comments about what a disastrous name it was. And one wag said "Didn't they realize that S-E-I-D spelled dies backwards?" And you know, things got way out of hand very quickly. And I think people lost focus on the major content of the report, which was really I think an excellent evidence review that really helped shift the way people should be thinking about this illness.

Dana Brimmer: Thank you. So our next...

Dr. (Lucinda Bateman): Oh, I was just going to add that this - I - my presentations of the diagnostic criteria to clinicians outside the field has been very well received. So I think these resonate and they're coming to be more and more accepted. The whole concept of this illness is being more broadly accepted since the IOM report.

Dana Brimmer: Thank you. The next question for our guest speakers, the 2015 IOM report urged a revisit in no more than five years. Are any of you aware of a movement towards a fresh look at the topic by the IOM? Dr. Clayton, I'll start with you again.

Dr. Ellen Clayton: I have not heard anything about that. I mean as you know, the IOM basically performs the work that it's asked to do. So I think that if there were a movement by funders to say we need to update this -- in light of the new knowledge and what other things I suspect that there would be -- a - that they would be willing to take that on. But I confess I haven't anything about it.

Dana Brimmer: And Dr. Bateman and Dr. Rowe?

Dr. Peter Rowe: Likewise. Haven't heard anything.

Dr. Lucinda Bateman: Yes, likewise. I haven't heard anything either. And I hope I see such a thing.

Dana Brimmer: And our next question, for all three panelists, the IOM focused on the diagnostic aspect of MECFS. Are you aware of any upcoming work on treatment guidelines? And your thoughts on a work group for developing such guidelines. Dr. Clayton, we'll start with you again.

Dr. Ellen Clayton: Well as I - I actually haven't heard about any of this work at the National Academies. But obviously there are a variety of professional organizations that do this kind of work. I mean that is the major source of - I mean that's a major topic of consensus groups of all kinds of organizations. And certainly it was beyond our - we weren't asked to address that issue but I would certainly hope that -- as the evidence becomes more available -- that the groups who were involved in that, you know, proceed with reviewing that literature. Because it's really, really important that we know how best to treat these patients.

Dana Brimmer: Dr. Bateman?

Dr. Lucinda Bateman: Yes. I don't know of any specific work on treatment guidelines, but I will comment a little about the conundrum. Treatment guidelines are generally made from the evidence. So they're evidence based and they're based on treatment trials. And there really have been no treatment trials specifically for ME/CFS. That said, I think that we have fallen short in terms of borrowing and using treatment trials that apply to people with ME/CFS, such as trials of medications for pain

amplification or restless legs or sleep. And those things can be applied with - maybe with some good guidance and you know, care.

But it's very, very important that we move forward with clinical trials to test the safety and the efficacy of the drugs even that we commonly use to treat symptoms of ME/CFS. Because there are differences in how people with ME/CFS and fibro respond to people who really don't meet the ME/CFS criteria but have all the criteria for fibromyalgia. So this is something that we are hoping can be done once the collaborative research centers get a little further down the road. And we do have you know, collaborations of different clinics that are in a position to implement trials of medication relatively quickly. The problem is you know, the - planning the protocol and funding these protocols. So we're hoping that's down the road.

Dana Brimmer: And Dr. Rowe?

Dr. Peter Rowe: Just -- I'm not sure if this is the intent of the question -- but in terms of clinical guidelines that are available and out there, the IACFS ME organization -- the professional organization for people who work on this problem -- has produced a primer on how to manage ME/CFS. And I think Cindy was one of the co-authors of that. And a group of us -- brought together by Ken Friedman and others -- just published a pediatric version of the primer. And that's available through an open access journal called Frontiers in Pediatrics. So if people need those kinds of - that kind of guidance those documents -- which were put together by a consensus by a number of people with lots of experience with ME/CFS -- are available.

I would echo Cindy's comments about the lack of funding for the - for especially pediatric trials. It's astonishing that one effective treatment that was proven in a randomized trial by Kathy Rowe 20 years ago has still not been replicated. Partly because the funding for that kind of study would be enormous in the United States. Probably cheaper in other countries where there's a national health care system. But that desperately needs to be done. We need the kind of organization that has helped advance the fields of pediatric oncology, where almost every child who gets one of those illnesses in the cancer field is entered into a protocol so that they're getting the very most recent and best treatments. But also that protocol is then being used to see what else can be refined. We're a long way from that and we're a huge amount of funding away from that but hopefully that could change. I think if we had centers that were linked and shared protocols we could really make much quicker progress in this illness.

