

UNITED STATES OF AMERICA
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
 MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

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January 28, 2011
 8:00 a.m.

Hilton Washington DC North
 620 Perry Parkway
 Gaithersburg, Maryland

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KAREN B. DOMINO, M.D., M.P.H.	Temporary Non-Voting Member
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ANDREW WINOKUR, M.D., Ph.D.	Temporary Non-Voting Member
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INDEX

	PAGE
CALL TO ORDER - Thomas G. Brott, M.D.	244
PANEL INTRODUCTIONS	244
CONFLICT OF INTEREST STATEMENT - Olga I. Claudio, Ph.D.	247
APPOINTMENT OF TEMPORARY NON-VOTING MEMBERS - Olga I. Claudio, Ph.D.	249
GENERAL ANNOUNCEMENTS - Olga I. Claudio, Ph.D.	250
FDA RECAP	
Lawrence Park, A.M., M.D.	251
Peter G. Como, Ph.D.	256
Allison Komiyama, Ph.D.	258
FDA Q&A	260
FDA QUESTIONS AND PANEL DELIBERATIONS	
Question 1	270
Question 2a	309
Question 2b	322
Question 2c	335
Question 2d	342
Question 3a	347
Question 3b	388
Question 3c	388
Question 2c and 3b	390
Question 4	412
Question 5a	419
Question 5b	462
Question 5c	467
Question 5d	469
Question 5e	472
Question 5f	474
ADJOURNMENT	478

MEETING

(8:04 a.m.)

DR. BROTT: I would like to call this meeting of the Neurological Devices Panel to order.

I'm Dr. Thomas G. Brott, the Chairperson of this Panel. I'm Professor of Neurology and Director of Research at the Mayo Clinic in Jacksonville, and my area of expertise is in focal brain injury and stroke.

And I would like to go around the table again, as we did yesterday, because we have additional members, all of whom were able to participate yesterday using our web system. And could we start with Dr. Eydelman.

DR. EYDELMAN: Good morning and welcome. My name is Malvina Eydelman. I'm Director of the Division of Ophthalmic, Neurological and ENT Devices at FDA.

DR. DOMINO: Hi, I'm Karen Domino. I'm Professor of Anesthesiology and Vice Chair for Clinical Research at the University of Washington, Department of Anesthesiology and Pain Medicine, and I'm a neuroanesthesiologist with an adjunct in the Department of Neurologic Surgery.

DR. GOODMAN: I'm Wayne Goodman, a psychiatrist and Chair of the Department of Psychiatry at Mount Sinai School of Medicine in New York.

DR. McDONALD: Bill McDonald. I'm a Professor of Psychiatry at Emory, and my area of expertise is in treatment-resistant depression, particularly in the elderly, and ECT and neuromodulation techniques.

DR. KIM: I'm Scott Kim. I'm a psychiatrist and a bioethicist from the University of Michigan, Ann Arbor.

DR. WINOKUR: Andy Winokur. I'm a Professor of Psychiatry at the University of Connecticut School of Medicine and Director of Psychopharmacology at the University of Connecticut Health Center, and we have an active psychopharmacology clinical trials program at the Institute of Living in Hartford.

DR. DUFF: Kevin Duff, a neuropsychologist and Associate Professor in the Department of Neurology at the University of Utah.

DR. PAULSEN: Jane Paulsen, Professor of Neurology and Psychiatry at the University of Iowa, and I'm a neuropsychologist.

DR. CLAUDIO: Olga Claudio, the Designated Federal Officer, FDA.

DR. STEBBINS: I'm Glenn Stebbins, a Professor of Neurological Sciences at Rush University Medical Center in Chicago.

DR. PEAVY: I'm Guerry Peavy of the Department of Neurosciences at the University of California, San Diego, with an emphasis in neuropsychology and dementia.

DR. GOOD: Good morning. I'm Dr. David Good, Professor and

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Chair of Neurology at Penn State University in Hershey.

DR. GORDON: Mae Gordon, Professor of Biostatistics and Ophthalmology at Washington University, St. Louis.

DR. ANDERSON: Karen Anderson. I'm in the Department of Psychiatry and the Department of Neurology, University of Maryland. I'm a neuropsychiatrist. My area of specialty is movement disorders, including Huntington's disease, Parkinson's disease, and deep brain stimulation for those disorders.

DR. ROSS: I'm Chris Ross from Johns Hopkins. I'm Professor of Psychiatry and also Professor of Neurology, Neuroscience, and Pharmacology. I do research on neurodegenerative diseases like Huntington's and Parkinson's. I also do research on schizophrenia and bipolar disorder. I attend on a geriatric psychiatry unit, and we have considerable experience with pharmacologic and ECT treatment of major depression and other disorders.

DR. ELLENBERG: Good morning. I'm Jonas Ellenberg, Professor of Biostatistics and Associate Dean at the University of Pennsylvania School of Medicine.

MS. CARRAS: I'm Michelle Carras, the Patient Representative.

MS. STOKES McELVEEN: E. Francine Stokes McElveen, General Counsel, Coppin State University.

MR. MUELLER: Good morning. David Mueller. I'm the Industry

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Representative.

DR. BROTT: Thank you.

At this meeting, the Panel will discuss and make recommendations regarding the possible reclassification of devices indicated for use in electroconvulsive therapy.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Dr. Olga Claudio, the Designated Federal Officer for the Neurological Devices Panel, will make some introductory remarks.

DR. CLAUDIO: Good morning, everyone. I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws are covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in

today's meeting and to the public.

The FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, the members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the possible reclassification of devices indicated for use in electroconvulsive therapy.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S.C. Section 208 and Section 712 of the Food, Drug and Cosmetic Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Mueller is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Mueller and Associates Consulting.

We would like to remind members and consultants that if the discussion involve any other product or firm not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationship that they may have with any firm at issue.

Drs. Richard Meisch, Andrew Winokur, Wayne Goodman, Christopher Ross, and Michelle Carras have been appointed as temporary non-voting members of the Neurological Devices Panel for the duration of the meeting on January 27 and 28, 2011.

For the record, Dr. Ross is a consultant to the Peripheral and Central Nervous System Drugs Advisory Committee in the Center for Drug

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Evaluation and Research. Ms. Carras, the Patient Representative, Drs. Winokur, and Goodman are consultants to the Psychopharmacologic Advisory Committee in CDER, and Dr. Meisch is a consultant to the Drug Safety and Risk Management Advisory Committee in CDER. These special Government employees have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

These appointments were authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for the Special Medical Programs, on January 25, 2011. Thank you.

Before I turn the meeting back over to Dr. Brott, I would like to make a few general announcements

Transcripts of today's meeting will be available from Free State Court Reporting, Inc., telephone (410) 974-0947. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the podiums. The press contact for today is Sandy Walsh. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

Finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

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Dr. Brott.

DR. BROTT: We will now hear a brief recap from the FDA.

DR. PARK: Good morning, everyone. I'm glad to see everybody here today, and it looks like we have new faces as well. My name is Lawrence Park. I'm a Psychiatric Medical Officer at the Center for Devices and Radiological Health, Office of Device Evaluation, Division of Ophthalmic, Neurological and ENT Devices. This morning we're reconvening the Neurological Devices Advisory Panel on the 515(i) reclassification process for ECT devices.

Before the Panel begins its deliberations, I'd like to offer a very brief summary of the presentation that we gave yesterday. In addition, in response to questions from the Panel yesterday, we have also prepared some additional slides which are new material, and they won't be included in your packets. These new slides basically are addressing some of the questions that came up yesterday.

To review the goal, the goal of this Advisory Panel meeting is to obtain feedback regarding classification of electroconvulsive therapy devices. Panel members are requested to keep in mind the following questions to guide their deliberations:

Should ECT devices remain Class III devices and require premarket approval?

Should ECT devices be reclassified to Class II and require

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premarket notification, 510(k)?

Of note, recommendations regarding classification may vary across indications for use. In other words, determinations of safety and effectiveness may be different based on the existing data for each specific indication and therefore warrant a different classification.

Yesterday's FDA presentation began with Ms. Shulman providing a general discussion of regulatory issues regarding device classification and reclassification, and this presentation is represented in Slides 1 through 17 from yesterday morning's slide packet.

Then Lieutenant Commander Cunningham provided a brief overview of ECT clinical considerations and regulatory considerations specific to ECT. These are included in yesterday morning's slide packet, Slides 18 through 29.

Dr. Georgiopoulos presented the description of the FDA assessment process and safety review. Her presentation is found in the afternoon slide packet. This is Slides 3 through 7. And then she provided reports of information from the public docket, Slides 8 through 14, manufacturer docket, 15 through 18, and MAUDE database, Slides 19 through 24.

Dr. Georgiopoulos then described the process of how FDA identified all reported adverse events and, from that, all key risks of ECT and the adverse events that became the focus or the subject of a more focused

literature review. This discussion can be found in the afternoon slide packet, Slides 25 through 36.

Dr. Como reviewed the findings of the FDA systematic review of cognitive and memory adverse effects. These are Slides 37 through 62 in the afternoon packet.

Dr. Krulewitch presented the findings of the cognitive meta-analyses conducted by FDA. These are Slides 63 through 73.

Dr. Komiyama reviewed the data on neuropathological changes associated with ECT, Slides 74 through 89.

And I presented the FDA effectiveness review, Slides 90 through 118, and then a treatment of the key risks and mitigating factors. That's Slides 119 to 143.

Again, our strategy was to identify all adverse events reported from all sources and then, from this list, to make a determination regarding the key risks of device use, that is, risks that could significantly influence the risk/benefit profile of the device. This and the next slide are a list of all reported adverse events from all sources.

From this initial list, FDA identified key risks, which were then organized into three categories: medical/physical risks of ECT, cognitive and memory dysfunction, and device malfunction.

Under medical and physical risks were adverse reactions to anesthetic agents and neuromuscular blocking agents, alterations in blood

pressure, cardiovascular complications, death, dental or oral pain, pain and discomfort, physical trauma, prolonged seizures, pulmonary complications, skin burns, and stroke. Each key risk was then briefly characterized and potential mitigating factors were discussed. I won't review all of these key risks here, but I can do so at the Panel's request.

In addition, cognition and memory were also briefly characterized as key risks and potential mitigating factors were also discussed. With regard to concerns about inadequate informed consent processes and/or forced treatment, one potential mitigating factor that was discussed was the requirement of a more rigorous informed consent process, including a checklist of all known risks of device usage, to be reviewed and signed off item by item by the treating physician and the patient.

Finally, mitigating factors to address device malfunction, such as good manufacturing practices, quality system requirements, and the international safety standards, were reviewed.

During the Panel's deliberations of the questions posed, please keep in mind the requirements of Class II and Class III devices. Class II devices cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of such a device, and there is sufficient information to establish special controls to provide such an assurance. Class III devices are those for which general and special controls cannot be established to provide reasonable assurance of

the safety and effectiveness of such a device and therefore a PMA is required.

So now we'll go into the additional information in response to Panel questions.

In response to the question about the prevalence of mood disorders and particularly major depression, here's some information with regard to that. This chart is adapted from Ron Kessler's National Comorbidity Survey replication from 2005. The reference is provided on the slide.

If we look at this chart, we see that the lifetime prevalence of mood disorders across the lifespan was found to be 20.8 percent. If you look at major depression alone, that's that blue bar on the left side. The lifetime prevalence across the lifespan is 16.6 percent. And if you go across in the different age categories, you can see the prevalence from 18 to 29 is 15.4 percent, and for ages 30 to 44 it's 19.8 percent, which is the peak. Ages 45 to 59 is 18.8 percent, and then over 60 is 10.6 percent.

In addition -- they're not represented on the chart -- Dr. Kessler also provides information about the age of onset, and for mood disorders the median age of onset is 30 years old, and that range is 25 years, so between 18 and 43 years old. I hope that answers or addresses some of the Panel's questions about that.

Next, I'd like to ask Dr. Como to come up and address some of the questions regarding cognitive and memory dysfunction. After that, Dr. Komiyama will come up to address some of the issues surrounding

neuropathological changes, and then I will come back up and discuss a little bit more in depth the efficacy data.

DR. COMO: Good morning. Again, my name is Peter Como. I'm a neuropsychologist and lead reviewer in the Neurodiagnostic and Neurotherapeutic Devices Branch in the division.

I believe it was Dr. Duff who had asked for some additional information about the Autobiographical Memory Interview, and I was able to find the paper, and I have that PDF file on a flash drive, which would be available to the Panel members should they wish to review it. But I did take the liberty of making a few additional slides just to at least show the committee what's the content. I believe that was your question, Dr. Duff.

So this is it. I apologize. I had to cut and paste this from a poor quality of a PDF that we got through interlibrary loan at FDA. But as you can see, this is the original paper by Kopelman et al. in the U.K., the Autobiographical Memory Interview, and it's basically broken down into two sections.

The first is what they call the autobiographical incidence schedule, and as you can see, it's broken down into three sections, in terms of recollection of events from childhood, early adult life, and then, as I mentioned yesterday, more recent events.

And there's a scoring system that, based on the quality of the response, you can get anywhere from zero to three points, and then there's

some suggested prompts that the clinician can use to try and gain a more accurate scoring. So if the person doesn't remember a particular thing, they can prompt a little bit and maybe get a lower score.

And then the next one is what they call the personal semantic memory schedule, which is broken down into four sections, again, that have more detailed information about their background, in terms of recollection of family members, again, things related to childhood, early adult life, and recent information.

I reread the paper last night and tried to kind of get a better sense of the scoring system, and I must admit, I was a little confused about how they go about scoring it.

I then reviewed the ECT literature, and essentially what has transpired since the original paper was that various researchers and clinicians have sort of adapted and modified this. That may raise some questions about the psychometric properties of the adapted scales because they don't present reliability and validity data for those scales. There is data available for this, and I believe it's in the Executive Summary. On page 136 of the Executive Summary, there's data about the retest reliability and the validation.

So the subsequent iterations of this scale have been adapted, but in reviewing the literature on ECT, they do retain these two sections with some adaption. So I believe the data still is relatively good when we made the conclusions about the Autobiographical Memory Interview.

So I'll stop there and perhaps we can wait until afterwards if there's additional questions about this, and I'll turn it over to Dr. Komiyama.

DR. KOMIYAMA: Hello, my name is Dr. Allison Komiyama, and I'm a neurobiologist working at FDA in the Center for Devices and Radiological Health, Office of Science and Engineering Labs. So I wanted to address the question yesterday brought up about the review of both the rodent and human literature.

So in the animal electroconvulsive shock studies, I reviewed 46 focused on the rodent model. Thirteen of these articles mention neuroproliferation as an outcome of ECS when looking specifically at the hippocampus, cortex, amygdala, or prefrontal cortex. Six studies mentioned neurodegeneration or neuron loss or -- due to ECS treatments. However, one article only saw this outcome when the rat was pretreated with caffeine.

Seven articles found no acute or long-term changes in brain morphology. Eighteen papers mentioned changes in expression or specific proteins such as BDNF, NGF, FGF-2. These papers hypothesized that the mechanism of ECT is neuroproliferative or neuroprotective in nature, based on the current understanding of the pathways to which these molecules belong. Changes in some of the molecules did not occur until preadolescent stages in rats.

One article looked for single-strand breaks in DNA and found no breaks in the hippocampus of any ECS-treated rats. One study

investigated CSF biomarkers of damage in rats, concluding that there was no neural damage due to ECS.

I reviewed 20 human electroconvulsive therapy studies, some of which were mentioned yesterday. Two articles are directly of autopsy data of deceased patients that have received ECT. Five articles looked specifically at biomarkers of damage in the blood serum and cerebral spinal fluid. One study looked at ratios of regional cerebral blood flow and concluded that patients receiving ECT did not suffer long-term brain perfusion abnormalities.

Six studies utilized magnetic resonance imaging, four of which concluded that ECT did not cause acute or delayed changes in brain structure, whereas two others concluded that there were marked increases in frontal white matter and hippocampal volumes after ECT treatment.

One study used computer tomography in depressed elderly patients and found no association between ECT and global cortical atrophy of ventricular size, but found a relationship between frontal lobe atrophy and ECT.

I'll pass it over, back to Dr. Lawrence Park.

DR. PARK: I also wanted to take a little bit more of a detailed review of the effectiveness systematic review and also ask the Panel and the Panel Chair whether they would like FDA to go into a little bit more depth in the effectiveness meta-analyses.

DR. BROTT: I would ask for the Panel's opinion on this. It may

be more helpful to be able to ask you questions that are specific to the issues that come up as we answer the questions, rather than going through a summary of what we did yesterday. And I'm just looking for nods around the table. That's acceptable.

DR. PARK: Okay, for both the systematic review and meta-analyses?

DR. BROTT: Let's look for some nods again. Yes, we're seeing agreement.

DR. PARK: Okay, we will be ready for questions then.

DR. BROTT: Excellent. I'd like to thank the members of the FDA for this additional information.

And before we proceed to the questions, I noted, as these supplementary presentations proceeded, that we had some interest from the Panel members to ask a question or two before we begin deliberating on the questions. I would ask the Panel members again to identify yourselves before the questions. I would also ask that we keep the questions very focused and likewise the responses. Thank you.

Dr. Kim.

DR. KIM: This is Kim from Michigan. Dr. Como, about the AMI, I gathered, given the nature of the questions, they're not really validated by actually confirming the truth or the actuality of the answers. Is that true?

And the second is, how many of these studies actually employ

controls, you know, similar controls, people equivalently depressed and so forth?

DR. COMO: Sure, let me answer the second question first.

Only the original paper that I cited used a control sample of -- I think it was a small n of around 14 to 20 controls. The rest were in clinical studies of patients undergoing ECT, and hence there really wasn't any control, except for those randomized to sham. And I think I presented that data yesterday.

To answer your second question, actually there was a little bit of a way to validate the response. So in patients, at their baseline session, when they gave a response in some studies, not all, but in some studies there was a corroborator, a family member or someone else, who then said to the clinician, yes, that's true, so that they could mark that as a positive recalled event so that when they did the reassessment after treatment, they knew they had the right answer. So there was some attempt to have a corroborator in some of the studies, but not all.

DR. BROTT: Thank you. Dr. McDonald.

DR. McDONALD: This is Dr. McDonald. I didn't have a question for you, Dr. Como. I had a question for the neuropathologist.

DR. BROTT: Dr. Komiyama, could you come to the podium?

DR. McDONALD: The studies that you cited, it's frequently known that patients with more structural brain changes tend to be more treatment resistant and therefore go to ECT, and that's different from saying

that ECT caused the brain changes themselves.

Can you comment on that? Are the studies looking at an MRI before and then after ECT or just looking at a group of patients who got ECT?

DR. KOMIYAMA: The MRI studies specifically are looking at before and after.

DR. McDONALD: And how far after the ECT were these studies done? So these were studies that compared scans before and after?

DR. KOMIYAMA: Yes. I'll have to get back to you on that.

DR. BROTT: I'll tell you what, why don't we come back to the answer.

Dr. Goodman.

DR. GOODMAN: Yeah, along the same lines, I was looking at one of the references that was cited, the Shah paper, and in that case it would suggest that -- I think you sent that around, correct? Yes, the BJP paper, 2002, Shah's the first author. It's about chronic treatment-resistant depression, right fronto-striatal atrophy. And they talk about, in the limitations of the paper, that the atrophies observed could be attributed -- could be an index of the severity of the illness rather than attributable to the ECT. You'll see that in the limitations, although it could be argued that the differences where the effects of ECT, there's little current evidence that ECT can produce permanent hippocampal and other structural changes, and they go on to talk about how it could be the index of severity.

DR. BROTT: Thank you, Dr. Goodman.

Ms. Carras.

MS. CARRAS: Two questions for Komiyama. First, in some of those studies that are done with -- supposedly before and after ECT, I understand that the inclusion criteria do not exclude patients who've already had ECT in the past, but they had to have it within -- earlier than six months before. So really you are including patients who've already had ECT in some of those studies, if I understand correctly. Okay. So that's my first question.

And my second question is, in Ito's paper in 2010 --

DR. KOMIYAMA: I'm sorry, which one?

MS. CARRAS: Ito's 2010 paper, Effects of ECS on -- sorry -- "Effects of Repeated Electroconvulsive Seizure on Cell Proliferation in the Rat Hippocampus." I don't know if that was one of the studies you cited.

DR. KOMIYAMA: Yes.

MS. CARRAS: The thing that's difficult for me as a Patient Rep is thinking about how Ito discusses several models of what might be going on in terms of antidepressant effects of ECS or ECT, and it seems clear that it's not -- we don't understand what level of ECS or ECT might have what type of effect on brain changes. He separates out, for example, neuroproliferation with mossy fibers sprouting. And it's all very fascinating, but I think we spent a lot of money on these studies, but we still don't really understand what's

going on. So do you have any comments on that?

DR. KOMIYAMA: I agree with that. I think there are quite a few shortcomings with all of the studies.

MS. CARRAS: Thank you.

DR. BROTT: Okay, Dr. Ellenberg.

DR. ELLENBERG: I think it would be beneficial, certainly for me, but perhaps for the whole Panel, for Dr. Park or Dr. Eydelman to give us the practical meaning in terms of the issue of access for patients to ECT for reclassification from Class III to Class II.

DR. EYDELMAN: So as you heard yesterday, currently it is a Class III device for which we have been receiving 510(k)'s, which normally is a premarket application used for Class III devices.

So should the Panel choose to classify all of ECT indications or any of the ECT indications as Class III, then FDA would -- and should FDA accept your recommendation, then FDA would call for PMAs, or premarket approval applications, for those indications which would be classified as Class III.

The content of the premarket application could vary depending on the input we get from the Panel, i.e., whether it's the degree and the depths of a clinical trial perhaps that the Panel feels that would be needed. The time frame for requirement for postmarket approval is not set in stone, and this is again something that we can go -- we can ask for it as soon as one

year or we have asked for it as far as 30 months past the classification into Class III.

So the sponsors would be asked to submit an application, but once again I want to stress that it won't be an overnight requirement. So the companies would be given a chance to collect the information which we would require for premarket approval for those indications.

DR. BROTT: Understandably, the response that you or anyone at FDA would make to Dr. Ellenberg's question is, you know, somewhat speculative. To give us some context, I think some of the information may have been in the packet.

One could ask, well, how many 510(k)'s have been submitted and acted upon over a period of time as some index? Because if we left it at Class III, of course, those 510(k)'s would have to be PMAs. So could you provide us some information in that regard?

DR. EYDELMAN: That information is actually in one of the slides that, I believe, Brad Cunningham presented yesterday morning. But the 510(k) applicants -- and I can pull up the number.

DR. BROTT: I think it was in our packet.

DR. EYDELMAN: Yes, it's definitely in your packet, and it's in the morning presentation. But regardless of how many 510(k) applications we got, that's how many different manufacturers, since inception of ECT, asked to be cleared. From my understanding, there are currently two

manufacturers who are actively manufacturing ECT devices. So it would affect those two, plus any manufacturers who would want to come in with a brand-new ECT device from now until on.

DR. BROTT: Thank you. Dr. Ellenberg.

DR. ELLENBERG: I'm sorry. I understand everything that you said, but it's not absolutely pinpoint clear to me what would happen with a reclassification. Would all companies, extant companies, be prohibited from the manufacturing of this? Would everything be withdrawn from the market? How does this affect the access to patients? This is a major question yesterday from the floor, and I just simply don't understand what would happen.

DR. EYDELMAN: Again, the companies, for the manufacturing that would be Class III, would be asked to submit premarket approval in order to proceed. But in the interim, nothing would happen to them. So in other words, it would be a smooth process to the market until the premarket application is submitted. But after the particular length of time that the companies are given, they would have to comply with the rest of the FDA's requirements in order to stay on the market.

DR. ELLENBERG: So, excuse me, I'm really having a problem with this. So to summarize what you just said, in effect, if the requirement for a PMA, or whatever, was stipulated because of the down-classification --

DR. EYDELMAN: Yeah.

DR. ELLENBERG: Excuse me. If the process is successful, there should be no cut in any way, shape, or form that would harm access for patients.

DR. EYDELMAN: Correct.

DR. ELLENBERG: Thank you.

DR. BROTT: Dr. Ross. And as a reminder, we will have to cut this short in a few minutes so we can get to the questions where, again, these issues can be readdressed.

Dr. Ross.

DR. ROSS: Yeah, actually I had one, to ask a question about the neuropathology. But before I do that, maybe if I could just follow up with this because I think this is really a critical question and I'm not sure I understand.

When you said the companies would be required to submit PMA, does that mean that they would be required to do a new clinical trial, or what exactly would that mean in practice?

DR. EYDELMAN: So premarket approval application has to demonstrate safety and effectiveness of each device in standing on its own, and usually it involves a clinical trial. The nature of the clinical trial can vary, and again, the requirements of what would be needed to assess the safety and effectiveness is something that FDA would delineate after we hear all of your comments.

And to come back to the question asked earlier, it's on Slide 25,

there were nine 510(k)'s that were submitted from 1984 to present, so far.

DR. ROSS: Okay. And then could I ask my neuropathology question? So to follow up on the neuropathology, because I think this is, again, an important issue -- first of all, I just wanted to thank Mr. Moxon, who submitted a number of articles at the request of the committee yesterday. And I've read through those articles about both animal and human studies, and my take on them is twofold.

First of all, most of these are old articles. The major CT study was a study by Dolan et al. from 1986, which, again, as we've just discussed, did find a correlation between greater atrophy in patients who had received ECT than patients who had not, but could not exclude the possibility that those patients had a more severe disease to start with and in fact specifically said that there was no dose, no treatment number relationship between the number of treatments and the cortical atrophy, which in their view "would appear to rule out a causal relationship."

And then, to go to the animal studies, I think, at least from, again, the studies that were just submitted, my take is it seems to me there's lots of evidence for changes in the brain with ECT, and as Dr. Goodman has pointed out, those are the same kind of changes you see with antidepressant treatment. In fact, the best way of getting -- a very good way of getting neurogenesis in the brain of rodents is to have them do physical exercise. We now understand the brain to be much more plastic than we had previously

appreciated.

So my question for you is, would it be a fair summary of this literature to say that ECT induces changes in the brain, which may relate to the therapeutic effects, but that there's no clear evidence for any "brain damage" caused by ECT?

DR. KOMIYAMA: Yes, I think that's correct. I'd like to get back to the question previously, for the MRI studies.

DR. BROTT: I'm not sure your microphone is on.

DR. KOMIYAMA: Sorry, I wasn't being close enough. The average time taken for the MRIs was between -- was one week before and after for one of the papers, or two weeks before and two weeks after, maximum.

DR. BROTT: Final question, Mr. Mueller.

MR. MUELLER: Yes, thank you. Dave Mueller. A question for the FDA, not specifically for right now but in preparation for our later discussions. Can we, the Panel, get a copy of one or both of the current ECT machines' instructions for use, maybe not the whole thing but the indications, contraindications, word of caution to adverse events, so that when we're going through all the different labeling questions in our Panel Pack here, we can see what is currently being stated versus in the future?

DR. BROTT: Thank you. At this time we will focus our discussion on the FDA questions. Copies of the questions are in your folders.

Panel members, in order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Could we please see the first question?

Dr. Good.

DR. GOOD: The FDA was going to give us some information on effectiveness as well, I think. We didn't hear that yet. There's going to be review of that. Was that true?

DR. BROTT: We, I think, agreed as a group that we could ask them questions.

DR. GOOD: Okay, but there's not going to be any review at all. Okay.

DR. PARK: So I did defer that to the Panel's decision on that. But all of that information also is in the Executive Summary.

DR. BROTT: The first question.

To inform the FDA's decision on reclassification, the key risks presented by ECT must be identified, and a determination must be made regarding how and whether sufficient information exists to establish controls to mitigate those risks. The FDA has identified the following key risks of ECT (in alphabetical order) in the FDA's review of the Public Docket, the Manufacturer Docket, the Manufacturer and User Facility Device Experience (MAUDE) Database, and in FDA's literature review.

Could you put those up? And while you take a look at those,

we are asked to provide feedback to the FDA, whether or not this is a complete and accurate list of the key risks presented by ECT. We are asked to comment on whether we disagree with inclusion of any of these risks, or whether we believe any other risks are among the key risks presented by ECT.

So should all of these be included or not? And should we have additional key risks or not? First of all, is the question clear?

Dr. Duff.

DR. DUFF: Can we hear from the FDA how they define key risks? Is there some more specific information that they use?

DR. EYDELMAN: That was actually in the packet yesterday, on one of your slides, and I believe Dr. Park is pulling up the actual slide.

DR. BROTT: Do we have to use slides for every answer? Is there a statutory definition of key risk?

DR. PARK: There's no statutory definition. The review team, in terms of trying to figure out which risks we needed to focus on, really tried to start with an overall comprehensive list from all sources. So that's the potentially significant adverse events list, and then it went down to what we believed were the key risks.

So the key risks are the ones that we felt, number one, were reported in the literature to a significant degree and that they demonstrated significant frequency of occurrence and severity and also demonstrated association with ECT device use. And those were the risks that we thought

we needed to take a look at to see whether there were potential mitigating factors, whether those mitigating factors would be effective in sufficiently mitigating the risk of ECT for either Class II or Class III use.

DR. BROTT: Thank you. Well, we have quite a list here, so let's go down the list. It's in alphabetical order. And, again, our question is, should it be included or not, and should we add or not?

So the first is adverse reaction to anesthetic agents or neuromuscular blocking agents. Could we get opinions from the Panel members to whether or not it's appropriate to include this as a key risk?

Dr. Domino.

DR. DOMINO: Well, since general anesthesia is used, I think it is appropriate to include it as a risk.

DR. BROTT: Does anyone think it should not be included as a key risk?

(No response.)

DR. BROTT: Could we just nod if we all agree that it should be included as a key risk? And I see that all members of the Panel are nodding.

The second is alterations in blood pressure.

Dr. Goodman, do you think that alterations in blood pressure should be included as a key risk?

DR. GOODMAN: Yes, because it seemed like they were a common concomitant of the procedure.

DR. BROTT: So you agree?

DR. GOODMAN: Yes.

DR. BROTT: Do any Panel members disagree that alterations in blood pressure should be included as a key risk?

(No response.)

DR. BROTT: Do we all agree that it should be included? Again, just indicate by nodding. And I'm seeing all of us nodding.

(c) Cardiovascular complications.

Dr. McDonald.

DR. McDONALD: That should be included, and probably alterations in blood pressure could go under it.

DR. BROTT: Does anyone think that cardiovascular complications should not be included as a key risk?

(No response.)

DR. BROTT: Do we all agree that it should be included as a key risk? I see that we all agree.

Death is listed -- or, excuse me, cognition (disorientation and confusion) is listed as a key risk.

Dr. Kim, do you believe that this should be included as a key risk?

DR. KIM: Yes.

DR. BROTT: Is there anyone who thinks it should not be

included as a key risk?

DR. GOODMAN: I agree that it should be, but it's also important to -- in terms of attribution, it could be related to the general anesthesia as well, if it's in the immediate period following the treatment.

DR. BROTT: I certainly would agree with you. Do the Panel members agree with that statement? Yes, Dr. Anderson.

DR. ANDERSON: Also, I agree it should be included, but going on with the idea of time frame, are we supposed to specify here, are these immediate risks or are these more long-term risks?

DR. BROTT: I think that, you know, when -- I think that a risk in the labeling is infrequently broken down by time, in terms of immediate, short term, long term. Our packet, of course, breaks things down quite specifically.

Dr. Eydelman.

DR. EYDELMAN: For the purpose of this question, let's not break it down by time, let's just identify if it needs to be included in there.

DR. BROTT: So we were on cognition, and I think we were all in agreement.

DR. KIM: But --

DR. BROTT: Yes, I heard a but. Dr. Kim.

DR. KIM: I'm sorry. Sorry, Mr. Chairman. I'm not sure I agree with Dr. Goodman's statement about that being attributable to anesthesia

only, or it could be.

DR. BROTT: No, I don't think she was -- I didn't hear her say that.

DR. KIM: Okay. Yeah, I didn't quite understand him.

DR. BROTT: Yeah.

DR. KIM: So I take back my statement.

DR. BROTT: Are we in agreement not to parcel it out at the moment, to leave it as written? And Dr. Anderson agrees with that. I think she was pointing out a distinction that we agree with. But for this purpose, that key risk is acceptable.

The next key risk is death.

Dr. Winokur.

DR. WINOKUR: I think, based on the data that we've heard about so far, it would have to be mentioned. And I think the question of attribution is much more unclear. But the current standards of informed consent, where we can't say it's not potentially involved, would mean that it would have to be mentioned.

DR. BROTT: Does anyone disagree that death should be included as a key risk?

(No response.)

DR. BROTT: Do we all agree that death should be included as a key risk? We all have nodded.

The next is dental/oral trauma.

Dr. Duff.

DR. DUFF: Yeah, it does seem like there's sufficient evidence to say that that's a risk.

DR. BROTT: Does anyone disagree that dental/oral trauma should be a key risk?

(No response.)

DR. BROTT: Are we all in agreement that it should be a key risk? And we are.

The next is device malfunction as a key risk.

Dr. Paulsen.

DR. PAULSEN: Yes, it should be included.

DR. BROTT: Does anyone disagree that device malfunction should be a key risk?

(No response.)

DR. BROTT: Do we all agree that it should be a key risk? Very good.

Next is memory dysfunction.

Dr. Stebbins.

DR. STEBBINS: Yes, that should be included as a key risk.

DR. BROTT: Does anyone disagree?

(No response.)

DR. BROTT: Do we all agree?

The next is pain/somatic discomfort.

Dr. Peavy.

DR. PEAVY: Yes, included.

DR. BROTT: Does anyone disagree? Dr. McDonald.

DR. McDONALD: I would just add nausea, just to be clear. It's not on it. That could be somatic discomfort, I suppose.

DR. BROTT: How about pain/somatic discomfort, including nausea, would that be acceptable wording for you? And is that acceptable wording for everyone on the Panel? Does anyone disagree with that wording?

(No response.)

DR. BROTT: Very good.

The next is physical trauma.

Dr. Good.

DR. GOOD: Yes, it can be mitigated, but it should be included.

DR. BROTT: Does anyone disagree?

(No response.)

DR. BROTT: Do we all agree? I'm not seeing everyone nod.
Yes, Dr. Duff.

DR. DUFF: Was there more information or more examples from the FDA's review as to what physical trauma they were referring to?

DR. BROTT: Dr. Park.

DR. PARK: Larry Park from FDA. Mainly, these types of complications were seen in the earlier literature before the full use of general anesthesia and neuromuscular blocking agents. They typically were fractures, long-bone fractures, sometimes for tibial compression fractures or, as you can imagine, contusions or other soft tissue injury from the tonic-clonic motor activity from the seizure.

DR. DUFF: So is there any updated safety information about how frequently those events occur now with more advanced procedures being used in ECT?

DR. PARK: Our estimate, I believe, was uncommon or rare. So at the present time, in the typical practice of ECT using a general anesthetic agent and succinylcholine, usually we see little to no muscular activity.

DR. BROTT: Dr. Ross.

DR. ROSS: One possibility, if we do keep this, might be to include the dental and oral trauma with it, and then that would be kind of a more inclusive way to put it.

DR. BROTT: Do we know if there is any -- if there's been any surveillance on falls following ECT?

DR. PARK: Larry Park, FDA. I'm not aware of any systematic review of that, though, in the MAUDE database, I believe, and in some of the -- in the public docket report, there were several, I think, less than 10,

reports of falls afterwards.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: I recommend some further description under this. And I think physical trauma is too vague, so I would recommend some wording.

DR. BROTT: What do you recommend?

DR. PAULSEN: I would want to defer to the Panel for someone to assist with that. I've heard fractures, contusions.

DR. BROTT: Would physical trauma, including dental/oral trauma, be acceptable wording?

DR. PAULSEN: Okay.

DR. BROTT: Dr. McDonald.

DR. McDONALD: I think your point of falls is a risk of ECT. I also think you can see physical trauma in the recovery room, if someone has postictal agitation. Since that's part of the treatment, I think it's fair to include it. But I do agree, it's a vague term that we would have to -- but I would assume the FDA would.

DR. BROTT: The problem with being specific is the lack of specific data in general, not necessarily with this. You know, with writing labels, I think that could be a problem. So physical trauma, including dental/oral trauma, is that -- Dr. Kim.

DR. KIM: Maybe you could clarify the purpose of this list. Is it

for the purpose of the review of reclassification? You used the word labeling. So it would help me to know what the exact purpose of identifying these risks are.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: So in order to try to delineate potential mitigating factors, whether it goes into Class II or Class III, we need to figure out what is the safety profile of a particular device.

DR. KIM: So it's an entirely different question from labeling? Is that fair? It's a different question from labeling?

DR. EYDELMAN: Correct.

DR. BROTT: Very good. Next, we have Ms. Carras.

MS. CARRAS: Michelle Carras, Patient Representative. I would ask that we not include dental/oral trauma within physical trauma because, if I understand correctly, the dental/oral trauma is more of anesthesia related, using the bite block and that kind of thing. So I think it's a little bit different way of preventing it.

DR. BROTT: So you think the mitigation could be different enough to make this is a separate -- Dr. Good.

DR. GOOD: I disagree. I think, especially in the pre-anesthesia days, it was a major risk. It's not anymore, but potentially it's a risk. I defer to my anesthesia colleague.

DR. BROTT: Dr. Domino.

DR. DOMINO: Karen Domino. I would group both of these together. The dental/oral trauma result is of a seizure. The physical trauma also could result as a seizure as well.

Yes, succinylcholine or another neuromuscular blocking agent is given. The dose that's given is titrated to kind of balance the time that the patient is paralyzed, so that they can wake up by the time that the general anesthetic agent is gone, so that they now can resume normal breathing and normal neuromuscular function. So I group them together.

I did like the thing, physical trauma and dental/oral trauma, and I like leaving physical trauma vague because it could be a variety of things, including falls, IV infiltrations, and other things. I like leaving it non-specific, other than dental/oral trauma added in.

DR. BROTT: Is the Panel in agreement with Dr. Domino? I see a preponderance of agreement with Dr. Domino.

Dr. Stebbins.

DR. STEBBINS: Just a quick question about falls. It seems that falls really are not related to physical trauma, but they may be a cause of physical trauma, and if they are an independent risk, then perhaps they should be listed separately.

DR. BROTT: I'm not sure that I saw, in the Executive Summary, which I read and I'm sure all of us read very carefully, data that would allow us to be that specific. Dr. Kim, would you agree? Dr. Park, would you agree?

DR. PARK: I would agree, yes.

DR. BROTT: So I would propose that we maintain the wording as Dr. Domino has suggested. Do we have agreement? Dr. Stebbins, is that okay?

DR. STEBBINS: Yes. It's just that I don't think you want to include falls under trauma.

DR. BROTT: Well, we're not using the word falls, okay? Thank you.

The next is prolonged seizures. And I think -- yes.

DR. GORDON: Yes, I agree that it should be included.

DR. BROTT: Do we have anyone who disagrees with prolonged seizures as a key risk?

(No response.)

DR. BROTT: Do we all agree? Excuse me, before we nod, Dr. McDonald.

DR. McDONALD: You can have a tardive seizure. The seizure can appear to stop and then restart. It's the reason you have an EEG available. So that's not a prolonged seizure, it's a tardive seizure or a late seizure. It's very rare, but that can occur. So perhaps you could say prolonged or tardive seizures.

DR. BROTT: I think that's quite appropriate, given the level of evidence that we have, and I think that's an excellent suggestion, myself. Do

we have any member of the Panel who disagrees with Dr. McDonald?

(No response.)

DR. BROTT: Dr. McDonald, can you restate that wording?

DR. McDONALD: Prolonged or tardive seizures.

DR. BROTT: Do the Panel members, could you indicate by nodding, whether you agree with that suggestion by Dr. McDonald? And I'm seeing concurrence. Thank you.

The next is pulmonary complications.

And we're up to Dr. Anderson.

DR. ANDERSON: Yes, I agree, that should be included.

DR. BROTT: Does anyone disagree?

(No response.)

DR. BROTT: Do we all agree? Very good.

The next is skin burns.

Dr. Ross.

DR. ROSS: Maybe I missed it, but I don't recall. Could you just remind us whether that's still a concern?

DR. PARK: This is Larry Park from the FDA. I would say that reviewing the MAUDE database and the public docket, it's difficult to get a sense. But if I were to make a statement about it, it seems like the skin burns were really an earlier type of concern, though I would believe that they still do occur, given the reports from those sources. It doesn't occur at any great

frequency, and generally speaking, most practitioners of ECT would say that that is an avoidable risk, given proper skin preparation and the use of conductivity gel.

In addition, most of the -- I think both of the current manufacturers have an impedance monitor so that they know if the contact is not good and the impedance is too high, that the stimulus will not occur.

DR. BROTT: How old is the MAUDE database?

DR. PARK: The MAUDE database was initiated in 1994, I believe. That's the computerized, our computer --

DR. BROTT: Understood. And what is the input from the MAUDE database with regard to this key risk?

DR. PARK: It's 1996. And skin burns, there were 17 events reported from 1996 to present.

DR. BROTT: Dr. Ross.

DR. ROSS: It's something I've never seen nor heard of, but since it's been reported, I think it's reasonable to include it.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Why doesn't it just fall under physical trauma?

DR. PARK: Part of the reason I think we separated it out was it was reported separately and it appears to have different mitigating factors.

DR. BROTT: Are we okay with including it? And I'm seeing consensus. Does anyone disagree?

(No response.)

DR. BROTT: Thank you. The next is stroke.

Dr. Ellenberg.

DR. ELLENBERG: Yes, I believe it should be included.

Jonas Ellenberg.

DR. BROTT: I would like Dr. Good's opinion.

DR. GOOD: Well, I've had a concern about this. I think, looking at the MAUDE database and at some of the other -- even the public docket, it's got to be extraordinarily rare, and I'm not sure that this is causative. I suppose the only potential would be if you had a tremendous rise in blood pressure somehow related, that somehow that resulted in an intracerebral hematoma. So I guess that's a potential cause of stroke here. I think it's extremely, extremely rare. I have some mixed feelings about including it.

DR. BROTT: Yeah, I agree with Dr. Good. I think this should not be a key risk. I was not convinced by the evidence, which I looked at very carefully as well. So I would suggest that -- well, I would agree with Dr. Good.

Dr. Domino.

DR. GOODMAN: Karen Domino. There have been rare reports of rupture of intracerebral aneurisms. For instance, hypertension is a very common response. It's transient. It can be controlled if the anesthesiologist chooses to control it.

To me, I would see it just under a cardiovascular complication.

I mean, stroke is a cardiovascular complication. So is myocardial infarction, ischemia. And so I would favor eliminating it from number (n), not specifying it particular, but to me it falls under a cardiovascular complication.

DR. BROTT: Dr. Good.

DR. GOOD: I'm agreeable with that.

DR. BROTT: The suggestion has been made by Dr. Domino.

Does anyone disagree with Dr. Domino's suggestion?

(No response.)

DR. BROTT: Do we all agree with Dr. Domino's suggestion?

And I see consensus.

Now, we've gone through the key risks recommended by FDA and provided our feedback. Are there other risks that you believe should be included as a key risk?

Dr. Good.

DR. GOOD: I think this deserves discussion. We heard from the floor yesterday the concern about suicide, and we also heard quite a bit of discussion about suicide being common in people with depression. But the issue was raised from the floor, and I believe that there's a few instances in the MAUDE database and the public docket, and I think we should at least discuss it.

DR. BROTT: I would like input from the Panel members.

Dr. Goodman. Excuse me, Dr. McDonald.

DR. McDONALD: Some good evidence-based studies are that ECT clearly reduces suicide risk, and it would seem like we, given the confound of people being depressed and in the midst of ECT, I think it would be a mistake to put suicidal -- increase in suicide risk in it. It's known that bitemporal ECT can quickly cause a resolution of symptoms and a decrease. And this is good evidence-based data from controlled clinical trials.

DR. BROTT: Ms. Carras.

MS. CARRAS: Michelle Carras, Patient Representative. That information that I explained that I'd like to discuss earlier, this might be a good time for me to do that, if I could take a few minutes.

DR. BROTT: We're really not set up to have presentations, but you can make your --

MS. CARRAS: We did have one yesterday.

DR. BROTT: Pardon me?

MS. CARRAS: We did have one yesterday with Dr. Ellenberg. And this provides what I think is robust human evidence that the Panel should consider.

DR. BROTT: Regarding?

MS. CARRAS: Regarding various adverse effects of ECT and also --

DR. BROTT: We're specifically on suicide right now.

MS. CARRAS: Suicide is part of it.

DR. BROTT: Could you give us the information on suicide?

MS. CARRAS: It's difficult to take this without the context that I wanted to present it in, but I found a set of data that included user reviews of ECT. So I'm not trying to ascribe any sort of reliability or validity to this data. It is simply human experience that anyone can have access to.

The total number of entries was 418, and of this, 63 percent reported adverse effects. Fifty-one percent reported memory loss. One Patient Reported becoming extremely suicidal at the end of his ECT treatment, the night of his final ECT treatment.