Dana Brimmer: Thank you. We now have some questions for Dr. Unger at the CDC. The first question, given the extreme and decades-long crisis that has arisen from the lack of availability of safe and effective clinical care for at least one million Americans with ME/CFS, what are CDC's timeline and plans for sharing accurate diagnostic and treatment information with American medical doctors and medical centers?

Dr. Elizabeth Unger: CDC certainly agrees there's an urgent need to educate physicians and other health care workers about ME/CFS. And we covered this in today's call, but education initiatives are a large part of our current work. And once we develop these materials we hope they'll be used by other stakeholders -- such as medical professional organizations, advocates, and other educators -- to disseminate this information beyond CDC's initiatives. Because it's clearly going to take more than CDC's efforts to really get the message out.

The CFS Advisory Committee on Education -- sorry -- the CFS Advisory Committee's Work Group on Education has developed a sort database of educational initiatives and options that should be supported and then monitored and evaluated. And these initiatives include projects of government at all levels as well as foundations, professional and advocacy groups, and others. And -- as our speakers indicated -- there really is a critical need for ME/CFS treatment guidelines. And for the federal agencies to be able to promote them. They need to be developed according to standardized transparent methods for incorporating review of the available evidence as well as consideration of expert opinion. And that's particularly crucial for ME/CFS where -- as we've been - as has been commented on -- there's a lot of clinical data but not so much clinical trials. So we have been exploring this through conversations with experts in federal guideline development. And we've learned that the guideline development process can be anticipated to be long, but it - notably this process allows for public engagement. CDC has agreed - to develop a plan for development of treatment guidelines. And this plan will be reviewed by HHS agencies as well as the CFS Advisory Committee.

Dana Brimmer: Great, thank you.

Dr. Peter Rowe: Could I add one thing there...

Dana Brimmer: Yes, go ahead, Dr. Rowe.

Dr. Peter Rowe: Just - it probably doesn't need to fall entirely to the CDC. I just wanted to read something about a state health commissioner who made a difference. And this is Dr. Howard Zucker in - who's the New York State Health Commissioner. And he sent out a - his letter that goes to the 85,000 doctors in New York State. And he has updates about things at different times. And this one was about the opiate epidemic and the second was about ME/CFS. And he said "Next time a patient complains of long-standing and debilitating fatigue I'd urge you to consider whether the patient has ME/CFS, the hallmark of which is post-exertion malaise" and goes on to make a very nice description of the illness. And he ends by saying "As physicians I hope you'll make MECFS a part of your differential diagnosis when evaluating patients. Few things are as detrimental to a patient's health and well-being as not being taken seriously when presenting a problem to a health care provider. To learn more about the illness from the patient's perspective, consider watching this Ted Talk by Jen Brea who shares her journey with the disease." So I think we can enlist the help of our different state health commissioners to make sure the illness is treated in a serious manner.

Dr. Ellen Clayton: Actually, that's inspiring.

Dr. Lucinda Bateman: Yes.

Dr. Ellen Clayton: Well said, right?

Dana Brimmer: Well thank you. That is actually a wonderful way to end our call. And we're getting to near the end of the call and I want to thank all of our guest speakers today. Dr. Bateman, Dr. Clayton, and Dr. Rowe as well as Dr. Unger. We appreciate you taking the time to be with us today.

And we also want to thank the participants on the call for your time and interest. Please remember to submit questions and ideas for future topics and speakers and direct the correspondence to MECFSSEC@cdc.gov. More information about the CDC MECFS program is also available on the CDC ME/CFS website.

And both of the links that are listed today - are listed at the bottom of the communications email you received also direct you toward the CDC website. Once again, thank you everybody for your participation and we look forward to having you join us again for our next call.

Dr. Lucinda Bateman: Thank you.

Dr. Ellen Clayton: Thank you.

Coordinator: This will conclude today's conference. All parties may disconnect at this time.

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