DR. BROTT: Thank you. Dr. Goodman.

DR. GOODMAN: I don't think suicide should be included. I do think that mania should be included, induction of mania. Certainly if you have somebody who's bipolar depression, you can have that induction. So I want to add that to the list.

DR. BROTT: We'll come back to mania. We're still on suicide.

DR. GOODMAN: Okay. So I'm going to say why I don't think the suicide. This is given in my context. I actually chaired the FDA advisory panel that voted for the black box for suicidality associated with pediatric use of antidepressants and voted for the black box. But there was more data available at that time that included a signal in the sham control, and I don't see those data here.

So in this particular case, it's much more likely that any reports

of suicide have to do with failed treatment. Certainly ECT does not work 100 percent of the time, and that is more likely in this particular case.

Particularly, you're starting with a group that often are suicidal, and that's the reason that you're administering ECT.

DR. BROTT: Thank you. Dr. Kim.

DR. KIM: Yes, I wanted to just add some numbers perspective for what Dr. Goodman just said. We had the paper that was discussed yesterday, by Nuttall et al., and that was a consecutive person database, so it's a very good database, about 2,200 people who went through 17,000-plus ECT treatments, and as you recall, they were able to identify 18 deaths within 30 days. Two of those were suicides.

Now, considering the baseline of these folks who are severely depressed, over 2,000 people, if someone told me over 2,000 people who were depressed, who needed ECT, 30 days later just only two suicides, I would think that's pretty good. So I think I would strongly agree that we shouldn't add suicide to the list.

DR. BROTT: Dr. McDonald.

DR. McDONALD: And just to piggyback on that. If you look at the suicides in that case, they're young people. They got one treatment. One had suicide four days after that one treatment, one 17 days after. So you would make the assumption that perhaps they committed suicide because they didn't get ECT.

And the paper I cited is Kellner 2005. Twenty-nine percent -- 29 1/2 percent reported suicidal thoughts and acts at baseline. After one week of ECT, three ECT sessions, that went down. At two weeks, down. And by the end of that, there was only 20 percent of the original group that had the ECT, thoughts at the beginning, had them at the end. They were monitoring it carefully. There was no increase in suicidal thoughts. I think we have to go with this kind of evidence base.

DR. BROTT: Thank you. Dr. Good.

DR. GOOD: I agree. I brought it up only for discussion because it was an issue raised from the floor yesterday.

DR. BROTT: Are we in agreement that suicide should not be added as a key risk? And I see that we do not have unanimous, but overwhelming support, that it not be added as a key risk.

The next question was Dr. Goodman's suggestion that mania be added as a key risk.

Dr. Goodman.

DR. GOODMAN: I wanted to see if anybody seconded that suggestion.

DR. BROTT: I see two people. I see Dr. Kim and Dr. McDonald seconding that suggestion.

Dr. Stebbins.

DR. STEBBINS: Within the MAUDE database there is a listing of

general emotional psychiatric side effects. I wonder, within that, do you have a breakdown of what those were? Was mania cited as one of those?

DR. PARK: The MAUDE database descriptions are variable in nature, and I would say that a lot of the descriptions were not sufficient to make a diagnosis.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Again, I would defer to other members of the Panel who have more experience in administering ECT than I do.

DR. BROTT: Dr. Ross.

DR. ROSS: Well, just speaking from my clinical experience, one occasionally sees a brief period of mild elevation of mood, but I've never seen and I've never heard of, in the experience at Hopkins over the past 20 years, a substantial period of mania after a series of ECT treatments.

DR. BROTT: Dr. Good.

DR. GOOD: One always hears about this anecdotally, but I'm not sure what the evidence is here. I didn't really see anything in our packet about it, and I don't know the answer. I hate to go on anecdotes.

DR. BROTT: That would -- well anyway, Dr. Goodman.

DR. GOODMAN: I'll withdraw my suggestion.

DR. BROTT: Is that agreeable to the members of the Panel? And I'm seeing overwhelming support for that, but we'll ask Dr. Kim if he wishes to pursue.

DR. KIM: No. I thought I read something in the packet about this specifically, and I just wanted to ask if the FDA had any last word on this because there was a mention of an adverse effect of hypomania or mania.

DR. PARK: This was mentioned in Dr. Georgiopoulos' section, looking at the different potential significant adverse events and again trying to describe them a little bit. First, in the MAUDE database there were two reports of mania. I'm sorry, I guess it wasn't parceled out. And in our literature review, my recollection is that there were maybe two or three articles reporting manic switching after ECT. So we believe that does it occur.

Again, my recollection from those papers is that it's not long lasting. Many times, clinically, it can be managed the way that we would manage idiopathic bipolar illness.

DR. BROTT: Is that acceptable to you, Dr. Kim?

DR. KIM: Yes, I defer to those who've reviewed this more carefully. Thanks.

DR. BROTT: Dr. McDonald.

DR. McDONALD: Well, I think, though, to go back maybe with Dr. Ross, if you have a patient who's being treated for a bipolar depression, they're certainly at risk of a manic episode. Now, you may not have a controlled study with somebody, but you do see people switch that are -- and that's a very -- I don't know that it's not a reasonable risk to put down.

DR. ROSS: On the other hand, ECT is good for mania. I'm not as

familiar with the literature on the switch with depression, but my impression is that there's more substantial evidence for antidepressants inducing a switching to mania in bipolar patients. Maybe Dr. Goodman can comment on that. Whereas, with ECT, I think it's quite a different situation.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: No, I'd actually just add to your side of the argument that often antidepressants, in fact, routinely antidepressants are administered concomitantly, so it could be that the antidepressants are inducing the switch and not the ECT itself.

DR. BROTT: Ms. Carras.

MS. CARRAS: Michelle Carras, Patient Rep. As a person who has bipolar disorder, if there were the slightest chance of something inducing mania, I would want to know about it.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: I just wanted to point out that you could identify a risk for a specific indication. It does not have to be an identical list for all of the indications.

DR. BROTT: We have on the table that Dr. Goodman withdrew his suggestion that this be added as a key risk. Do we have agreement with Dr. Goodman? You can indicate by nodding. And I'm seeing overwhelming, but not unanimous, support for Dr. Goodman withdrawing that suggestion.

DR. GOODMAN: Unanimous support for my ambivalence.

Thank you.

(Laughter.)

DR. BROTT: So with regard to Question 1, Dr. -- yes,
Dr. McDonald.

DR. McDONALD: Can I add just one more? We've recently become aware that cochlear implants can be damaged by ECT. It's in the cochlear implant device. It would be worth adding that since it's relatively unknown.

DR. BROTT: The FDA Executive Summary did have a review of concomitant or ECT administration with electronic devices and battery powered devices. And I'm wondering, before we -- if we could ask the FDA if there's any data with regard to -- that they determined with regard to cochlear implants.

DR. EYDELMAN: I don't believe we have any data to that effect. However, I'd like to point out that something like that can be handled easier as a labeling warning or precaution.

DR. BROTT: Thank you. Dr. McDonald, is that acceptable to you? Thank you.

So with regard to Question 1, Dr. Eydelman, the Panel has carefully considered Question 1 in detail. It's the Panel's consensus that the key risks identified by the FDA seem appropriate. Modifications have been suggested, which I note -- which I'm sure have been noted. And that's the

feedback from the Panel with regard to Question 1. Is the FDA --

MS. CARRAS: Excuse me, Dr. Brott.

MS. CARRAS: Ms. Carras.

MS. CARRAS: I'd like to propose another key risk.

DR. BROTT: Okay.

MS. CARRAS: This is really difficult to describe without reading, and because of my psychiatric disability I find it much easier to type things out and read them back. But if you don't feel like I have the time to do that, I'll do my best to explain it.

DR. BROTT: That's fine. Could you identify your key risk first and then provide the rationale that you wish to present?

MS. CARRAS: Given the lack of evidence about the long-term effects of ECT, the persistent findings --

DR. BROTT: No, excuse me, could you provide -- the way we have it, you know, (a) through (n), what's the key risk, first?

MS. CARRAS: Psychological trauma.

DR. BROTT: Fine. Now go ahead.

MS. CARRAS: May I read? Thank you. Given the lack of evidence about the long-term effects of ECT, the persistent findings in the literature of memory loss and the robust human experience of the large of numbers of patients who have described their experiences in various forms, the list of key risks should include psychological trauma. One moment,

please.

Any sort of bias or a conflict of interest is a big concern of mine as a patient advocate. To that end, when I prepared for this meeting, I sought out sources of information that had the potential to be free of the traditional forms of bias that may influence reporting in the medical literature. As the official voice of the patients, I chose to examine a relatively new form of information that presents the robust human experience of hundreds of patients' reviews of ECT that were posted to a health information website. I would like to take a few minutes to provide some information about my initial content analysis of these data, to provide a better picture of what patients say when they are not composing their most careful impressions of ECT to present to a group of researchers or a regulatory agency.

I entered user-submitted reviews of electroconvulsive therapy into a database. I excluded reviews that clearly referred to another person who was having the ECT. That excluded a comment that was not clear as to whether the user himself had the ECT done, that were an attempt to provoke, such as you guys are insane to have this done, or were duplicates.

I recorded the variable's name: worked, which was the status label chosen by the member from the available choices of the drop-down menu on the website. The available choices on the website are working/worked, somewhat worked, too soon to tell, considering, and not working. The next variable was condition, which was the member's diagnosis

as chosen on the website, and notes, which was an edited version of their review, if present.

I created the variables' adverse effects. It was coded positive if the comments field listed any adverse effects such as memory loss, headache, muscle ache, cognitive dysfunction, suicidality, or cardiac event; negative if comments stated that there were no problems; and left blank otherwise. I did the same with memory loss and lasting effects.

I also coded a field for again, which was whether the user would do it again or recommend it to someone else. And I tried to get at the subjective experience by coding whether the user had a good experience or a superlative experience, felt like it was lifesaving or miraculous; also whether they had a bad experience or felt like it was devastating.

On the date that the reviews were retrieved, the website claimed that 721 members had submitted reviews for ECT and that 66 percent find electroconvulsive therapy helpful. Four hundred and eighteen unique records were created. Of these, 265 contained comments that could be analyzed. The others consisted of username, diagnosis, and status label.

Most respondents categorized themselves as having depression, 83 percent. Most the remainder, 12 percent, had bipolar disorder. Other diagnoses included self-injury, anxiety, personality disorder, Asperger syndrome, OCD, PTSD, schizophrenia, and some medical conditions.

The claim that 66 percent found ECT helpful was mostly

supported by the analysis, which found that 65 percent categorized ECT as either having worked or somewhat worked.

When all entries were included, the breakdown of status label shows that while most categorized as worked or somewhat worked, 33 percent felt that ECT did not work and 10 -- or 2.4 percent -- I'm sorry -- marked too soon to tell.

Comments were recorded by 63 percent of the users, yielding an impressive number of spontaneous reviews of ECT by people who have supposedly experienced it firsthand. While there's no way to verify whether these submission truly represent people's firsthand experiences with ECT, given the popularity of self-help and support websites, it seems likely that at least the majority of these posts reflect actual user experiences and opinions.

Further content analysis was conducted on the 263 entries. Of great significance was the number of users who reported adverse effects, 62.6 percent, and memory loss, 51 percent. Note that the adverse effects included memory loss as well as other effects such as headaches, muscle aches, cognitive impairment, suicidality, and cardiac events. Two users reported having to be resuscitated during the procedure. Of the users who reported adverse effects, 80 percent reported memory loss, .6 percent reported no memory loss, and 19 percent did not mention memory loss as an adverse effect.

Seventy-nine out of the 416 entries, 19.23 percent, mentioned

lasting effects of ECT. While the APA described the potential for persistent effects on memory to be rare, almost one in five users in this analysis reported having lasting problems with memory.

Many users reported the experience itself as being either good or lifesaving or bad or brain destroying. To assess the frequency of these reports, I created variables to look at whether they had a good or a superlative experience or a bad or horrible experience. Two users reported a good experience, while 24 users reported a bad experience. Beyond that, 17 users reported the experience as superlative, submitting comments such as lifesaving, saved my life, a miracle, the best thing I ever did, and worked wonders. Another 27 users described the experience with a negative superlative such as brain destroying, destroyed my brain, a nightmare, haunted by the loss of memory, or that the experience was horrible or barbaric.

While coercion did not appear to be a common problem with these reporters, three did mention coercion as an issue and another implied coercion in the comment, disgusting, did not work, they thought actually I was insane.

While previous research studies exist that address patients' experiences with ECT, this collection of observations from an Internet source provides a rich source of qualitative information for clinicians and researchers to use to get a better immediate feel for that individual variation that's the

cause of the present controversy. These responses seem to indicate that memory effects are the norm rather than a rarity and that persistent effects of ECT, while occurring in a minority of patients, can be either devastating or not of concern when weighed by the patient against the subjective benefits of treatment.

Some populations may be more vulnerable to the devastation from memory loss. One respondent with Asperger syndrome noted that it erased my memory and only partial return. So others are happy for the unreactive zombie, but I am distraught at the loss of all my files on how to survive socially, and it doesn't treat depression except acutely while a vegetable.

The wording of some of the superlative comments points to the need to consider the ramifications of using ECT in vulnerable populations, especially in the absence of fully informed consent.

DR. BROTT: Ms. Carras, how much longer do we have?

Because you've gone --

MS. CARRAS: One minute.

DR. BROTT: -- well beyond -- fine.

MS. CARRAS: The following responses should serve to highlight the need to ensure patients are choosing ECT autonomously: worse choice I've made in a long time; worse thing I've ever decided to try; worst mistake of my life; the worst choice ever in my life; had a significant personality

change; stopped belief in God; not indicated and done without authorization.

Thank you for listening. I have a binder here with all the responses printed out, and I'd be happy to share the data file with anyone who'd like a copy.

DR. BROTT: Thank you, Ms. Carras.

Dr. Park, would you respond with regard to the suggestion regarding physical trauma -- psychological trauma? And then I think I'd like the Panel members, at least some of them, to respond.

DR. PARK: Yes, Larry Park from FDA. First of all, I would like to thank Ms. Carras for presenting that very rich description of some people's experiences of ECT. I believe we get a flavor of that also from the public docket responses and the responses that you all may have received on the CD that were responses to this particular meeting. Those are very important to contextualize what the range of experience might be with the procedure. So we did take those into account.

As Dr. Ellenberg discussed yesterday, while that data is very important, it also suffers from some limitations, and the main limitation is that there's no denominator. So we're not sure of the occurrence of these certain events, which is why we tried to go to the next step and estimate occurrence from systematically collected data.

Some of the experiences, I would say many of the experiences that Ms. Carras discussed, I do believe, are incorporated in many of these key

risks. She did mention memory loss as being a major issue, and we definitely want to highlight that in item (h) on this Panel question here, memory dysfunction.

With regard to using the specific terminology, psychological trauma, I think that psychological trauma in psychiatry has a certain denotation, meaning really being sort of more related to our diagnosis of posttraumatic stress disorder. And in the descriptions that Ms. Carras read, I would have to say that those descriptions, while compelling of experience, did not really parallel what we would believe to be a posttraumatic stress disorder.

DR. BROTT: Thank you, Dr. Park.

Dr. Duff.

DR. DUFF: I think, yeah, from what we heard from the public docket, there are at least a vocal minority of folks that experience ECT as a traumatic event, and it seems that it occurs more frequently than death, and I don't know that it necessarily should be viewed as any less severe for those individuals as it seems to plague them for years and years and years afterwards. Is that accurate?

I mean, is it any less, it's less -- I mean, it's more common than our most severe key risk, death, but I don't know that we can necessarily say that it's any less severe for those individuals that experience it.

DR. BROTT: Dr. Goodman.

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DR. GOODMAN: No, I can't agree with that. It would seem to me that in addition to all the excellent points that Dr. Park made, that some of the commentary we heard yesterday, some of the popular depictions of ECT, including *One Flew Over the Cuckoo's Nest*, show ECT done in a very different era. I mean, I guess we could talk about mitigations, but it's radically different and we talked about some of those differences.

And I can perfectly understand that if I was subjected to ECT in an institution, held down without anesthesia or muscle relaxants, that would be a very highly traumatizing experience, and in that case I would list it. But not in the way it's done in the modern control systems under conditions. I can't see including it, and I would agree that it would not typically be characterized the way we do in thinking about a traumatic event that could lead to either acute or posttraumatic stress disorder.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: I think I agree with that, but I do note that in the public testimony as well as in some of the information we received, that the response to the memory loss seems to be particularly troublesome to many patients and does seem to be traumatic in some way.

DR. BROTT: Dr. McDonald.

DR. McDONALD: I would agree with Dr. Goodman. I think that if ECT is done appropriately -- a lot of what we've heard are doctors not giving informed consent, of people being subjected to ECT in a traumatic way. It

doesn't relate to the way we're saying to do ECT.

Now, I'm just pulling up two of the latest articles that show increased quality of life for the bulk of patients who are followed over time after ECT, showing a dramatic increase in quality of life. I think including it does little to inform the patient. I don't think it would make sense to include it.

DR. BROTT: Dr. Ross.

DR. ROSS: I also agree that the term psychological trauma, as a standalone, would not be a useful one. But I do think we have certainly heard many, you might call them anecdotal, but a minority of people who are very troubled by the memory loss in particular. And one possibility I'd like to suggest is modifying (h) to say memory dysfunction (particularly retrograde autobiographical, anterograde memory, which in a small minority of patients can be very disturbing), or something like that, which in a minority of patients can be troublesome. And that would capture the, perhaps --

DR. BROTT: Yeah, currently --

DR. ROSS: -- but a significant number of people who are very disturbed by that.

DR. BROTT: Currently it says, you know, we don't -- we do have a qualifier. Take a look. It says memory dysfunction. And while I read this, maybe you can think about some wording. Memory dysfunction (particularly retrograde autobiographical memory, anterograde memory). One could put a

comma, for instance, memory dysfunction, which may be particularly troublesome for a minority of patients. Would that be acceptable?

DR. ROSS: That's the kind of thing I'm thinking of, yes.

DR. BROTT: Is that wording, memory dysfunction, which for a minority of -- pardon me -- which for a minority could be particularly troublesome. And we can wordsmith.

Dr. Domino.

DR. DOMINO: I had the feeling it wasn't just related to the memory dysfunction, and so to me it seemed perhaps a term such as emotional distress or some -- I'm not a psychiatrist, but some kind of some term that doesn't have a connotation for a diagnosis but can convey some element of emotional distress.

DR. BROTT: Yeah, I did a lot of homework, as we all did, and you know, one of the very prominent textbooks I read referred to the subgroup of patients who had a remarkable response to ECT.

And, you know, I appreciated Ms. Carras' statement with regard to the percentage of people who had a remarkable recovery. She cited, I think, around 68 percent who felt that they responded, and I think it was around 15 to 20 percent who had a remarkable recovery, and it was very close to the percentage of people who had the problems that she mentioned.

Now, there are limitations, but in that textbook I didn't see anything with regard to a minority or a small minority of patients who had an

emotion, or however we want to characterize it. And I'm not sure Dr. Domino's suggestion is inappropriate. I'm not competent to make that determination as a neurologist.

Dr. Goodman. Dr. Paulsen.

DR. GOODMAN: Yeah. I haven't seen why we should be considering this procedure any different from the use of a similar procedure with similar risks for any medical or surgical condition.

Doing the case of surgery for a broken limb or a gallbladder, talk about the effects of psychological trauma from the recovery experience, you may talk about the specifics in terms of some of the complications that can occur along the lines we're talking about in the context of ECT. But I imagine there's a whole host of medical procedures, surgical approaches, that could be psychologically traumatizing, and I don't see why we should single out ECT in the case of the treatment of patients with mental disorders.

DR. BROTT: Dr. Goodman, I'm sure many of us thought about that very thing. I thought about coronary artery bypass graft surgery. What's the consent process in something that we all agree would be life-threatening in the key risks? I think your general point's very well taken.

Dr. Paulsen.

DR. PAULSEN: I have a question and then a comment. My question is, are these key risks that we identify to be language that goes into the informed consent? Is that the purpose? Because we said it's not for

labeling. So is the purpose the informed consent?

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: Not necessarily. The purpose is to try to delineate the safety profile of the device for the future, so as to understand how to mitigate these best.

DR. PAULSEN: So if we don't have -- if it isn't for informed consent, that does sound like something that needs to be in the informed consent. We do it regularly. We say this may cause emotional distress.

DR. BROTT: We will be coming to that.

DR. PAULSEN: Okay.

DR. BROTT: And I would say at this point, we're now at quarter to 10:00. And, Dr. Eydelman, continuing our summary on Question 1, I've already summarized our response. I would say, with regard to the added possible key risk of psychological trauma, I'm not sensing that the Panel is able to provide you a consensus in that regard.

DR. PAULSEN: I do have a comment. I said I had a question and a comment.

DR. BROTT: Go ahead.

DR. PAULSEN: Okay, my comment is, I wasn't aware that the FDA did not consider qualitative data analysis. It sounds like we're not appreciating the qualitative data analysis. We've had this now from at least three different sources.

The way that you do qualitative data analysis has nothing to do with the denominator, and it needs to be stated that what you do in qualitative data analysis is you obtain enough data until you reach what's called saturation. Saturation means that you have continuity in a voice. And I've heard it clearly. We've heard it from the MAUDE database, we heard it from this database, we heard it from multiple sources.

So it seems to me that maybe one difference is we should start to consider qualitative data analyses as well as quantitative data analyses. So I'll stop there.

DR. BROTT: Thank you. We have to move on to Question 2.

Dr. Duff.

DR. DUFF: I just think, you know, as a point, is when you have heart disease or a broken arm, you don't think it reflects yourself. Okay, I think when you have a mood disorder or depression, it somehow relates to yourself and that not responding to the treatment says something perhaps about yourself or some individuals. And so I think that is a different way of looking at it than other --

DR. BROTT: We will have to go on to Question 2. So I hope that we can bring up some of these points focused on the decisions that we have to make. But on Question 1, I think we've provided the feedback that Dr. Eydelman requires.

Dr. Eydelman.

DR. EYDELMAN: Yes, thank you.

DR. BROTT: Dr. Park, could you read Question 2?

DR. EYDELMAN: I'm sure Brad Cunningham will.

LCDR CUNNINGHAM: This is Brad Cunningham. I'll read that into the record.

Question Number 2:

Below are the potential regulatory controls FDA could apply to ECT to mitigate medical/physical risks of ECT (i.e. adverse reaction to anesthetic agents/neuromuscular blocking agents, alterations in blood pressure, cardiovascular complications, death, dental/oral trauma, pain/somatic discomfort, physical trauma, prolonged seizures, pulmonary complications, skin burns, and stroke):

- a. Restricting ECT device use to physicians with specific training and/or experience with the administration of ECT;
- b. Physician labeling recommendations for:
 - i. pre-ECT assessment (including pertinent history, physical examination, EKG, echocardiogram, chest x-ray, pulmonary function tests, lab tests, and neuroimaging)
 - ii. ECT procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen

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- saturation)
- iii. The appropriate use of general anesthesia, neuromuscular blocking agents by a licensed anesthesiologist during the ECT procedure
 - iv. pre-ECT dental assessment and the use of mouth protection (bite blocks)
 - v. Electroencephalography (EEG) monitoring during and after the procedure
 - vi. Adequate skin preparation and the use of conductivity gel during electrode placement
- c. Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment
- d. Requirement for further premarket studies (either pre-clinical [bench or animal] or clinical) for significant changes in device technology or new indications for use.

Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the medical/physical risks of ECT.

DR. BROTT: Thank you. And as a reminder, the FDA is not empowered to control the practice of medicine. The FDA is empowered to regulate the use of medical devices. Is that correct, Dr. Eydelman?

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DR. EYDELMAN: We do not regulate the practice of medicine.

DR. BROTT: Thank you. So let's go through these, as we're asked to do. The first is restricting ECT device to physicians with specific training and/or experience with the administration of ECT.

Mr. Mueller.

DR. GOOD: Mr. Chairman, can I ask a question?

DR. BROTT: Yes.

DR. GOOD: This is for FDA. I just want to clarify something I heard before. This is regardless of classification. Mitigation has nothing to do with classification.

DR. EYDELMAN: That's correct.

DR. BROTT: Mr. Mueller.

MR. MUELLER: I would like to know, what is the specific training requirement? Is this a board certification? Is this is a proctoring? Is it 20 years of experience? What is going to be the required level of training and/or experience?

DR. BROTT: I would suggest that it would be very difficult to be specific because the practice of medicine and these devices have to be used within state laws, and they vary by state, in terms of the laws and by the hospitals, in terms of the required JCAHO credentialing process. I think it would be very difficult. This is just my perspective. It would be very difficult for us to get too specific or prescriptive, and for the FDA likewise. And so I'd

ask Dr. Eydelman to comment.

DR. EYDELMAN: We would like to know the Panel's recommendations as to what kind of expertise they feel are needed, and then we'll take that into consideration in making our recommendation.

DR. BROTT: Thank you, Mr. Mueller.

Ms. McElveen, do you have an opinion on that, on (a)?

MS. STOKES McELVEEN: Yes, as to (a), I think it's clear that you need someone who is qualified. What's also important, I think, is someone who has had ample use of the necessary equipment to administer the ECT. I assume that's part of the training. I don't know. But I think, clearly, you must have some prior experience before actually using it on a patient and that the use must be limited as more or less being classified as the -- it's a device of last resort, that other alternatives have been used and this is the only measure left available for this particular patient.

DR. BROTT: I guess I'll ask Panel members to volunteer at this point. A couple of things. We need some guidance. A suggestion has been made that we consider how this wording should be changed or not, and there's been a suggestion that ECT, this somehow addressed whether it can be used as primary therapy. I'm not sure that's appropriate for this particular one, to address whether it has to be secondary, which was a suggestion that Ms. McElveen just seemed to make. So let's ask for input in terms of wording here or rejection.

Dr. Duff.

DR. DUFF: Mr. Chairman, I was just remembering that APA has some training guidelines. Is it possible that we could at least get a copy of those to perhaps use those as a guide?

DR. BROTT: I think we could get a copy of those. Dr. Park, you put them in our packet, as I recall.

DR. DUFF: Oh, I'm sorry, are they one of the -- I didn't see them in the --

DR. BROTT: I didn't see the guidelines, but we do have the reference, I think.

DR. PARK: The issue with the APA guidelines is that it comes in a book.

DR. DUFF: Oh.

DR. PARK: So we did not supply electronic copies of that, and I'm not sure if we have the book here. I don't believe that we do.

DR. DUFF: I just thought them being, you know, an important body and consumer of these, that we might at least be able to use that as some guidance.

DR. BROTT: Yeah. Again, I'm not sure how detailed the FDA can become, or specific.

Dr. Paulsen.

DR. PAULSEN: I think the wording is good. I would remove the

or, so it's restricting ECT device use to physicians with specific training and experience.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: I guess we're trying to get at what the answer is. So in other words, does it need to be a board-certified psychiatrist? As an example, something to that effect.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: Two things. One is I don't think that this is the appropriate place to discuss primary versus secondary interventions. This is looking at physical and medical complications. The other is that the use of physicians, the word physicians. What about qualified physician assistants or other types of paraprofessionals that have been cropping up more recently? Or do you want to restrict it just to M.D.'s?

DR. BROTT: Dr. Ross.

DR. ROSS: I'd suggest that it do be limited to physician, but not to psychiatrist. I don't think you need to be a psychiatrist to administer ECT, but you need to be a psychiatrist to prescribe ECT, would be my view anyway.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Yeah, well, I disagree with that. But I think it should be a psychiatrist because of the -- ultimately that's the person who's going to make the final decision about the appropriateness of that patient. Some of this puzzles me a little bit. Every hospital --

DR. BROTT: Let me just ask a question in response. If a psychiatrist prescribes a diagnosis, a condition for which this indicated, does it then make the next person not qualified to administer it?

DR. GOODMAN: No. No, I wouldn't say that. But it certainly has been demonstrated, in the many years that we've been doing ECT, that psychiatrists can be properly trained to administer this procedure. With these kind of safeguards in place, every hospital I've been to, there's been a very formal credentialing process at both the hospital level and the departmental level. There are guidelines. We don't have them in hand, but there are extensive guidelines on training.

DR. BROTT: The reason I ask is access. You know, other psychiatrists in, you know, somewhere -- what is the access for psychiatrists? In other words, I could see a situation where you might prescribe a therapy, but it might not be that there would be a board-certified psychiatrist available to provide it.

DR. GOODMAN: I might trust a neurologist to do this, too.

(Laughter.)

DR. GOODMAN: So I might expand the qualifications.

DR. BROTT: Thank you, Dr. Goodman.

Dr. McDonald.

DR. McDONALD: I think the idea of giving the treatments isn't just pushing a button, and I think it's very important because discerning

delirium from response, from depression, from mania, I think that you have to have a qualified physician actually giving the treatment. Pushing the button is one small part of the treatment.

And we've heard a lot from patients that it's this lack of communication with the physician. The physician wasn't listening to me. I never got informed consent. And informed consent should be before each treatment, not just at the beginning and go do it and come back.

And I think hospitals have in place a credentialing process, and as part of that they credential people to do ECT. I don't think the FDA should be involved in that. I think we can make recommendations to training programs.

DR. BROTT: Is this wording okay with you?

DR. McDONALD: No, I don't think -- I think hospitals --

DR. BROTT: No, how would you -- so you would not --

DR. McDONALD: Hospitals should credential people specifically for ECT.

DR. BROTT: So you don't agree with this?

DR. McDONALD: I don't agree with that.

DR. BROTT: Dr. Ross.

DR. ROSS: Actually, can I ask a question? It seems to be assumed that it's only given in hospitals. Is that necessarily the case?

DR. BROTT: No, no, that was just an example.

DR. EYDELMAN: Dr. Brott?

DR. BROTT: Yes?

DR. EYDELMAN: I believe Dr. Park just looked up the APA --

DR. BROTT: Great. Excuse me, excellent.

(Laughter.)

DR. BROTT: Great.

DR. PARK: So I just want to thank the audience member that did have a copy of the APA guidelines here.

So basically what it says -- and I'll just straight from the text. "Privileges to administer ECT should be granted only to psychiatrists who meet formal documented criteria set by the organized medical staff. Before an applicant can administer ECT on an unsupervised basis, the facility's medical director should establish that these criteria are met. The medical director should use qualified personnel to assist with this determination, including outside consultants as appropriate. The applicant's education, training, experience (including history of past ECT privileging), and demonstrated skills should be the specific determinants in the granting of ECT privileges. The extent of training and experience required should be at least sufficient to satisfy the educational and training recommendations described in Chapter 15. Medical licensure, satisfactory completion," et cetera, et cetera.

DR. BROTT: Thank you. Ms. McElveen.

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MS. STOKES McELVEEN: Are there any limitations or restrictions as to where the ECT should be administered, either in a hospital or is one's office sufficient?

DR. EYDELMAN: Well, as far as FDA restricting devices, it talks about the practitioner, not the location. Was your question about the APA guideline or about what we're asking?

MS. STOKES McELVEEN: I'm referring to APA guidelines.

DR. EYDELMAN: Sorry. Larry.

DR. PARK: You can go ahead with the conversation, and I'll look for that information.

DR. BROTT: Fine, we have a lot of work to do today. I would just mention, editorially, I'm impressed that our psychiatrists have not really determined with as much precision the length of the seizure, and we're going to be confronting that later. And that worries me a little bit in terms of restricting. The other thing is the APA guidelines are put out by the APA.

(Laughter.)

DR. BROTT: So on this particular point (a), let's just get a sense of the Panel. How many think that this restriction is appropriate and how many do not? And first I'll ask for hands on how many think this restriction -- because this would be a restriction. Yes.

DR. EYDELMAN: Could you qualify what you mean by this restriction?

DR. BROTT: (a), Restricting ECT device use to physicians with specific training and/or experience with the administration of ECT.

DR. EYDELMAN: Right.

DR. BROTT: It appears that we will not have a consensus for this, Dr. Eydelman, and I think we need to get some input from the Panel. We could either do it by raising hands or going around the table. What would people prefer, raising hands? Raising hands. And the Chair will defer.

So how many are in favor of this restriction in general? And how many would oppose this restriction in general? So we have a consensus, not unanimous by any means, that a restriction with regard to (a) is appropriate.

Now, with regard to wording of the restriction, are there any suggestions with regard to a nice, acceptable, persuasive rewording of (a)?

Dr. Kim.

DR. KIM: Mr. Chairman, I'm just asking you whether we are actually wordsmithing this particular issue today.

DR. BROTT: They need feedback. Remember we're not voting today. Nothing that we do has any statutory --

DR. KIM: Okay. In that case we can give general recommendations.

DR. BROTT: Absolutely.

DR. EYDELMAN: Yes.

DR. KIM: Okay. I think that I just want to respond to what you said. After all, this is from the APA. I'm not sure exactly what you all meant by it.

DR. BROTT: What I meant was -- and I'll be very explicit -- one could predict a priori that a recommendation from any professional organization will have a conflict of interest with regard to recommendations they make inside or outside medicine when it has to do with their group versus the rest of the world.

DR. KIM: Yes.

DR. BROTT: And no means would I wish to impugn my own organization, the American Academy of Neurology, but I can tell you that -- and Dr. Good, I think, would agree that when we issue guidelines, we have a conflict of interest.

DR. KIM: Yes. And I think I agree and acknowledge that. On the other hand, we can't get around the fact that the folks who are most experienced and would have the most frontline sense of what would be safe and effective use of this are the very same people. So it's an unavoidable conflict.

And I would suggest that FDA look at the training requirements and credentialing requirements that professional bodies have established, that are public and are in use, as a guide for specific language.

DR. BROTT: Yeah, Dr. Paulsen.

DR. PAULSEN: I don't understand the hesitancy. This is the professional organization for psychiatry, and the patients getting ECT are psychiatric patients. It would be like saying we're not going to ask the cardiologists how to do their open heart surgery. It makes no sense.

I understand what you're saying about conflict of interest, but you know, we do tend to take the whole conflict of interest thing too far. These are experts. There's not a competing agency. I mean, when you go to psychological associations, there's like three different ones because they all war about it. But let's just agree that the main professional organization for this specialty should be included. I see no reason we're saying it should be according to APA guidelines.

DR. BROTT: Dr. Ross.

DR. ROSS: I'm not sure we need to be so specific here, but I might be willing to withdraw my suggestion and leave it be psychiatrists. I mean, I do take the point that the treatment is a psychiatric treatment and it should be administered by a psychiatrist. I think that's reasonable.

DR. BROTT: Dr. Peavy. Oh, did you not -- oh. Dr. Good. Excuse me.

DR. GOOD: I don't think we should be any more prescriptive than this. I think that we've said enough. I'm fine with this as it stands without providing more detail. I think this can be something that can be worked on later by the FDA.

DR. BROTT: A final comment, Dr. Ellenberg.

DR. ELLENBERG: I guess I address this to Dr. Eydelman. My sense is, from the Panel discussion and from the audience, that things like informed consent and how one uses this procedure is not uniform across practice locations, what have you.

So I guess I would like to consider the use of a uniform informed consent, and I'm well aware of how difficult that would be, and the use of some general guidelines in using this procedure, accounting for the type of patient, et cetera, also extremely difficult to do. And my sense is I don't think that that's regulation of medicine, regulation of the practice of medicine. I think it's simply trying to get uniformity in the way this is done so that many of the complaints we've seen wouldn't happen.

DR. EYDELMAN: That's correct. And we'll come to these in the later questions.

DR. BROTT: Yeah, I think we do. Very good.

So next is (b), physician labeling recommendations for pre-ECT assessment, and then we have six different physician labeling recommendations.

So, Ms. Carras, could we start with you, with regard to -- you know, all of us were caught a little bit off balance here. (i) is recommending or asking us to discuss pre-assessments just before ECT, and stated are, including pertinent history, physical examination, EKG, echocardiogram, chest

x-ray, pulmonary function test, lab tests, and neuroimaging.

Do you have an opinion on that? Do you have an opinion on (i)? And if you don't wish to express an opinion, that's fine.

MS. CARRAS: I think if there is some way we can develop surveillance that would require that, or work it into a recommendation for clinical studies, then that would be the bare minimum.

DR. BROTT: Okay, I'm going to go on to Dr. Ross because these are physician related, certainly not exclusive to physicians. But, Dr. Ross, could you just go through, with regard to these items, history, physical examination?

DR. ROSS: Yeah, certainly a pre-ECT workup is important, just as for any surgical or other procedure, and history and physical examination and an EKG, probably a chest x-ray, lab tests. I think neuroimaging is reasonable. I'm not sure an echocardiogram or pulmonary function tests are indicated, unless there's some indication from the history and physical examination that those would be necessary. I think this may be appropriate but a little bit too extensive.

DR. BROTT: Yeah, I would ask Dr. Domino. I would tend to agree. I work with echoes and pulmonary function tests quite a bit myself.

In this setting, Dr. Domino, without anything from the history to indicate the need for an echocardiogram or pulmonary function test, every day, let's say on an everyday basis, do you think this should or should not be

part of a required workup?

DR. DOMINO: I don't think it should be part of the required workup. In fact, I would be not specific about the required workup, other than saying pertinent history, physical examination, and additional evaluation based upon the -- it would be anesthesia and psychiatry or, of course, a medical assessment. There's no evidence an EKG, echocardiogram, chest x-ray, or pulmonary function or even laboratory tests would really be indicated as far as the anesthesia.

DR. BROTT: How about the EKG? You know, in the packet -- in the packet, you know, that was provided to us, it seemed that this was something that is part of the routine already, and I may be wrong on that.

DR. DOMINO: Well, the thing is, in a 20-year-old without a history of heart disease, probably one wouldn't do an EKG. You would use EKG monitoring intraprocedure. If there was some abnormality there, perhaps you want to get one. But I don't think they need it preoperatively.

DR. BROTT: And let me just ask Dr. McDonald and Dr. Goodman. What's the practice that you're aware of with regard to EKG?

DR. McDONALD: We do EKGs in almost everyone. It'd be rare not to. And we would get electrolytes in almost everyone.

DR. BROTT: Dr. Goodman. Dr. Kim.

DR. GOODMAN: Yeah, I'd agree.

DR. BROTT: Dr. Kim. Okay. Dr. Domino.

DR. DOMINO: I just want to make a point that a lot of these preoperative tests are commonly done, but there's no evidence they're at all helpful, and they do cost a lot. So I would leave it to a judgment of a consultant, like an anesthesiologist, in order to decide whether these are indicated based on the patient's comorbid diseases.

DR. BROTT: And this is not unrelated. We come to the anesthesiologist later, and it would seem to me that that would be a very nice recommendation. If we have a list that includes an anesthesiologist, it would seem to me that we could be more general with regard to the workup because that's the anesthesiologist's responsibility. Is that okay with people, to leave this one general? And then, if we decide not to, we'll just agree now that if we decide later not to require an anesthesiologist, we'll need to come back to this one? Is that okay?

Dr. Domino.

DR. DOMINO: Well, I do want to make a point that you may want an anesthesiologist for the preoperative assessment but not necessarily for the procedure itself. So, you know, we can discuss that at that point.

DR. BROTT: Okay, how about -- pardon me? Yeah, how about pertinent history, physical examination, and appropriate -- and other studies as appropriate for the patient?

Dr. Domino.

DR. DOMINO: Yes, I agree.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Given the primary outcome very well is cognitive deficit, I think a pre-ECT cognitive -- objective cognitive exam needs to be conducted.

DR. BROTT: Yeah, that comes a little bit later.

DR. PAULSEN: It doesn't go here in the pre?

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: If you can go back to the beginning of the question. Go a slide back. These only are to deal as they relate to medical and physical risks of ECT.

DR. PAULSEN: Sorry.

DR. BROTT: Good, thank you. Yeah, Dr. Stebbins.

DR. STEBBINS: Just a quick question. And probably you've answered already about your suggestion. But the neuroimaging seems really non-specific. Is there any reason to do that?

DR. BROTT: Well, we took that out, yeah.

At this point, I'm told that we need a break. Now, yesterday our discipline in return was not good. Okay. So we will start whether the Panel members are here or not, before 10:30.

(Off the record.)

(On the record.)

DR. BROTT: Okay, I'd ask the Panel members to be seated.

So I think we're on the second part of Question (ii). We covered pre-ECT assessment. Number (ii) is ECT procedure monitoring and it says, ECT procedure monitoring (including EKG, blood pressure, pulse, respiratory rate, and oxygen saturation).

And I'm going to begin with Dr. Domino on this one.

DR. DOMINO: My suggestion is to modify it to say, according to the American Society of Anesthesiologists standards for monitoring during general anesthesia. In reality, what it does, it does include these things, the respiratory rate. During general anesthesia we often monitor ventilation within title capnography. I think citing the standard is appropriate.

DR. BROTT: We do have that conflict of interest situation which we do need to at least think about, you know, formally and in an unbiased way. The other thing is -- we'll get to you in a moment, Dr. Eydelman -- you know, I wonder how often these are modified?

And Dr. Eydelman.

DR. EYDELMAN: That was exactly my comment. We don't usually refer to something that undergoes constant revisions.

DR. BROTT: So back to you, Dr. Domino.

DR. DOMINO: Well, then, if you don't -- I mean the thing is, it is a standard for monitoring. I believe the nurse anesthesia organizations use that as well. I guess if you want to have these specific things, I would say, instead of respiratory rate, you might use ventilation as different

terminology.

DR. BROTT: Right, that's CO₂, though, isn't it, technically?

DR. DOMINO: Well, ventilation is controlled during these procedures and at one point they're apneic. So respiratory rate seems meaningless, to me, during the procedure. So ventilation is the typical technical word that's used.

DR. BROTT: Okay.

DR. DOMINO: Ventilation can be assessed in a variety of manners, and we could leave out the entitled capnography, but that is a standard for general anesthesia. But I would say ventilation.

DR. BROTT: I think that's good. You know, as a physician, I think that's excellent. And the others are okay with you?

DR. DOMINO: Yes.

DR. BROTT: Do we have comments from other Panel members on Dr. Domino's recommendation? Ms. Carras.

MS. CARRAS: Would it be appropriate to just say something like current clinical standards for general anesthesia monitoring?

DR. DOMINO: That seems fine to me, but if you want to specify that these are what these they are.

DR. BROTT: Yeah, I actually -- well, other input from Panel members? Dr. Gordon.

DR. GORDON: I want to distinguish between monitoring during

the procedure as opposed to the procedure monitoring, which could be three, four, six months out. So I think there needs to be a term that clearly identifies intraoperative, some language similar to that, so it's during the procedure.

DR. BROTT: Dr. Domino, do you have -- that seems innocuous to me. Do you have a problem with that?

DR. DOMINO: It seems like a good idea.

DR. BROTT: Fine.

DR. DOMINO: I would say, yeah, during the ECT procedure, intra-ECT procedure monitoring. Also I see the word pulse. Pulse. I would use the word heart rate.

DR. BROTT: Yeah, I agree. Do we have any problems with those suggestions? I think they made a lot of sense. Do have anyone who disagrees with the suggestion as modified?

(No response.)

DR. BROTT: Okay, let's go on to (iii), the appropriate use of general anesthesia, neuromuscular blocking agents by a licensed anesthesiologist during the procedure.

And, Dr. Domino, I'm going to go to you. Anesthesiologist. Is that appropriately specific? A nurse anesthetist?

DR. DOMINO: I think we need to use the term anesthesia provider. In a number of states in this country, the certified registered nurse

anesthetists are allowed to independently provide anesthesia without supervision from an anesthesiologist. So I think, to be consistent with Medicare and CMS guidelines, we need to use the word licensed anesthesia provider.

DR. BROTT: That makes good sense. Does anyone disagree with that?

(No response.)

DR. BROTT: Okay. The next is number (iv), pre-ECT dental assessment and the use of mouth protection (bite blocks).

Dr. Domino, you're here for a reason.

(Laughter.)

DR. DOMINO: The pre-ECT dental assessment is part of the anesthesia preoperative assessment, and yes, the use of mouth protection or a bite block is necessary. I'm happy to leave it as is.

DR. BROTT: Okay. And what gets done -- I'm just curious -- in terms of the assessment?

DR. DOMINO: In a preoperative assessment, a pre-procedure assessment, it would include examination of the airway, which includes the dentition and mouth. It includes, well, a history and physical evaluation, and the evaluation specifically focuses usually on airway, including dentition, heart, lung examination. In some cases a neurologic examination as well.

DR. BROTT: Thank you. The next is (v),

Electroencephalography monitoring during and after the procedure.

I'm going to go to Dr. Good.

DR. GOOD: Yes, I agree with this. The question I have is, how long after? And I honestly don't know the answer to that. So I defer to my colleagues who perform this procedure.

DR. BROTT: Any input from the Panel members on the duration of EEG monitoring? Dr. McDonald.

DR. McDONALD: Dr. McDonald. Until the seizure is terminated.

DR. BROTT: I actually think that's an excellent suggestion. It not only provides safety, but should anyone decide in the future to try to learn how long the seizures last.

DR. McDONALD: We know that. We haven't come to that yet.

DR. BROTT: Excellent, I'm glad to hear it. So you're suggesting, during and after the procedure, until the seizure has terminated. I think that's an excellent suggestion. Does anyone disagree with that? Dr. Good.

DR. GOOD: Just a question. We heard before about the rare delayed seizure that occurs. How soon afterwards do you see that, usually?

DR. McDONALD: Well, that's a good point. It could be minutes or occur in recovery. I don't think you just leave the leads on waiting for it to occur. You look for clinical symptoms and then you might put the leads back on. But I think, in general, you're taking the leads off.

DR. BROTT: How long do the leads stay on after the seizure has ended? Just kind of a rough idea for those of us --

DR. McDONALD: They came off relatively quickly because you're trying to get the patient ready to go into the recovery room.

DR. BROTT: Okay. So the way it's written here, plus your wordage, verbiage, is that agreeable to people? Dr. Peavy.

DR. PEAVY: Would you want to add continuous? I mean, that may be implied by until the seizure terminates. But the way it's worded, there could be an interval in there without it.

DR. BROTT: It seems like another innocuous addition. Dr. Ross, any problem with that?

DR. ROSS: It just seems superfluous. The seizures only usually 20 seconds to max a minute or two, but --

DR. BROTT: Continuous? Anybody have a problem with continuous?

(No response.)

DR. BROTT: Okay. Adequate skin preparation and the use of conductivity gel during electrode placement. Does anyone have objections to this?

(No response.)

DR. BROTT: Okay. So with regard to (i) through (vi), Dr. Eydelman, is that sufficient? Excuse me just a moment. Dr. Kim.

DR. KIM: Yeah, Mr. Chairman, I have a question. I just wanted to go back to -- I thought there was an issue left open about whether we thought there should be a licensed anesthesiologist, about pre-ECT workup. And it was my impression that Dr. Domino was going to address that question. I could be wrong.

DR. BROTT: Oh, yeah, you're correct. We agreed to go back to (ii), if a licensed anesthesia provider were not involved. Now we've agreed that a licensed anesthesia provider must be involved; therefore, they have responsibility to make sure that what we agreed upon for the pre-ECT assessment was carried out.

Dr. Ross.

DR. ROSS: Just to clarify. So what that means is we took out all of the lab tests from (i) because we decided there was an anesthesiologist to assess; is that right?

DR. BROTT: My recollection was that we stated, including pertinent history, physical examination, and laboratory tests thought appropriate. Okay? Right.

Okay, Dr. Good.

DR. GOOD: I think there's different types of histories. You have a psychiatry history, too, in addition to a history from an anesthesiology provider. I would just leave it where it is, physician labeling recommendations pre-assessment. It doesn't designate what type of

provider or a physician is going to --

DR. BROTT: Oh no, no, no, no.

DR. GOOD: Okay.

DR. BROTT: The provider language is in --

DR. GOOD: Right.

DR. BROTT: -- bullet point number -- let's see -- number (iii).

DR. GOOD: So maybe I'm confused. What's the question here, then, right now?

DR. BROTT: Dr. Kim -- pardon me?

DR. KIM: I am confused. I must have misunderstood what Dr. Domino said, and I wonder if she could address whether what I stated was accurate.

DR. BROTT: Fine.

DR. DOMINO: It's Karen Domino. I think leaving it as a licensed anesthesia provider, part of the -- I mean, there is a preoperative or a pre-procedure assessment as part of our care. So I don't think it needs to be specified in number (i).

DR. BROTT: So to recap so that we're clear, we're on Question 2, under (b), pre-ECT assessment (including pertinent history -- not specifying the kind of history -- physical examination, and appropriate laboratory assessments).

And (iii), the appropriate use of general anesthesia,

neuromuscular blocking agents by a licensed anesthesia provider during the ECT procedure.

DR. KIM: This is just a question. Does the fact that the overall section, what you just read, falls under (b), is that correct? And the entire section is labeled under physician labeling. Does that create any ambiguities? If other people don't think so, I'm willing to defer.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: I don't believe it does. We have two kinds of labeling that's specifically for the patient versus the provider. So what we're trying to say is that the provider will be notified of the following.

DR. BROTT: Is that acceptable, Dr. Kim?

DR. KIM: Yeah, absolutely.

DR. BROTT: Very good.

(c) Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment.

Dr. Ellenberg.

DR. ELLENBERG: In terms of informed consent, this section is entitled medical and -- I'm sorry -- to mitigate medical/physical risks. Item (c) appears to be going on to, essentially, informed consent. So as a technical point, maybe this shouldn't be under this section or whatever. But that's not critical. This is not quite informed consent, and I wonder if it would make

sense to bring up informed consent here.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: Let me just clarify.

DR. ELLENBERG: Okay.

DR. EYDELMAN: What we're trying to ask -- if you go back, Brad, if you could go back to the beginning of the question. We're discussing risks specific to the medical -- specifically medical and physical risks, and as such, we're trying to delineate all of the potential mitigating factors, one of them being that the patients are specifically informed about these risks and are asked to sign, as I described yesterday -- let me just refresh the Panel's memory.

So in addition to informed consent, twice before in CDRH we have utilized something called acceptance of risk and informed decision agreement. So it's an additional form that actually delineates each one of the risks and then has the physician and the patient initial under each one. So what we're asking in this particular question is if that kind of form, in your opinion, is needed to mitigate the medical and physical risks of ECT.

DR. BROTT: What were those two examples?

DR. EYDELMAN: The breast implants and the implantable miniature telescope for MD.

DR. BROTT: For what?

DR. EYDELMAN: For MD, age-related macular degeneration.

Eyes.

DR. BROTT: Yeah. It's an implantable telescope?

DR. EYDELMAN: Implantable miniature telescope.

DR. BROTT: Where does it go?

DR. EYDELMAN: In the eye.

DR. BROTT: No, I know the eyes.

(Laughter.)

DR. BROTT: Do you know where in the eye it goes?

DR. EYDELMAN: Yes, I do, I'm an ophthalmologist.

DR. BROTT: Yeah. Where? Where does it go?

DR. EYDELMAN: It gets implanted and it gets implanted in the posterior segment of the eye.

DR. BROTT: Okay. Dr. Ellenberg, does that answer your question? Because you're still recognized.

DR. ELLENBERG: Thank you. It may have, but I'm still puzzled. To me, I don't see anything about informed consent in this document. But here, certainly this is part of that process. So I would prefer to see informed consent as a whole package, then. Certainly the checklist makes a lot of sense.

DR. BROTT: From a technical point of view, you know, I think it was very clear what you stated and with the examples that you gave. What role does the FDA have legally in terms of informed consent?

DR. EYDELMAN: Well, this form, the acceptance of risk that I'm describing, then becomes a mandatory addition. Then we have an enforcement right over that particular form. So what we're saying is by including it, we're saying every manufacturer then supplies this form to the practitioner and the practitioner --

DR. BROTT: Understood. Are there other legal options for the FDA to impact upon the informed consent process?

DR. EYDELMAN: Not readily available.

DR. BROTT: Dr. Ellenberg, does that answer your question?

DR. ELLENBERG: It answers my question. But would there be any objection, in item (c), to say that this is a mandatory amendment to the informed consent process or the informed consent form? To make the complete package.

DR. EYDELMAN: Okay. Well, the informed consent form is not part of the labeling. This would be part of the labeling. So we're trying to delineate who is in the picture.

DR. ELLENBERG: I understand that.

DR. BROTT: Dr. Ellenberg, I'm not sure that, for instance, IRB --

DR. ELLENBERG: Uh-huh.

DR. BROTT: -- or our medical center would allow FDA to tell us everything that has to be done with regard to the informed consent process. Nor do I think the FDA has legal authority to do that. What we're hearing, in

my interpretation, is that this is the option that they have to impact upon the informed consent process.

DR. ELLENBERG: Thank you.

DR. BROTT: So I think this is where we should discuss the informed consent issue, understanding that in my hospital and yours, there are no FDA-informed consent documents that have to fulfill the Belmont report and, you know, all the stuff that informed consent documents have to do.

Dr. McElveen, you're our lawyer, correct?

MS. STOKES McELVEEN: Yes. As to the checklist, I think it would be extremely helpful that we use lay language and that a copy of the document be sent to the patient's home as well.

DR. BROTT: Dr. Ross.

DR. ROSS: Well, I think this sounds reduplicative of the informed consent process. We already have a very extensive informed consent process which is regulated by the IRB and goes through all kinds of institutional oversight, and to me this adds really a significant burden to both the patient and the provider, which could be an obstacle to the patients getting the treatment. I'm not in favor of this.

DR. BROTT: Dr. Eydelman, could you provide us, please, the statutory language with regard to burden?

DR. EYDELMAN: Well, I can't provide you statutory language in

a moment. I can look it up, the exact language.

DR. BROTT: Yeah, but could you give us a general -- because this has been addressed in the statutes.

DR. EYDELMAN: Right. If I could just address what Dr. Ross was commenting on. I wanted to delineate specifically the difference between the general informed consent versus what we proposed. This was utilized for the cases where we felt that the patient information -- informing the patient of specific risks was of utmost importance and that there was some issues of patients' recognition of the risks as it was done previously. So the specific issue is unique to the informed consent or the population that is being consented.

This is the situations where we've utilized this particular form. And, yes, it might be duplicative of the effort. However, since the informed consent varies, the regular informed consent varies from institution to institution, very often it just says that -- it doesn't delineate the specific risks. It just rests on the two or three general highest risk assessments, and that's the biggest difference.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Yeah. Would you be able to provide us with examples of the two that you mentioned, what the checklist would look like? It's very hard for me to deliberate on this without that context of seeing how it would appear. Do you list it alphabetically, in which case death would be

number four on the list? How do you contextualize it? Because I don't worry as much about the extra workload as it providing some misinformation or something that conflicts with what we're going to have in the informed consent, which will have a lot more layers of qualifiers in there.

DR. EYDELMAN: So it is actually on our website, and after lunch I'll be happy to pull it up if you want to defer to that.

DR. BROTT: Yeah, I think that would be a good idea. I don't think we have to slow down our deliberations to do that. But the cut and paste was done very nicely overnight by the FDA staff, and I'm sure, in the next five minutes, they can have it ready for us.

DR. EYDELMAN: Give us 10.

(Laughter.)

DR. BROTT: Dr. Kim.

DR. KIM: Yes. I'm a little concerned about the language that Dr. Eydelman used. She suggested that these would mitigate the risks and burdens. I just don't see how informed consent would actually mitigate any of the risks or burdens of any of those things. I can see that you -- for a particular individual, this perhaps could enhance informed consent. But that's an entirely different issue from these actual risks being mitigated.

So I think that should be very clearly stated because if the suggestion is somehow that there's evidence that people checking these things off will actually reduce the risk of memory loss, I think that's clearly

false. So that's one.

DR. BROTT: Let me ask you -- jump in. I think that Dr. Kim makes a good semantic point. Can we just make this Question Number 6? Should patient labeling require? Okay. Well, let's just make it Question Number 6 --

DR. EYDELMAN: That's fine.

DR. BROTT: -- because I think it's misplaced.

DR. KIM: Yeah.

DR. BROTT: Then we could go back to it at the end of our discussion, after we get through -- up to 5.

DR. EYDELMAN: And then we'll present our visual at the time.

DR. BROTT: Yeah, how's that? Then we'll be more informed.

DR. KIM: So we don't need to talk about informed consent currently?

DR. BROTT: Correct.

DR. KIM: Okay.

DR. BROTT: So let's go on. You made a good point.

(d) Requirement for further premarket studies (either pre-clinical [bench, animal] or clinical) for significant changes in device technology or new indications for use.

And, Dr. Ross, let's start with you.

DR. ROSS: Well, there seemed to be two questions or maybe

several issues here that are kind of bundled together, changes in device technology or new indications for use. We're going to get to indications for use in Question 5, so let me defer that.

But significant changes in device technology, my concern about that is that the instruments seem to be evolving over time and there are improvements in them. How do you determine what's a significant change and what requires a full placebo or a full clinical trial or not?

Sorry, I don't think I can give you a clear answer because I don't think I understand the question.

DR. BROTT: Well, I think that's a good point. Let me ask Dr. Eydelman a question. Would it be appropriate if we changed significant to which would impact either safety -- which could potentially impact either safety or effectiveness?

DR. EYDELMAN: Yes, probably safety being most important.

DR. BROTT: Okay, but we could put effectiveness as well?

DR. EYDELMAN: Yes.

DR. BROTT: So take out significant and put in basically the statutory words, which are safety and effectiveness. And now you're back on the program.

Dr. Ross.

DR. ROSS: Well, let me ask again for some clarification. So this would be -- when you say further premarket studies, this would be a clinical

trial? I don't think an animal -- can you give us some guidance on what you're looking for here?

DR. BROTT: I think they want your opinion and our opinion. But, Dr. Eydelman, go ahead.

DR. EYDELMAN: Basically, the ECT devices, if we look at the technological changes, we usually think of it as the preclinical information. So we could draw some kind of a box around -- these are the parameters within which the ECT devices that we know that have been cleared to market so far have been operating in.

And the question is, in your opinion, if tomorrow we get an application for a device that has the current or the frequency, et cetera, et cetera, some of the electrical or some other preclinical parameters outside what we're used to seeing, do you believe that then we would need to ask for premarket?

DR. ROSS: Yeah. Okay, that's helpful. I think part of my problem is we're going to address some of these parameters in the next question, and it seems to me that this question more logically falls after that question because it's how would we address a change, yet we haven't yet discussed what are the current parameters.

DR. EYDELMAN: Actually not, because the following question talks about narrowing down further the parameters that are currently on the market. This question talks about going beyond the box of the parameters

that are already on the market.

DR. BROTT: One thing to consider is that if this does read, Requirement for further premarket studies for changes that could potentially affect safety and effectiveness, I mean, I think that that's general enough that we could agree that that should be done.

DR. ROSS: Yeah, okay, I take that point. So I would be in agreement with that.

DR. BROTT: Dr. McDonald.

DR. McDONALD: The only corollary is that the changes may be done because there is sufficient premarket studies and that's why the changes are being done.

DR. BROTT: That would be recognized. You know, just as an example, with carotid stent technology, there are new -- and Mr. Mueller may even know -- there are changes such as a new stent, a tapering stent, an over-the-track stent, a new protection device. Some of them impact safety and effectiveness. Many of them do not.

Language such as this would be -- could be used by the FDA and the company, you know, industry, to guide and provide reasonable guidance without being overly burdensome. It certainly has worked very well on the stent side, the language like this, and I think it could work very well here.

Mr. Mueller.

MR. MUELLER: Yes, thank you. David Mueller. I agree with

you that the stent probably does have this kind of language. However, these stents are Class III and, therefore, per the regulations, any change that could potentially affect safety or effectiveness has to be analyzed or --

DR. BROTT: See, that was my -- the reason I mentioned it --

MR. MUELLER: Right.

DR. BROTT: -- because all the changes that I mentioned did not undergo clinical studies.

MR. MUELLER: Right, they are preclinical. However, the key word here in this, currently written as it is here, with the word significant change is statutory language and does fall within the 510(k) Class II testing and wording. Therefore, I would recommend we keep it as significant change. It has already been defined in the regulations and FDA guidance.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: I think we understand what the Panel is coming for, and we can leave the wordsmithing until later.

DR. BROTT: Fine.

DR. McDONALD: Just a minor point. We're going to talk about brief pulse ECT. This is a perfect example of something to come on the market that does affect safety, probably improve safety, may change efficacy. Would we require the companies, before they roll that out, to do these studies? That's the concern I have.

DR. EYDELMAN: Once again, no, we're talking about going

outside of the box that is currently already on the market, or that the engineers and preclinical scientists at the FDA will determine if it would significantly affect the outcomes.

DR. BROTT: So before we go on, do we leave it as significant or impact -- potentially impacts safety and effectiveness? What do you prefer?

DR. EYDELMAN: I don't think it matters.

DR. BROTT: Okay. So let's go on, then, to 3. Dr. Cunningham, could you read 3 for us?

LCDR CUNNINGHAM: All right. This is Brad Cunningham.

DR. BROTT: Oh, just before, Dr. Eydelman, are you satisfied with --

DR. EYDELMAN: Yes, thank you.

DR. BROTT: -- the feedback that you've had for Question 2?

DR. EYDELMAN: Yes, thank you.

LCDR CUNNINGHAM: Question Number 3:

Below are potential regulatory controls FDA could apply to ECT to mitigate risks of adverse cognitive and memory effects (especially with respect to anterograde and retrograde memory functioning):

- a. Physician labeling recommendations for:
 - i. Exclusive use of brief pulse (1-1.5 msec) waveform stimulus
 - ii. Use of ultrabrief pulse (0.3 msec) stimulus

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- iii. Exclusive use of unilateral nondominant electrode placement
 - iv. Use of bifrontal electrode placement
 - v. Limiting frequency of treatment to a maximum of twice weekly during a course of ECT
 - vi. Monitoring cognitive status prior to ECT and throughout the course of treatment
- b. Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment.
- c. Requirement for further premarket studies (either pre-clinical [bench or animal] or clinical) for significant changes in device technology or IFU.

Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the cognitive and memory risks of ECT.

DR. BROTT: Very good. And so physician labeling recommendations for. And, again, this is to mitigate cognitive and memory effects. And we're on (i), exclusive use of brief pulse waveform stimulus.

Dr. Good.

DR. GOOD: The problem we're getting into here is that of efficacy because some of the literature that we've looked at says that there's

different efficacy for some of these parameters, and to get to the point where we're having labeling recommendations, we're making decisions about treatment. I'm a little bit confused. So it might mitigate the cognitive.

DR. BROTT: Yeah.

DR. GOOD: It might not be effective.

DR. BROTT: I think this might be an appropriate time, Dr. Park, to go over what you proposed telling us before with regard to effectiveness. And, again, if there's a way to tease out these different technical methods with the seizure itself, that would also be helpful.

So, you know, as a neurologist, I'm wondering, you know, why it should make a difference where the electrical current and how much is given if a generalized seizure involving all of the brain follows.

Dr. McDonald, you're ready to comment. Are you? Can you comment on that before Dr. Park? The seizure versus the electricity.

DR. McDONALD: Oh, okay. So there's very good data to show, as Dr. Park said yesterday, that subconvulsive stimuli are ineffective, that you have to have a seizure in order for it to be effective.

In terms of the seizure and the wavelength, there's been data that would show that delta fade-aways lead to better outcomes. There's data that shows --

DR. BROTT: Independent of the seizure and the duration of the seizure?

DR. McDONALD: I'm talking about the waveform. The waveform actually can predict outcome. Postictal suppression is very good at predicting outcome, independent of the seizure length. The seizure length doesn't appear to be as important as the quality of the seizure.

The reason seizures are interrupted at, you know, a minute, up to three minutes, is because you get more postictal confusion if the seizure persists for three to five minutes. But there's never been a good correlation of the length of the seizure with the seizure. But as the data that was presented yesterday, it also has to do with the amount above the seizure --

DR. BROTT: You just have entered quite a few variables. You know, the type, the way it's given, and now you're talking about the quality, the postictal duration.

DR. McDONALD: Right.

DR. BROTT: I don't recall these things being measured in the papers.

Dr. Park.

DR. PARK: This is Larry Park from FDA. First of all, I want to thank Dr. McDonald for providing that synopsis of part of the literature the FDA did not specifically go into. So in the data that we presented yesterday, we didn't parse out each and every one of the variables that Dr. McDonald has just mentioned. That doesn't mean that I would take that as, you know, because we didn't present it -- I'm glad that Dr. McDonald did do that.

What we did present yesterday was pretty much a straightforward look at, you know, whether the treatment is effective or not, and looking at really what the standard changes in treatment parameters were.

So, first of all, to go over the summaries of the already published reviews and meta-analyses, these were our conclusions about what, as an aggregate, this body of literature said: first, that ECT effectiveness is demonstrated only in the period immediately post-ECT to one month; ECT is more effective than sham or placebo; ECT is more effective than some antidepressants; limited evidence that ECT is more effective than repetitive transcranial magnetic stimulation; limited evidence to support the effectiveness of ECT for elderly patients; and an estimate of the overall response rate of 72 percent. And, again, that was compared to a placebo or sham of about 40 percent, I believe.

Also bilateral ECT is more effective than unilateral ECT, though moderate and high doses of unilateral ECT may be as effective as low dose bilateral. Low dose unilateral may be no more effective than sham. And for unilateral ECT, increasing dose increases effectiveness and may increase memory and cognitive impairment. Also, presence of psychotic symptoms may predict better response.

For schizophrenia, ECT effectiveness is demonstrated only for the period immediately post-ECT to one month. Conflicting data suggest ECT

may be more effective than antipsychotic medication for the acute episode. ECT is associated with greater likelihood of being discharged from the hospital, and there's limited evidence that ECT may reduce relapses.

For other indications, as you can see here, limited evidence for mania and mixed states, that ECT is effective. There's a lack of randomized controlled trials for catatonia, and there's no evidence that ECT is effective for schizoaffective disorder at any time point.

DR. BROTT: Dr. Ross.

DR. ROSS: Regarding schizoaffective, is that no evidence in the sense that it's been studied and the study was negative or there's not data?

DR. PARK: Probably both. So there are about 14 studies and a number of them have yielded negative results, meaning that there was no difference, no detectable -- no significant difference between the ECT group and the comparator. In a couple cases, that comparator was sham.

DR. ROSS: And roughly how many patients? Just roughly, your guesstimate.

DR. PARK: Actually, I don't remember the number of those off hand. I'm sure they're fairly small studies as well.

DR. ROSS: If I could just follow up. I mean, it's just a little puzzling. The clinical experience is that ECT is good in affective disorder and in schizoaffective disorder but not in schizophrenia, and yet these data seem to be -- it's hard to imagine how it could be useful for schizophrenia but not

schizoaffective disorder if it's useful for affective disorder.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: I think a point that was left off your summary slide that gets to Dr. Good's comment is specifically where you say gains in efficacy are achieved only at the expense of increased risk of cognitive impairment. It seemed to be kind of what he was talking about regulating the practice, trying to mitigate one of the side effects.

DR. PARK: Point well taken.

DR. BROTT: Dr. Good.

DR. GOOD: I spent some time last night trying to get some feeling for other reviews that have looked at this, and I thought one place to look at this should be practice guidelines. And since the APA is a big fat book and I didn't have that to look at last night, I went at the NICE, the U.K. guidelines, and there's one from 2003 and there's one from 2009. And here's one from 2003. Now, in the 2009 they say nothing else has really developed with the overall effectiveness of ECT.

But from 2003, just reading a couple of sentences, the assessment report review stated from 90 randomized controlled trials in individuals with depressive illnesses of different degrees of severity, overall, they provide evidence that real ECT, where real current is applied, it's more effective than sham in the short term. But then they also say that the quality of these studies was not the standard of today. So, you know, again, we're

dealing with somewhat soft stuff here.

In the 2009 one -- and I would refer you to that if you're interested, it's in your package -- they're really talking more about unilateral versus pulse, ultrashort pulse, saying that studies are ongoing. So it's pretty soft stuff, and not everybody might agree with this. Some of the other reviews don't entirely agree with some of these components. So I'm not quite sure where to go with this.

DR. PARK: So for your review, of course, basically we presented our conclusions trying to assimilate all of the different practice guidelines --

DR. GOOD: Right.

DR. PARK: -- as well as the systematic reviews and meta-analyses. There are occasions where there will be some conclusions expressed that are differing. However, I think, as a body, this is what we came up with. We would be open to discussion, of course, on any of the points.

DR. BROTT: One more question of Dr. Park.

DR. McDONALD: Can you go to the last slide? It's Dr. McDonald. There just are parts of this that -- you said that ECT was ineffective for the elderly. I think you went forward. Did you go forward or go back? Yeah.

DR. PARK: You want for depression, the last slide.

DR. McDONALD: Depression. I'm sorry. ECT actually has been

shown in randomized trials to be very effective in the elderly. In fact, age predicts ECT response.

And I think that for bipolar disorder, there was a review in the *American Journal of Psychiatry*, with Sackeim in 1991, that showed there was a tremendous amount of evidence in support of it. The trials may not be randomized controlled trials, but I think there's a wealth of evidence, particularly when you consider safety and the safety of being bipolar with manic not responding to medication.

I think ECT has dropped off in schizophrenia simply because we have modern medications that were pretty effective and it wasn't as effective as it was in affective disorder.

But I was surprised too, as Dr. Ross, given the clinical response of patients, particularly a condition like catatonia, where we would say it's a lifesaving treatment and we do not have a lot of other options.

DR. PARK: This is Larry Park from FDA. Those points are well taken as well, Dr. McDonald. What I would say is that we're strictly trying to make conclusions based on the literature.

And in clinical practice, for instance, in the case of catatonia, it's widely accepted that ECT is a treatment of choice. However, if you look at the literature, given the nature of catatonia, the severity and the frequency, there are no randomized controlled trials for that. So I think part of the conclusion of these reviews, you know, it is fairly data driven.

So while there is no data for that, if you look at the practice guidelines, oftentimes the practice guidelines will be slightly different than the reviews, and the practice guidelines do indeed recommend that catatonia be an indication for use.

DR. BROTT: Well, I think that's a very good point. In the Executive Summary, you know, things are broken down pretty clearly that way so that as Panel members we have the opportunity to look at that.

DR. McDONALD: Just one comment, because age clearly -- elderly patients clearly have a higher response, and that is in the literature. That's O'Connor's paper. It had 273 people in it, showed there was a direct effect of age and that older patients responded better than younger patients.

Since we start to look at risks, we don't want to start to take some of these facts into account, saying that the elderly have a lower response rate and don't benefit from ECT because they clearly benefit from ECT.

DR. BROTT: The first author on that one again.

DR. McDONALD: It's O'Connor. And I'll send it to Dr. Claudio and she can print it.

DR. BROTT: Was it in our packet?

DR. McDONALD: I don't know.

DR. BROTT: Well, maybe you could send it to us.

DR. McDONALD: Okay.

DR. BROTT: We have one more question. Then we have to go on. Remember, this question is mitigating factors.

Dr. Ellenberg.

DR. ELLENBERG: Thank you. I'd like to address the first three points on efficacy from Dr. Park's slide, and those points in the beginning related specifically to general efficacy. So the main result yesterday revolved around the fact that there are five RCTs that the FDA thought were the best evidence available, and the meta-analysis used only 200 patients. That's a small number of patients.

The confidence interval for the point estimate of efficacy was really, really wide. The HAM-D score increased about 7.1 points for those that aren't on ECT compared to sham. But the confidence interval around that was enormous so that a patient looking at this would think, well, I might actually have a reduction in the HAM-D score or I might have an increase in the HAM-D score of 14.2.

I don't know and I don't think anyone knows whether or not this large confidence interval is due to the inherent variability of the procedure or it's just that we have a small sample size. FDA considers this difference clinically important.

So my question to the Panel is whether or not we as a group are convinced of the efficacy because I think, as we go through on the other deliberative questions, that has been our assumption so far that I assume

we'll consider. So is the group convinced this is efficacious?

DR. BROTT: Thank you. So, remember, this particular question is focused on mitigating risks, for cognitive risks. So let's go forward now. We're on (a), physician labeling recommendations. And I think that we're up to Dr. Anderson. Exclusive use of brief pulse waveform stimulus.

DR. ANDERSON: I can't comment on the technical parameters specifically, but I would agree with the prior comments, that I wouldn't want to over-recommend or begin a process over-regulating how ECT is delivered for individual patients.

DR. BROTT: You know, all of these have to do with what Dr. Anderson just stated. And so they're all related. And I'm wondering if we could have comments with regard to her reservation, and that is, should we be recommending, or not, how this is given?

Dr. Goodman.

DR. GOODMAN: I share those concerns, and it's going to come up again in that list, which I don't see up there, but I can try to imagine it, including the frequency at which you deliver it. I wonder and I'm not sure who's the best one to answer, maybe another member of the Panel, is I could imagine that this conversation comes up with a prospective patient, where you sit down and you weigh with the chances that they'll get more benefit out of parameter X, but that may be at the expense of some increased risk of side effects. Do you take that into account in your discussion with the patient

in setting those parameters?

So if the patient in the discussion, informed consent process, says, well, I really want to get better, I don't care that much about the memory loss, I'll take my chance, versus the other one, really, I don't want any chance that I'm going to be left with irreversible memory problems so let's try the settings that mitigate that risk first, does that kind of dialogue take place and does it have a place in the medical management of patients using ECT?

DR. BROTT: How would you word that?

DR. GOODMAN: That's why I mentioned it as a question.

(Laughter.)

DR. BROTT: But, seriously, the FDA needs words.

Dr. Eydelman.

DR. EYDELMAN: In light of Dr. Goodman's comment, what I wanted to point out is if the Panel feels that instead of exclusive use of a particular brief pulse, it's more important to inform, then you can recommend that the labeling has a particular warning or precaution that needs to be communicated to the patients. That is under your purview.

DR. BROTT: And I think that could be appropriate for (i) through (v). Could you look at (i) through (v), Dr. Goodman, and see if you would agree with that? They're (i) through (v).

DR. GOODMAN: I think it would be appropriate, but I'll defer to

other members of the Panel with greater expertise and knowledge of the database.

DR. BROTT: Dr. McDonald.

DR. McDONALD: I think it's appropriate to discuss these issues with the patient. I think that, for instance, the use of brief pulse, we have a paper that just came out, showing that it was ineffective to use brief pulse with low dose bitemporal ECT. I think that it's a little premature to make those types of recommendations.

Treating people twice a week clearly causes fewer memory side effects than three times a week, but it would also take -- you still have to do the same number of treatments, approximately. It could take you six weeks to do all the treatment, whereas you might consider it with someone who had a lot of cognitive problems who was perhaps older. And it really is the practice of medicine.

I think the one topic on there that I certainly agreed with was the use of brief pulse waveform as opposed to sine wave. But the scope of the brief pulse doesn't include -- it should be maybe .3 to 2 milliseconds. That was the one thing that we do have pretty good data on, that sine wave causes more memory problems and is not more effective than brief pulse. But the others are a matter of practice, and exclusive use of unilateral nondominant electrode placement does not make sense. They're different.

DR. BROTT: Did the available machines deliver sine wave?

DR. McDONALD: No. Well, you can get a sine wave machine, yes. They're sold in India, so you could get them. And there are hospitals. There was a study that was done with Joan Prudic. Harold Sackeim did a study looking at New York hospitals, and there were still hospitals in the '90s using sine wave machines. So that's probably what they've been using all along. And I think people have reported, I think, sine wave is more effective, sort of just as a matter of reporting it, that they've had some experience. But we have very good evidence that brief pulse machines are safer and equally as effective as sine wave.

DR. BROTT: You know, it's a little bit of a problem because if you look at cholecystectomy and you looked at open cholecystectomy versus endoscopic cholecystectomy, all your statistics from open cholecystectomy are 20 years old, 30 years old, 40 years old. The safety is going to be better today for a variety of reasons that don't relate to whether or not it was an open cholecystectomy.

DR. McDONALD: Well, this was an open trial -- it was an interesting study. They went to New York City hospitals, and they monitored patients who were getting ECT and monitored for cognitive side effects as well as --

DR. BROTT: But they did it for sine wave contemporaneously?

DR. McDONALD: Um-hum.

DR. BROTT: Okay.

DR. McDONALD: And they monitored people just to see what's the practice in the community.

DR. BROTT: Are the psychiatrists comfortable with not using (i) through (v) but saying something about sine wave? Dr. Kim.

DR. KIM: I wanted to ask a question to FDA about that precise point because if these are -- as I understand it, none of the two machines actually can deliver sine waves, now currently marketed in the U.S., but I guess some hospitals could have old machines that they're still using. Does FDA have any authority over those old machines that are being used?

DR. EYDELMAN: Yes, we do, but this whole process that we're going through yesterday and today is aimed to help us get a better control of everything that's out there and that will get there. So I just wanted to add to that. Again, I just wanted to make sure that the Panel understands the time and the effort that we're making to go through each one of these.

Should you want to consider Class II for any of the indications, these could be -- any one of these or the combination of them could be written potentially as a special control, rather than requiring a particular manufacturer to provide data that is specific to their own device.

DR. BROTT: In response to that, does anyone believe that, among (i) through (v), one of these or all of these should be on the label as a special control to mitigate cognitive problems? Dr. Kim.

DR. KIM: No, I believe that (i) through (v), as stated, really is

regulation of practice of medicine and --

DR. BROTT: Okay. Do we have other input? Dr. Ross. And the question is, are any -- (i) through (v), or however you want to number them, should they be retained or not?

DR. ROSS: I think I'm in agreement with Dr. McDonald. I think the sine wave versus the brief pulse is really a device issue. The others are how the device is used in the practice of medicine. So, therefore, I would be in agreement with that.

DR. BROTT: Dr. Good.

DR. GOOD: So not being a psychiatrist, I admit, I'm pretty confused about this. But let me read one sentence from the most recent British review. It's two years old, so we'll take that into consideration. For cognitive impairment, which is what we're talking about, it's still not clear to what degree the tradeoff between efficacy and cognitive side effects can be avoided by manipulating dose and electrode placement. Then it goes on.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: Just to come back to the comment Dr. Kim just made, I want to make sure the Panel understands this is not regulation of the practice of medicine. We can lock out device parameters.

DR. KIM: I'm sorry.

DR. BROTT: That's his opinion.

DR. KIM: Can I clarify my comment?

DR. BROTT: Sure.

DR. KIM: Two things. One is that if the first point is read as sine wave versus brief pulse, then if the experts who --

DR. BROTT: Well, no, it's not written that way. Let's take sine wave separately.

DR. KIM: That's the way Dr. Ross took it.

DR. BROTT: Let's take sine wave separately and just deal with (i) through (v).

DR. KIM: Yes.

DR. BROTT: Okay.

DR. KIM: My sense is that I can well imagine a clinical practice in which, since we know, although many patients experience memory difficulties, not all will. And some patients who are very, very sick may be willing to take on extra risks in consultation with their physicians. And to preclude that kind of flexibility and choices, I think, in my opinion, would constitute the kinds of things that we wouldn't want FDA to do.

DR. BROTT: So I'm hearing a consensus, so far, that we're not in favor of (i) through (v). Are there members of the Panel that wish to present another opinion? Dr. Stebbins.

DR. STEBBINS: I think, as far as labeling goes, I would agree. But I like the comment of being able to require a conversation, at least, between the physician and the patient discussing these types of issues

independent of the consent process.

DR. BROTT: And that would be a discussion of dose and method of introduction of ECT -- of induction of the seizure.

DR. STEBBINS: Exactly, and its effect on cognition.

DR. BROTT: Okay, we'll take that under advisement.

Ms. Carras.

MS. CARRAS: Michelle Carras, Patient Representative. I'd like to say that I agree with -- I believe it was Dr. McDonald or perhaps Dr. Goodman saying that, in discussion with the patient, the patient may be willing to take on more risk for the potential benefit of the treatment.

I think, though, that the special consideration with informed consent -- and again, I'm reading because it's difficult for me to speak extemporaneously -- that we're using it on a vulnerable population who may have current cognitive impairment or emotional distress that makes it difficult to have a true understanding of the risks and benefits.

You know, my personal experience with psychiatry -- and we've heard it elsewhere -- is that there is sometimes a climate of coercion, whether it's real or perceived, and given that we don't understand why some patients feel devastated by the procedure, I think that we should consider a recommendation that not only should informed consent be clearly obtained after the capacity to consent is ascertained, it should be continuously ascertained during the process and during all of these discussions, and that

we should consider making a recommendation to the FDA that the potential risks of the procedure could be mitigated by prohibiting its use in patients who do not choose to use it voluntarily and with fully informed consent.

DR. KIM: Could I respond to that?

DR. BROTT: Yes, Dr. Kim.

DR. KIM: I think it would be disastrous, not your comments, but if we restricted this use to people who can only give their own independent consent. The reason for that is that we know there are many patients who are in life-threatening conditions, with catatonia, for instance, for whom we would legally prohibit the use of this treatment. I think that would be disastrous. So I feel very strongly about that point.

DR. BROTT: Okay, Dr. Eydelman.

DR. EYDELMAN: Just a point of clarification. When we talk about informed consent form or informed consent, we're talking about the individual or anybody who's signing and designated to sign for the individual.

DR. BROTT: Right. I think that we're hearing consensus on (i) through (v), that they're not necessary for labeling or do not help to mitigate cognitive and memory effects.

We're on now (vi), monitoring cognitive status prior to ECT and throughout the course of treatment.

Dr. Goodman. Gordon. Excuse me. Dr. Gordon, do you have an opinion?

DR. GORDON: I think it should be part of the recommendation. I'm very clear on the monitoring of cognitive status prior to ECT, although any baseline is still controversial. But not to have one is even worse. And I think we need further clarification as to, throughout the course of treatment, whether and how long that should be or might be.

DR. BROTT: And I'm wondering if we could have some -- on those points, I'm wondering if we can have some input from our neuropsychologist Panel members.

Dr. Peavy.

DR. PEAVY: I would make the recommendation that we monitor cognitive functioning, but if possible, to try to use a brief battery rather than just the MMSE.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: I think the wording needs to be maintained open enough so that you can prepare your cognitive assessment for each individual patient. So I think that saying it needs to be prior and throughout the course, it may be clear enough from my view, but I'd like to hear from Drs. Stebbins and Duff as well.

DR. BROTT: Dr. Duff.

DR. DUFF: Three neuropsychologists, the same opinion. That's unusual.

I agree that it needs to be monitored before and during the

course of treatment. It's probably some -- like with other monitoring suggestions that we've had, setting some kind of parameter of what's the course of treatment because obviously there are people that do maintenance ECT that may go on for years, and maybe we need to make some kind of recommendation on that.

But also, I would like to, if possible, include some idea that it's a more formal assessment because as it's currently written, it can be a typical cognitive assessment as how is your thinking and that, perhaps, could suffice for an evaluation as it's written, whereas if we included some other language about objective assessment --

DR. BROTT: Thank you.

Before we go to Dr. Stebbins, in the stroke field, when we try to look -- and Dr. Good may wish to comment -- when we try to look at the impact of a stroke where we all agree there's a focal brain injury, it becomes very difficult to assess the cognitive or other impact of the stroke if it's carried out at different times from the stroke.

And so I'd like the neuropsychologists, maybe, to address this, you know, how you word the formal -- or however you want to word the way we assess and also the time points of the assessment.

Dr. Stebbins.

DR. STEBBINS: Well, first of all, I agree that it needs to be done both prior to and throughout the course of testing. I also -- treatment.

I also agree that the testing needs to be more than just a question or mini-mental. I think that there needs to be some language in there specifying that it is a formal assessment of cognitive function. I think part of the problem with doing repeat neuropsychological testing is that a lot of tests don't have alternate forms, and so you can have learning effects and all sorts of issues like that.

So perhaps recommending a pre-treatment, a mid-treatment, and an end-of-treatment assessment might be the best and most efficient way to approach this.

DR. BROTT: Let me just throw something out and then you can amend it.

You know, you've got the problem with drugs, acutely. You've got the problem of variability, what time of day, what drugs they're on, how they're doing with their response to therapy over the first weeks and, just throwing this out, three months in one year. Now, could there be another time point or time points?

DR. PAULSEN: My opinion -- and clearly, there's conflict of interest here -- is that well, you can't just do this without being a licensed expert on how to do cognitive assessments because you're right, if someone just does it at these certain points in time and, you know, I've seen people do a full cognitive assessment on a patient who is fully delirious. It's an incredible waste of time. And I'm sure you've seen it, too.

So if you just specify these time points, it will become irrelevant very quickly. I would like to see it say words like objective and standardized and by a licensed, you know, card-carrying person who knows what they're doing because if you just specify the timelines, you could get garbage in/garbage out. I think somebody can evaluate whether it's time to do the pre, the post, and the end treatment.

DR. BROTT: The problem, though, if we go back and a year from now Dr. Ellenberg says your cognitive testing was done on 50 percent at one month, 30 percent at three months, 20 percent at six months, he's not going to accept it. So how do you respond to that?

I think that we do need to address the issue of time to get some kind of -- which is what we do with stroke. If we do it at different time points, it's really meaningless.

This side of the table. Dr. Good.

DR. GOOD: The difference between stroke and here, though, is that sometimes there's ongoing treatment, especially with maintenance therapy. And one of the -- at least in my reading -- one of the reasons that you might consider stopping maintenance therapy is if there's a major cognitive change. So there has to be, at least in that situation, some ongoing assessment.

Now, what type of assessment, I'd leave that to my colleagues. I think if we go back to some of the things we talked about earlier, with the

pre-procedure testing, we ought to leave it fairly vague. We did that with the examination of the tests prior to procedures. I'm not sure we ought to be too prescriptive here, either.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: I think one thing, when you propose looking at one year, at this point we don't even know what goes on at six months, so I think that that probably is not appropriate.

I do like the idea of having a pre-treatment of the acute treatment phase, pre-treatment, mid-treatment, and end-of-treatment. And then if maintenance ECT is recommended, then perhaps having those same type of marks for when you're going to be doing the testing.

I do like the idea of having and including in the language much like with anesthesiologists, you do specify who is going to be doing the testing because Dr. Paulsen is very correct; you could have someone who really doesn't know what they're doing, just giving us garbage.

DR. BROTT: Dr. Ross.

DR. ROSS: I do think stroke is not the best analogy because stroke occurs at one time point, and these patients have not just different lengths of treatment but also very variable courses of their illness.

And I would be in favor of being not overly prescriptive about what kind of testing needs to be done, but leaving it, as we did, for the medical and anesthesiological assessment that a cognitive assessment should

be done, it should be done by the psychiatrist practitioner, but not try to specify exactly what kind of assessment needs to be done.

Patients with depression, for instance, catatonic patients might -- it would be very difficult to specify particular tests.

DR. BROTT: I hear you loud and clear. What worries me is that, you know, all of the different evidence that we've been presented with regard to risk has focused, really, on this aspect of the treatment. And outside this room, the controversy focuses on this aspect of the treatment.

And it would be nice if the neuropsychologists and psychiatrists could come up with a framework where five years from now we're not in the position we are today.

Yeah.

DR. ROSS: But I think that there's really two different issues. One is more a research issue where it would be very important to standardize the testing and get results six months or a year or later, and I think one of the subtexts of this meeting is we really don't know nearly as much about ECT as we should, given what an important treatment it is.

But I think that's different from clinical practice, and I'm afraid if we start prescribing what tests be done at what time, then that's really determining the practice of psychiatry, of medicine, rather than an appropriate restriction on the device.

DR. BROTT: Dr. Winokur.

DR. WINOKUR: So I don't do ECT, but I refer patients from my psychopharmacological practice, so the perspective that I have, clearly, the pre-ECT baseline assessment is critical.

I think some form of ongoing assessment during the course and then after treatment, from my perspective, is very important because we not uncommonly have the dilemma of seeing patients who are improving in their depression, their mood symptoms, and showing signs of cognitive impairment, and having a more quantitative assessment of that to interact with our ECT colleagues to decide how to continue treatment is really very crucial.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: I agree. I don't think we should dictate the tests. I mean, many things happen once you start dictating at that level, so there are numerous reasons I wouldn't want to specify a battery.

But I do feel that it's key, just like with the anesthesiologists, that we have a licensed, trained person supervising this component and it can't be a psychiatrist. They're not trained in cognition nor cognitive assessment.

UNIDENTIFIED SPEAKER: I disagree with that.

(Laughter.)

DR. BROTT: Yeah, I think I might disagree, too. Is there -- can you just tell us about the licensing and training of neuropsychologists --

DR. PAULSEN: It is what we licensed psychologists are trained to do.

DR. BROTT: Is this a national license, a state license, you know, a medical licensed -- in the state?

DR. PAULSEN: Yes, yeah.

DR. BROTT: Okay.

DR. PAULSEN: That's how the psychology licenses are given and you know, there's -- it's a Ph.D. program. They need to be supervising this methodology.

DR. BROTT: But the psychologist, neuropsychologist, what is the license?

DR. PAULSEN: All psychologists are trained in assessment. The specialty would be neuropsychological assessment, which also requires a fellowship.

You know, it's just like anesthesiology. I'm not saying, you know, just like I said, I can't do the ECT because I'm not a physician, but I also don't believe physicians are trained in cognitive assessment.

And we have multiple examples of why that would not be helpful, and it might be one of the reasons that the primary outcome problem with ECT is cognitive impairment because cognitive experts were not included in this medical practice and they need to be.

DR. BROTT: Dr. Anderson.

DR. ANDERSON: I do agree with Dr. Paulsen's point about the need for formal assessment. However, I have a question back to her about access. Is this going to limit access in certain areas of the country? Are there enough neuropsychologists available or psychologists available widely across the country where ECT is also being done?

DR. PAULSEN: I think there's just as many psychologists as there are psychiatrists and neurologists (a); and (b) we do work under a supervisory practice as do these other professions where you have certified nurse practitioners, physicians' assistants, and psychometrists who work directly under our supervision.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Let me start out by saying I have great respect for the field of neuropsychology and my colleagues who are neuropsychologists on the Panel, and I think I know when I need their help, and maybe I need it more often than I think, but in -- I think the kind of instances we're talking about in terms of ongoing clinical evaluation, I feel that my own training has certainly schooled me in doing a cognitive assessment. It's an essential part of what psychiatrists do, particularly geriatric psychiatrists, are formally trained. It's a key part of residency training --

DR. BROTT: What would you do --

DR. GOODMAN: -- to do cognitive testing.

DR. BROTT: Let me get specific --

DR. GOODMAN: Or whatever other tests are required but --

DR. BROTT: So you do the first --

DR. GOODMAN: But I would defer to those who do practice ECT, but there are psychiatrists who have developed various rating instruments, including myself.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: Just wanted to point out, the question as it read originally did not get into subspecialties that will be administering the monitoring of the cognitive status, so we will be happy if you would just -- in other words, you don't have to go down that road.

DR. BROTT: I hear you, Dr. Eydelman, but I think the Panel members have indicated that this is an area of importance with regard to discussion.

And in that regard, let's see, we've -- we have the -- Dr. Kim.

DR. KIM: Yes, I think that this issue, we don't want the best to be the enemy of the good, and that's what I'm concerned about because I would always defer to Dr. Paulsen for assessment expertise and psychological/neuropsychological assessment; there's just no doubt about that.

The question really is, if we require something, what's the tradeoff? And even in a busy, urban, academic hospital, I can imagine setting

certain standards will impact access and availability for patients who really need this treatment. So I can see that -- so it really --

DR. BROTT: Let me ask you, what do you think about something along the lines of standardize? We have the language that was independent of specialty, something along those lines.

DR. KIM: I think -- well, I would rather have it close --

DR. BROTT: In other words, wording --

DR. KIM: I think the wording should be something like close cognitive monitoring before, during, and after, rather than specifying the exact --

DR. BROTT: I'm a little worried with what I heard from -- this is my bias, I'm a little worried about the Folstein. You know, I'm not sure the Folstein's very good. And if that's what's considered to be -- you know, to be the cognitive monitoring, that doesn't --

DR. KIM: Right.

DR. BROTT: That doesn't reassure me with what we've heard.

DR. KIM: Can I respond to that?

DR. BROTT: Sure.

DR. KIM: So as I understand, this condition is trying to mitigate the risk.

DR. BROTT: Correct.

DR. KIM: So I would suggest that we need to obtain enough

information to alter the course of what we're doing during treatment.

DR. BROTT: Yes.

DR. KIM: I mean, if what -- for instance, the most important period is before, to assess if this person has cognitive impairment, and then during the six, eight, ten courses of ECT. Now -- and after that, it's kind of -- it's more of a monitoring --

DR. BROTT: Well, to see if they get better or worse. I do the Folstein all the time. I'm familiar with it.

DR. KIM: I understand that.

And I guess, on the point of exactly what should be done during those weeks, I'm going to -- I'm happy to defer to people who are willing to balance the burden of that task with the necessity.

DR. BROTT: Okay, Dr. Ross.

DR. ROSS: I would favor leaving the language just as it is. I would point out that psychiatrists are licensed to examine the mental status of patients, and mental status includes the cognitive function of patients.

And particularly in this context, it's the cognitive status in the context of the emotional status that is the severity of depression, delusions, and hallucinations which may interfere with the patients being able to answer cognitive questions, and so I think we'd do much better not trying to be overly prescriptive.

DR. BROTT: And these patients are on drugs.

Dr. Stebbins.

DR. STEBBINS: Yeah, I think, again, getting back to the point of just looking at cognitive function I don't think is specific enough. I think you do need to have formal testing of cognitive function. And I think those words alone would be sufficient.

You want something that you actually have documented within the patient chart that was done and what the status was both before, during, and after. I think who does it is probably not as important; it's more of an independent choice.

DR. BROTT: What do the -- those who have taken a conservative approach think of the insertion of the word formal?

Dr. Ross, what do you think of the --

DR. ROSS: Well, first of all, I don't know what it means and --

DR. BROTT: Well, maybe it means going a little bit beyond monitoring. It's formal monitoring. I mean, I think I have a feeling that it adds a little more weight to it. But maybe there's a better word you could come up with.

UNIDENTIFIED SPEAKER: Objective.

DR. BROTT: It doesn't -- objective. What do you think of objective?

DR. KIM: I think these words are actually difficult words, and I like the phrase as it is. I think you could say clinical monitoring.

DR. BROTT: Understood. Drs. Kim, McDonald.

We're not reaching a consensus here, Dr. Eydelman, but we're trying.

DR. EYDELMAN: You're free to move on.

DR. KIM: I think I might have understood something.

I think clinical monitoring doesn't seem sufficient because, you know, my kind of eyeballing a person could be considered clinical monitoring, and that certainly would be insufficient.

I think the actual -- it's like what I ask my residents, did you actually ask the patient, right. I think that's what you're getting at more, and I do believe that should be a part of the --

DR. BROTT: So how would you change the wording?

So you -- Dr. Paulsen, do you have a way to change the wording to --

DR. PAULSEN: I think the proper words are objective and standardized.

UNIDENTIFIED SPEAKER: One speaker at a time, please.

DR. PAULSEN: I'm sorry.

UNIDENTIFIED SPEAKER: Thank you.

DR. KIM: I'm not sure --

DR. BROTT: Excuse me.

Dr. Paulsen, you were cut off there. What was your

suggestion?

DR. PAULSEN: The words to detect any cognitive decline and particularly in something as sensitive as psychiatric patients who are on medication --

DR. BROTT: What's the wording?

DR. PAULSEN: -- and mood disorders are objective and standardized.

DR. BROTT: What do we think about that?

Dr. Duff.

DR. DUFF: I'd be interested to hear what Dr. McDonald normally does, sort of, in practice as far as monitoring. My concern about just asking is again, you're asking somebody who may be already impaired, how is your thinking. And what we know from patients with, you know, dementia is that sometimes they don't have very good awareness. But Dr. McDonald would normally -- you do.

DR. McDONALD: We don't use an MOC. We use the Montreal Cognitive Assessment. It gives us a little bit more.

And, you know, we've talked about it, and the problem is retrograde autobiographical memory, that's very hard to test for, and if you want to use some of those tests, you're talking about hours, and we've already talked about how difficult it is to engage patients. Patients start off psychotic, suicidal, catatonic.

I think formal cognitive monitoring is important, I think it should be there, it should be in the chart, you should be able to see it and go back to it. Patients should be asked how their memory is.

But you actually have to talk to the patient each time and ask them how is your memory and then have them describe what the problems are, and the families are usually with them, somebody has to drive them, and you get an assessment from the family.

So I think you could be too prescriptive, and I don't think it will really help much at all. Somebody really needs to talk to the patient and do a formal cognitive assessment at each visit. I wouldn't be prescriptive about what that is, but it should be in the chart, it should be --

DR. BROTT: Well, we have now the suggestion of formal cognitive assessment. What do others think?

DR. GOOD: I agree.

DR. BROTT: Dr. Peavy.

DR. PEAVY: One more comment.

We're focusing on memory. I'm still disturbed by that, the term memory loss, because it's just so common, and I think that there -- certainly, evaluate memory, but also attention and language. Attention and language could affect memory, all kinds of memory. Language, I say, because of verbal memory, and there's more evidence that anterograde verbal memory is more affected.

So I'm wondering if we could put something like those three areas plus -- or including those three areas.

DR. BROTT: It gets difficult. I'd like to see if we could get some consensus here.

I am impressed, myself, in looking at the literature, that if something is not done here, I think this can mitigate risk. And I'm really not -- this, to me, looks like what was written 20 years ago, and that's why we have what we have today, and that worries me. Dr. McDonald has suggested the use of the word formal. We've had the words standardize, objective.

Dr. Goodman.

DR. GOODMAN: I was just going to reiterate that. I was going to go back to your earlier comment, and I think you're right in reading the mood.

DR. BROTT: Could you repeat what you just said?

DR. GOODMAN: Yeah. I agreed with you, was my main point, including your earlier comment that I think we need to put a little bit more teeth into the language and to reassure the public that we're going to be as diligent as we can be in scrutinizing, looking for, and monitoring memory and other cognitive impairment, and we're going to do our best using standardized measures, certainly adjusting them according to the condition of that patient. But we probably -- I don't think we have time here, but it would probably be worth it to do a little bit more work, trying to delineate

what scales we would use under which conditions so that there would be a more standardized database.

But I completely agree with you that this language needs to be strengthened.

DR. BROTT: I think we are hearing consensus on that point, Dr. Eydelman, that we feel that the memory impairment and other cognitive impairments that we've read about and heard about from the public are sufficient to strengthen this particular statement.

Words such as standardize, objective, formal have been used, and we would like the Agency to consider that in this particular point with regard to mitigating cognitive and memory effects.

DR. EYDELMAN: Thank you.

DR. McDONALD: On the end of that, it should -- until, and until cognitive status returns to baseline.

So if a patient leaves a course of ECT and their memory is impaired, you should be following them out formally until it returns to baseline.

DR. EYDELMAN: Thank you --

DR. BROTT: Does anyone object to that additional language?

Dr. Gordon. And, remember, we have a lot of work to do, okay?

DR. GORDON: That's right.

I disagree with that partly because all measures have variability, and what constitutes return to baseline is going to be fraught with problems.

DR. BROTT: She does have a point. Is it okay to leave that out so we can go forward?

DR. GOODMAN: Yeah. And the baseline could be bad.

UNIDENTIFIED SPEAKER: Exactly. It could get better.

DR. BROTT: Yeah, okay. So I think we've covered that point.

Now, it's eight minutes to 12:00. Our next one is patient labeling requiring use of a checklist of all known risks of ECT with each item to be signed off by both patient and physician. I think we can cover that the next five minutes.

Oh, well. That's right. Should we -- not Number 6, but before Number 5. Can we move that to Number 5, Dr. Eydelman?

DR. EYDELMAN: After lunch we're going to have some more slides for you to -- to present to you.

DR. BROTT: So you would like to break for lunch now?

DR. EYDELMAN: Yes.

DR. BROTT: Okay.

Now, with regard to lunch, we're halfway through Question 3. Question 3 is not the most difficult question. We have three questions to go after Question 3. I think an hour is too long.

It's been stated that well, we have to check out and so forth, but I really think we can't take that much time. I would like us to try to get back here at 12:30 to get started.

Dr. Eydelman, you think that's too short?

DR. EYDELMAN: Yes, because if you say 12:30, that means all the people here will go to the inside restaurant because -- and I don't think it's logistical --

DR. BROTT: Well, how about 12:40?

DR. EYDELMAN: I recommend an hour.

DR. BROTT: You live here.

(Laughter.)

DR. BROTT: Yeah. Well, we won't get into that.

Let's compromise and try for 12:45. If we can get reconstituted at 12:45, we'll start then. If we don't have a quorum, we'll have to wait.

Thank you.

DR. McDONALD: Can I just make --

DR. BROTT: Dr. Goodman.

DR. GOODMAN: No.

DR. McDONALD: McDonald.

DR. BROTT: McDonald, excuse me.

DR. McDONALD: Just one comment for Dr. Park. The O'Connor study was an NIH trial; it was not randomized. It's a recent trial, so it wasn't

randomized.

DR. BROTT: And keep in mind, members of the Panel, not to discuss these proceedings during lunch.

Thank you.

(Whereupon, at 11:54 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(12:49 p.m.)

DR. BROTT: We're now ready to reconvene.

And we were on 3(b), requiring the use of the checklist and
Dr. Park, you are --

DR. PARK: Not ready.

DR. BROTT: -- not quite ready? Okay. Just give us a thumbs-up
when you're ready. You're first up, okay?

(Pause.)

DR. BROTT: I'll tell you what, this (b) relates to the item for
mitigation of the medical/physical risks, as well, which we agreed to defer.

So why don't we finish 3, if the FDA's in agreement, finish 3(c)
and then come back to the checklist for both the physical and the cognitive.
Is that agreeable?

DR. EYDELMAN: Yes.

DR. BROTT: Fine.

So we're going on to 3(c) and this, again, to repeat, this is a
potential regulatory control that FDA could apply to ECT to mitigate risks of
adverse cognitive and memory effects: (c) Requirement for further
premarket studies (either pre-clinical [bench, animal] or clinical) for
significant changes in device technology or new indication for use.

When this came up with regard to the medical/physical, we left

it to FDA to wordsmith whether it's significant or safety and effectiveness. With regard to cognitive and memory effects, let's see, I think we're up to Dr. Stebbins, are we? Or did we cover you already?

DR. STEBBINS: No, you haven't yet.

DR. BROTT: Okay.

So I think Dr. Stebbins, we'll ask for his input on 3(c).

DR. STEBBINS: I'd say that with the same caveats that we had for 2, I would agree with it.

DR. BROTT: Anyone disagree with Dr. Stebbins?

(No response.)

DR. BROTT: I'm seeing no disagreement with Dr. Stebbins. Do we all agree with Dr. Stebbins? Excellent.

So with regard to Question 3, Dr. Eydelman, we have decided as -- or we've come to a consensus, as a group, that (i) through (v) are not necessary and will not help mitigate adverse cognitive and memory effects.

We've provided input with regard to strengthening Point (vi) with regard to cognitive status.

We've deferred (b), and we've agreed with (c).

Does that provide adequate input for the Agency?

DR. EYDELMAN: Yes. And I believe that we're now ready to go back to form of consent information.

DR. BROTT: Fine.

So now this is consent information, and it has to do, basically, is both points under 2 and under 3.

Dr. Park.

DR. PARK: Thank you. First of all, just to show you a picture -- I know the resolution's not very good here, I apologize for that, but this is an image of the implantable miniature telescope, and I would defer to Dr. Eydelman for a brief description of that.

DR. EYDELMAN: I think we should proceed to the form of interest.

DR. PARK: Okay, there we go.

So this is the type of form that has been used in the past for Acceptance of Risk and Informed Decision Agreement. Again, this is for the IMT.

DR. BROTT: Excuse me just for a moment, Dr. Park. I noticed it says page 15 of 17. Can you give us just the context of the overall form?

DR. EYDELMAN: So this form -- this is Dr. Eydelman.

This form becomes part of patient labeling, so just to step back, because there was a lot of confusion I heard this morning, we have a choice as to what kind of labeling we issue. For some devices where we feel that the patient needs to be informed in addition to the information that's communicated directly to the practitioner, we mandate something called patient labeling, and then that would delineate all of the usually similar

information, but in a different language, in a language that can be comprehended by a patient.

So this form that's called the Acceptance of Risk and Informed Decision Agreement becomes part of the patient labeling, and as such, we can enforce its use. So, basically, we're telling the sponsors, the manufacturers, that for every device that you sell, you need to provide this labeling to each patient and then -- I mean, to each physician, and then each physician has to provide patient labeling to each patient treated with that device and, as part of that, has to go through this particular checklist. That's why the paging number because it's part of the whole patient labeling.

DR. BROTT: What are the first 15 pages, first 14 pages?

DR. EYDELMAN: Well, in this particular one, as I said, it's usually device description, what it is, what condition, and treats who it's intended for, what are the warnings, precautions.

As I said, it's the information that's very similar to what's usually communicated to the physicians, but it's translated -- we have a special office that actually translates it into appropriate level of communication to the general patient population.

DR. PARK: So this, as you can see, is at the end of that labeling, and I apologize that the text is pretty small here. The other one is better, right?

DR. EYDELMAN: Yeah.

DR. PARK: So it's entitled Acceptance of Risk and Informed Decision Agreement. There's a description to the patient: "This is the last step in deciding whether you want to have intraocular telescope surgery. This agreement lists important risks of intraocular telescope surgery. Please review this agreement carefully with your eye surgeon. You should sign this agreement only if you are satisfied that each risk has been explained to you and you understand and accept each risk. If you accept each risk and sign the agreement, it means that you have decided to have intraocular telescope surgery. You must accept each risk and sign the agreement before you can have intraocular telescope surgery."

And then to the eye surgeon: "Please review this agreement carefully with your patient. For each item, initial if you are satisfied that the patient understands the item and has accepted it. Your signature confirms that the patient has completed and signed the agreement."

Those are the instructions, and then it breaks it down by item. So these are the items.

DR. EYDELMAN: Perhaps you can just read one or two just to get a flavor.

DR. PARK: Yes.

The first one, "I understand that the intraocular telescope is implanted in only one eye. The eye with the intraocular telescope provides central vision. I will need to use my other eye for peripheral vision when I

want to walk around." Another one, maybe the bottom one, which talks more about an adverse event, "I understand I may experience double vision after intraocular telescope surgery."

And then this form actually continues to the next page. I think it's two pages in length there.

DR. EYDELMAN: And, again, to delineate, obviously the risks will be specific to the device, but I think this gives you a general flavor for how these things are constructed.

DR. BROTT: You know, these patients -- this is very ironic, but they can't read, most of them, so what's happened? I mean, how does it work?

DR. EYDELMAN: Right.

So as I said, it's -- first of all, we did go through the font of the printed material so it's maximized at contrast, et cetera, but there is a provision that this has to be read to them if they're not able to read it themselves.

So that would be equivalent to who gets to sign in ACT if somebody is not deemed competent to understand it.

DR. BROTT: Questions.

Mr. Mueller.

MR. MUELLER: Yes, Dave Mueller.

There's an assumption on the form. I didn't see it specified

that there is an implied benefit. It seemed to say it's all risk, all risk, all risk, and if you accept the risks, go ahead, you know, and have the surgery. But is there anything in here saying that there is potential benefit and I believe that the benefit will outweigh the risks and that's why I'm going forward?

DR. EYDELMAN: Well, again, this is part of the patient labeling, and the first 14 pages in this particular case goes through the clinical studies that have demonstrated the outcomes of a clinical study demonstrating, hopefully, safety and efficacy profile of this particular device.

So that's, by being page 15 or whatever, that's the understanding that they have read through or have been read to the first few pages where they understood what they're getting into.

MR. MUELLER: I agree, but I would just think have one -- I mean, for our discussions, I think it would be good to have at least one signature, one initial, saying I have read other clinical or whatever we have here, and I believe that the benefits will outweigh the risk.

DR. EYDELMAN: Again, this form is specific to the acceptance of risk. This does not negate the general informed consent document that's usually required and given by the psychiatrist or by anybody else administering it. That is intended to be an addition to, to delineate specific risks that the patient is agreeing to.

DR. BROTT: Ms. McElveen, would you want to comment? Any legal aspect with regard to a patient signing upfront about risk/benefit?

MS. STOKES McELVEEN: I think that what's clear is that as long as it's explained in detail and the individual understands the nature of what they're agreeing to, it's acceptable. Again, this is just a checklist and there is another -- it is accompanied by another form specifically that would address the risk/benefit analysis.

DR. BROTT: Okay.

Was there anything else from the FDA before we proceed with the question?

DR. EYDELMAN: Just to say that the breast implant is very similar, and this one projected better.

DR. BROTT: Dr. Domino.

DR. DOMINO: Karen Domino.

I just had a question. So the beginning pages, what is it, up to 15 or so are an explanation of -- that the patient would also receive in addition to the standard informed consent process, they would have the explanation of efficacy and potential safety in that? This is stuff we skipped over.

DR. EYDELMAN: Again, this form is called Acceptance of Risk and Informed Decision Agreement. The understanding is -- I'm sorry if I'm being repetitive, but perhaps I didn't understand the nuance of your question, but the understanding is that the practitioners that administer the ECT will go through the usual process that they have been up to now to

obtain the normal informed consent. So this would be in addition to and would allow assurance that the patient actually understood each risk that could potentially be associated with this device.

DR. BROTT: Dr. Ross.

DR. ROSS: I'm just a bit concerned about patient burden again. You've got a 15-page explanation --

DR. BROTT: Seventeen page.

DR. ROSS: Sorry, 17-page explanation before this. We already do, at least in our practice at Hopkins, we already do a long and complex consent form, which is several pages long and lists risks and benefits already. These patients are often depressed, very difficult to mobilize. I'm just concerned that this is going to be a lot of burden for the patients.

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: Obviously, I defer the decision to the Panel, but what I wanted to point out is that if this gets accepted, this becomes standard for all of the ECT, and then the informed consent forms that the institution or each practitioner chooses to form could theoretically be adjusted to eliminate this not to be redundant.

DR. BROTT: Okay, let's try to tackle this, and I guess I'd ask that you turn back to Question 1 because that's where those key risks are. Okay, so can we have Question 1 up on the slides, (a) through (n)? And remember, we took out (n), and we recommended a little modification of a couple of

these.

But, first, the general issue of the checklist. Maybe we could tackle the general issue first, and I think we're with Dr. Stebbins again. Do you want to give us your opinion as to whether or not you think that the form that we saw or something like it is something that we would recommend to the FDA for ECT?

DR. STEBBINS: Yeah, I think that it's an important addition that would allow patients to discuss, again, give them sort of a formal opportunity to discuss this with their physician.

DR. BROTT: I'm going to ask Ms. Carras' opinion.

MS. CARRAS: Thank you. Michelle Carras, Patient Representative.

There are some guidelines provided by the National Institutes for Clinical Excellence on a better, what I consider to be a better informed consent procedure. I believe they do use a checklist, and they do reference patients' feeling of coercion contributing to a sense that there was not fully informed consent, so I support anything that will better regulate this.

DR. BROTT: Thank you.

Dr. Domino.

DR. DOMINO: I also am in support of a checklist. I think there are obviously areas of centers and physician practices that are excellent, and not everyone practices in a good standard, and this would allow, I think, to

reduce some of the variation and ensure that those who don't get adequate or don't have that adequate discussion in the informed consent process with the patient now would, at least, begin to touch upon these possible side effects and complications.

DR. BROTT: Do we have anyone who is opposed to a checklist?

Dr. Anderson.

DR. ANDERSON: Well, I appreciate that this would help to standardize it. I do think it would add to patient burden, as it has been said before. I think most institutions will want to keep their own language, so I don't think that will be allowed to replace part of the consent form from the institution with a checklist.

And another question I actually had is, we have our list of potential risks, but it's kind of hard to develop a checklist not knowing what the final language would be, and I don't think our task today is to develop the language for the questions.

DR. BROTT: Well, our task is to advise the FDA. We're not constrained in terms of the advice that we choose to give them.

DR. ANDERSON: Right, but for some of these, I think that the wording could be very lengthy, the wording might be potentially frightening to patients, so I have concerns about the wording.

DR. BROTT: More comments on the checklist?

Dr. Duff.

DR. DUFF: Just a brief comment.

You know, we had talked that if a patient is deemed incompetent or unable to sign the consent form, that a family member or some other designated individual could sign it for them. In research, when we encounter something like that, we also get assent from the patient where there would be some opportunity or some way of trying to gain that.

Some of the stories that we heard from the public were that they felt that they were sort of sent there by family members and that they had no control and -- or have there been instances like that in the past --

DR. BROTT: Yeah, let me ask Dr. Eydelman.

How long have the two checklists been in -- how long have they been out there? And what feedback have you had with regard to Dr. Duff's question?

DR. EYDELMAN: The IMT is out there about a year. The breast implants, do you have the year? We have to look up, it's about -- it's a couple years. So we can look up the exact year. It's less than five years, I can tell you that.

No, we did not hear anything to that effect so far.

DR. BROTT: And do you have any idea in terms of how many of the checklists are signed by the patient themselves or herself versus their legally authorized surrogate?

DR. EYDELMAN: I don't have statistics on that.

DR. BROTT: Do you have data that you haven't yet compiled?
In other words, do you have the ability to answer that question?

DR. EYDELMAN: Not readily.

DR. BROTT: Dr. McDonald.

DR. McDONALD: I think I agree with the patient burden, but even more than that, I'm not sure why ECT is being singled out for this. This is a procedure in which the patient has to be adjudged to be competent, that's one of the most important parts of the procedure, that they truly understand what the risks and benefits are. I don't think a checklist really does that. It will just get checked off. If someone wants to just run somebody through, hand them a consent and have them go on with it, they will.

We have a two-page consent form, the APA has a model consent form. If there's some reason after a couple of years ECT is being singled out for this, there are a lot of dangerous procedures in which we should have concerns about whether consent is being done, but why ECT?

DR. EYDELMAN: So I can address that. Dr. Eydelman.

As I mentioned before, we're trying to explore that option for devices where we hear from the patients that they have a significant concern that they underwent a procedure secondary to device intervention and did not feel that they were adequately informed. And from the public docket, that certainly was an issue that was raised over and over again, and we're

trying to come up with the best way to proceed.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Yeah, I partially sympathize with Dr. McDonald's point of view, but I think, to the degree that I share it, it's from the perspective of living in an academic medical center.

So I think what we're trying to do is make sure that there's at least a baseline level of standardization and coverage of possible risks as well as attempts to mitigate them across all centers independent of where ECT is being conducted. So for that reason, I support this.

I did have a question, and I think you said it, but I want it clarified, would a more detailed IRB approval for a consent form or some other hospital-based consent form supersede this, or would both have to be filled out, both be completed?

DR. EYDELMAN: Both would have to be completed because they're regulated by two different authorities.

DR. BROTT: Let me throw something out for discussion.

You know, we -- the point made about other procedures is certainly true with regard to major, life-threatening procedures that go on in medicine every day.

On the public docket within the literature that's been presented to us, in the reviews and in the guideline statements, concern really is focused around the cognitive and memory areas. While we agreed

that (a) through -- now it's (m) -- we agreed with those as key risks. I think, from everything that we've heard, they're in a different, really, category than these other things.

Would the Panel members, do they have ideas or input in terms of how to supplement or bolster the consent process to see that that major concern is confronted by the patient and their family?

Dr. Kim.

DR. KIM: Yes.

I agree with the point you made, exactly. I'm not so concerned about patient burden because a good, informed consent process, as described by one of the clinicians already yesterday, would involve a lengthy discussion of each of these points, anyway. So I'm not worried about that.

What I am concerned about is having a checklist of all, you know, how many items because it raises a question for whom are we doing this. If our concern is truly for the patient's benefit, then we should be emphasizing the key points that have recurred in all the docket items and in the history of this procedure, and that points to what you just said.

I think it has to do with cognitive impairment and memory issues. And by singling those things out, perhaps, for checklist, if we go that direction, I think that would be a very responsive -- and also, it points out that those are special items of concern because I actually am very sympathetic with what Dr. McDonald said for all these other items.

I mean, no other -- I don't understand why the usual risks of anesthesia would be singled out and you have the checklist. And what that's going to do is dilute the importance of those two items that we think are especially important.

And we all know that the practice of informed consent becomes writtenized [sic] and perhaps even trivialized the more we have a longer list of things. So I think that if our concern is for the patient's benefit, what we need to do is to sort of process this a little further and do what -- the kind of suggestion I think you were making.

DR. BROTT: Earlier, Dr. Peavy attempted to break down memory dysfunction and -- cognitive and memory dysfunction.

Do our neuropsychologists have an idea for a checklist with one or two or three items that could focus on this area of major concern among the patients and seen in the literature?

Dr. Peavy.

DR. PEAVY: It seems like to start with the areas that we have more evidence concerning memory, and so that would be the retrograde personal memory and the -- maybe anterograde, and to put it in language that the patients would understand.

And I guess, you know, to say that these are the things that people have the most problem with or complain about the most.

DR. BROTT: Is this something that we could leave to the FDA to

work on, to come up with one or two or three considerations focusing on this area?

Dr. Goodman.

DR. GOODMAN: I just want to say I want to strongly endorse Dr. Kim's point, particularly regarding kind of defeating the purpose of this, which is to dilute highlighting the main side effects. I think I would revise my own comments on this, that I think there should be a checklist, but it should be emphasizing the memory dysfunction in language that's understandable.

It could also be one, two, at most three other items that refer, say, to the set, the constellation, of symptoms that might be associated with anesthesia, maybe some other unknown risks, but not to have so many items that it gets lost in the details. Because then we'll be missing the point of these deliberations.

DR. BROTT: I think the point made about anesthesia, though, is a good one.

Dr. Ross.

DR. ROSS: Yeah, I think I'm beginning to understand the thought behind this, and I think if we do focus on what's specific to this particular device, it makes much more sense.

I would suggest, though, that the checklist had something like many patients don't have any -- or don't have substantial difficulty with memory; many patients do have substantial difficulty with memory; and

there is a subset who are very bothered by this difficulty with memory.

In other words, I don't think it's so important to delineate the neuropsychological subsets of the memory that are important, but to just give patients a sense of the range of possibilities. Some people don't have much trouble, most people have some trouble, but a small percentage have a really significant amount of trouble and that that's -- I think that's what we really want to get across.

DR. BROTT: Ms. Carras, what's your response to that?

MS. CARRAS: I agree entirely that some measure of subjective distress should be discussed very clearly and checked off by the patient.

DR. BROTT: What about that -- well, that's fine.

Dr. Stebbins.

DR. STEBBINS: I like the idea of focusing on these issues. However, I think one of the problems is we don't really know what the effects are, particularly long-term effects on memory. So I think that to try and say, you know, only a few patients have it may not really be accurate because we don't have that information.

DR. BROTT: Well, let's say, in doing consents over the years, we often don't have that information, which is why, for instance, it's infrequent in consent forms to see numbers, and our biostatisticians would -- they would not like that, but the reason we don't have numbers in consent forms is we don't usually have precise information.

Dr. Domino.

DR. DOMINO: Karen Domino.

There is a movement regarding shared decision making as a better way of the informed consent process, and this does rely on some interpretation of the literature with use of numbers in terms of success rates.

They can, of course, be argued whether the study is definitive, but the FDA's, you know, presented us with some information that could be distilled and put in that with references in that, and so that movement is trying to take down to the consumer, you know, some estimate of whether the procedure is effective and what the estimates of risk are.

DR. BROTT: Thank you.

Do we have agreement that a checklist would be acceptable if it included three or fewer items and focused on the concerns of patients and those concerns identified by the FDA?

Ms. McElveen.

MS. STOKES McELVEEN: Francine Stokes McElveen.

My concern is that, as a litigator, if, in fact, I represented a client who had come for treatment and goes to a physician who is so-called qualified and at some point I ask the question what are the ramifications of my using this device and you say well, predominantly, we find -- and you talk about memory and a few other things, later, when some other adverse event occurs, my number one question is why didn't you disclose to my client the

other possibilities that were out there that you were aware of?

DR. BROTT: But remember, we only have a checklist. In all of medicine, we've heard a checklist for two procedures, so this is really the practice of law today.

MS. STOKES McELVEEN: But my concern is that we who are aware of other conditions, what difference does it make if there's a mere checklist or a paragraph that clearly discloses all the possibilities that exist?

When you get a prescription, you get this little folded piece of paper that comes with the prescription, you open it up, it's ten pages long, but it tells you all the necessary conditions, everything you need to know about that particular medication.

And I'm saying that the patient has a need to know and that's what informed consent is about.

DR. BROTT: What if those things were included in the information that came prior to the checklist?

MS. STOKES McELVEEN: What is important is that the information is made available upfront before the patient makes that decision to utilize the equipment.

DR. BROTT: It's my understanding that that's what, in fact, these forms are designed to do. Is that acceptable?

MS. STOKES McELVEEN: That would be acceptable.

DR. BROTT: Do we have someone that's not in agreement with

that?

Dr. Eydelman.

DR. EYDELMAN: Just to clarify or expand upon the point, the whole purpose is to make sure that each one is understood, so by saying it was someplace else but I didn't sign for it, there is a little bit of discrepancy between that logic.

I mean, you can make the list short if you keep it vague, in other words, have more broad, encompassing terms. But to have a list saying Acceptance of Risk and Informed Decision Agreement, if you don't discuss the most severe risks, then it's --

DR. BROTT: Well, I think the Panel is not agreeing with you on that, and I think that the Panel made some very good points. Death is really not a realistic risk of this procedure in comparison to other procedures in which general anesthesia is used, yet it's the most severe.

And, you know, I think that's what I'm hearing from the Panel, and I also would agree with the Panel members, if we put 50 risks up, the three that are the most important, or the four, will definitely be diluted, particularly in this patient population.

Dr. Domino.

DR. DOMINO: Karen Domino.

I was just going to say many of these can be grouped into one set of categories in terms of anesthetic risks that includes (a), (b), (c), (d),

perhaps (e), death; certainly, dental/oral trauma, pain, somatic discomfort, physical trauma, pulmonary complications. You can even potentially put in skin burns, although it's not an anesthetic thing but it's related to the procedure, itself.

DR. BROTT: I'll just press you a little bit. Do you think that ECT, this should be separated off for ECT as opposed to other things that you do?

DR. DOMINO: No, I do not. But I think, because of the political context of this device, I think some type of guarding to make sure that the informed consent process occurs in a better way is helpful. I don't think you have -- oftentimes a standard consent form will detail many of these things in a single paragraph. It's not in a checklist form.

DR. BROTT: Would you be agreeable to, let's say, two categories, procedural and cognitive?

DR. DOMINO: Yes.

DR. BROTT: Does that seem reasonable? And we can have the FDA work on that, procedural and cognitive.

Dr. Ross.

DR. ROSS: Yeah, I think that's a great suggestion, and I think, particularly, if the cognitive had the kind of language that I just mentioned where it includes the minority of patients who have serious concerns about it and then you could lump, essentially, all the other things into one category and then it would be a simple checklist and it would be clear and wouldn't

dilute the --

DR. BROTT: Does anyone have any objection to mention of this minority concern that Dr. Ross has now mentioned on two occasions?

Ms. Carras.

MS. CARRAS: I just don't feel that we have adequate data that describes that a minority of patients have lasting effects or don't have lasting effects because it hasn't really been looked at.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: Yeah, I think it's the same point. We really don't know, so I don't think we can say.

DR. BROTT: So the procedural and cognitive is agreeable to you but not get too -- not try to get too specific?

DR. STEBBINS: Yeah, not try to break it down as to how often it happens.

DR. KIM: Mr. Chairman.

DR. BROTT: Dr. Kim.

DR. KIM: Could you clarify, what we're agreeing to is under the procedural category, we're recommending against having ten different checks under that category, right?

DR. ROSS: One check for ten different things.

DR. KIM: Okay. But under cognitive, I think we could have more than one, perhaps up to two. That's what we're talking about.

DR. BROTT: Remember, we're not deciding anything. We're providing our feedback and --

DR. KIM: I understand that, but --

DR. BROTT: Right.

DR. KIM: -- it sounds like we're deciding.

DR. BROTT: Yeah. That's certainly my understanding.

DR. KIM: Yes.

DR. BROTT: Do the other members of the Panel agree with Dr. Kim's interpretation?

DR. KIM: But I'd like to add one thing.

DR. BROTT: Uh-oh.

(Laughter.)

DR. KIM: Yeah.

Within one of those two cognitive checks, and I would like to echo what Ms. Carras stated, which is that I think it's reasonable to insert, in one of those two, that some patients find these cognitive impairments very distressing. I think that's already part of --

DR. BROTT: Yeah, I be surprised -- Ms. Carras, are you agreeable to that?

DR. KIM: Yeah, I think --

DR. BROTT: I think I heard something a little different with your response.

DR. KIM: I think her phrase was subjective --

DR. BROTT: Are the Panel members in agreement with Dr. Kim on that point?

COURT REPORTER: Ms. Carras, I didn't hear your response. I'm sorry.

MS. CARRAS: My response was yes.

COURT REPORTER: Thank you.

DR. BROTT: Does anyone disagree with Dr. Kim's suggestion?

(No response.)

DR. BROTT: Dr. Eydelman, we've addressed the checklist request, and the Panel is in consensus that a checklist is appropriate but that it should be designed so those considerations of greatest importance from the literature and perceived to be of the greatest importance by the patients are focused upon by the checklist.

Our specific recommendation is to have two categories in this checklist, one related to the procedural complications that we have discussed and the other to the cognitive complications that we have discussed.

Is that acceptable?

DR. EYDELMAN: Thank you for your recommendation.

DR. BROTT: Number 4. Could we have the FDA?

LCDR CUNNINGHAM: Question Number 4. Regarding neuropathological changes, the manufacturer and public docket both

indicated “brain damage” as a potential risk associated with ECT. However, FDA's review of the literature did not identify evidence of gross anatomical, histological, or immunohistochemical evidence, or evidence from biomarkers of injury, to support this association. Please discuss whether the existing clinical data support brain damage as a potential risk of ECT and, if so, how this risk can be mitigated.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: I agree that the existing clinical data does not support brain damage as a potential risk of ECT. I've reviewed the packet that Mr. Moxon provided us. I agree with the summarization made by Dr. Ross this morning that there's no evidence in that packet for brain damage.

I also reviewed the data in the literature review that was provided by the FDA pretty carefully, and I don't agree that there's any clinical data to support that brain damage occurs as a result of ECT. So I don't believe that we need to indicate brain damage as a potential risk associated with ECT.

DR. BROTT: I would ask you, and this relates to a comment earlier this morning, if, in fact, brain damage did occur in the setting of ECT in some patients, do you think that the studies carried out would've been sensitive enough to detect it?

DR. PAULSEN: Back to me?

DR. BROTT: Yes.

DR. PAULSEN: I do think the research is particularly old. I don't think they have sufficient research using the latest, greatest techniques. I think, given the data that we've been presented, there is no evidence. I think we don't know if there may be evidence of this using more cutting-edge techniques, but I don't think we have any indication that that exists with the current data.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: I more or less agree, although there are some troubling little studies here. The hypertrophy and the hippocampal region, the increased white matter, there's some PET studies and some spec studies showing hypo-metabolism in the frontal lobes long-term. I don't think there's definitive answers out there as to whether or not there's brain damage, but it looks like there are some changes that occur in the brain following ECT that have not been explained.

DR. BROTT: Dr. Good.

DR. GOOD: Yeah, essentially I agree. I think the problem here is the terminology brain damage, what brain damage means, and I think in the public docket and the general public, some of the memory loss might be interpreted as "brain damage." And I think most of us, as scientists and clinicians, would have a different interpretation of what brain damage is.

But I don't think there's any evidence of anything we've seen here that really suggests what I would call, as a neurologist, brain damage. I

don't like the idea that people are getting seizures, but I don't see any evidence that it's harmful based on what I've seen so far. But it is an area for rich research going forward.

DR. BROTT: Ms. Carras.

MS. CARRAS: I'm wondering if there have been any lawsuits related to people who have claimed brain damage.

DR. BROTT: Is Mr. Moxon still here?

MR. MOXON: Yes.

DR. BROTT: Mr. Moxon, could you address that question?

MR. MOXON: Yes, there have been a number of lawsuits. In fact --

DR. BROTT: Could you identify yourself?

MR. MOXON: Kendrick Moxon.

MECTA Corporation was sued six times. Each of the lawsuits asserted brain damage. They settled most all of them. None of those were reported to the FDA, by the way, directly contrary to the regulations requiring them to report adverse effects. And the expert opinions in each of those cases did find -- give evidence that there was brain damage.

DR. BROTT: Thank you, Mr. Moxon.

Other comments? Dr. Goodman.

DR. GOODMAN: Yeah, probably just reiterating some of the other comments and repeating myself a little bit, but yes, there's evidence for

brain changes, as mentioned before, with ECT, animal models, some from humans. There is certainly evidence for brain changes with chronic administration of antidepressants. There's also evidence of structural brain changes with learning, behavior therapy.

So there's a growing recognition that the brain is more plastic than we thought and so that we want to be careful not to misinterpret neurogenesis, changes that are associated with the therapeutic effect with damage which implies a loss of function or deterioration in function.

That said, I think there was at least -- this is a different category, but mention of rare cases where somebody might have an aneurism and they're hypertensive. But that, I think, falls into a different category and it's not what we're generally speaking about here.

DR. BROTT: Dr. McDonald.

DR. McDONALD: I would support that. I think there is evidence of brain changes but not of brain damage, certainly the way it's thought about, and I think that there's no data to support brain damage.

DR. BROTT: Dr. Duff.

DR. DUFF: Just briefly.

I mean, the changes in cognition have to represent something. I don't know that we can identify it the same way that we would a stroke or a head injury, but -- and maybe it's that we don't have the technology yet or we don't have the studies, but there's something to the --

DR. BROTT: Yeah, as a neurologist -- Dr. Good made his comment as a neurologist, and as a neurologist, I would say if someone came to me and said how would you design a study to detect changes in the brain in association with x seizures per year or 2x or 3x or 10x, I certainly would have done something different than what we've seen, and I think the evidence, even for brain change of any kind, is very minimal.

And I guess I would, as Chair, take the prerogative to challenge psychiatry, as a specialty, with 100,000 of these procedures being done every year, to do more to answer the questions that have been raised in the public docket, in the literature review, and by this Panel with regard to structural and electrical changes in the brain. We don't have good biomarkers, but we do have good structural measures of the living brain.

Dr. McDonald.

DR. McDONALD: That research is ongoing, and we would appreciate your support. There is research that's looking at where the brain changes occur that are related to memory, where the brain changes occur related to the therapeutic effect, and there are actually studies being done to try and limit those areas of the brain.

Psychiatry is concerned about this as any other specialty, and there is active research that really holds some promise. The magnetic stimulation therapy is a form of creating a seizure, but the seizure doesn't tend to generalize. So you could, perhaps, target the area where you think

you can have a therapeutic effect and stay away from the areas where there's a memory effect.

So psychiatry is very concerned about this. There is ongoing research. It wasn't presented, but I don't know that it would have been appropriate to have presented it. But it's a very active area of research and I -- you know, Dr. Park, to his credit, has come when we've given presentations at the APA and other groups to learn more about the types of research that's ongoing.

DR. BROTT: Thank you.

We haven't heard from our biostatisticians on this point. Can we have an opinion from the biostatisticians on this question?

DR. ELLENBERG: I have nothing to add to what's been said in the last discussion, thank you.

DR. GORDON: An important parameter predicting damage is always a risk exposure and the greater number, greater power, differences in -- all point in the direction of greater damage. We have virtually no solid data on memory deficits, other cognitive function at more than six months and a year.

I do not know what proportion of all patients receiving ECT therapy are on maintenance therapy, but it's my sense, having not seen anything from the FDA, comprehensive summary of literature, that we know a widge about long-term exposure.

So I would give this area a zero, and I would defer on our ability to say anything about safety in the absence of studies, in the absence of data. I think we should back off.

DR. BROTT: That was Dr. Gordon.

Any other comments on this question?

(No response.)

DR. BROTT: I think the consensus, Dr. Eydelman, is that the Panel has examined all the evidence that's been presented to them and that they have a consensus that there is not evidence today that's compelling that ECT is associated with brain damage. I think the Panel has expressed that the term brain damage is not particularly precise and is open to different interpretations.

I think the Panel not only has concluded that there's very little evidence to suggest brain damage, but there's also not great evidence to indicate brain change, and that the studies that have been done, to date, have not answered the question as to whether or not there may be instances of brain damage which have gone undetected.

Does that answer the question?

DR. EYDELMAN: Yes, thank you.

DR. BROTT: Number 5, FDA.

LCDR CUNNINGHAM: Question Number 5. Currently cleared IFUs, or indications for use, for ECT devices include the following:

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- a. Depression (unipolar and bipolar)
- b. Schizophrenia
- c. Bipolar manic (and mixed) states
- d. Schizoaffective disorder
- e. Schizophreniform disorder
- f. Catatonia

Please provide your overall recommendation for the classification (Class I or Class II) of the ECT device for each of the above indications. I'm sorry, Class II or Class III. Of the ECT devices for each of the above indications. I was thinking Class I.

DR. BROTT: So --

DR. EYDELMAN: Just to clarify, we're only discussing Class II and Class III.

DR. BROTT: Dr. Duff.

Oh, excuse me.

DR. GOOD: It's okay. Wasn't there a new Number 5 that we discussed --

DR. BROTT: We actually took care of that.

DR. GOOD: We're okay? All right.

DR. BROTT: We took care of that. This is the final question.

Dr. Duff.

DR. DUFF: So regarding depression, unipolar and bipolar, feels

like that the majority of the evidence that we've heard would support for a Class III still, is my opinion.

DR. BROTT: Do we have comments from other members of the Panel? Hang on.

UNIDENTIFIED SPEAKER: Sorry.

DR. BROTT: Who would like to comment?

Dr. Ross.

DR. ROSS: I'm sorry, but I'm still not 100 percent clear on what is going to be the significance of the distinction between Class II and Class III, and I would ask for further clarification on that point. I'm sorry, but this is a key question, and I need some clarification on that.

DR. BROTT: Dr. Eydelman, could you address this -- you addressed it previously in response to Dr. Ellenberg. Could you also give us some timeframe estimates, as well?

DR. ROSS: Also -- I'm sorry. Maybe some examples of other Class II and Class III devices. I know there were some in the Executive Summary, but just to kind of get us all oriented.

DR. BROTT: Yeah, a device that was changed from III to II and a device that was maintained at III.

DR. EYDELMAN: Okay, I'm going to defer to you on examples because I'd like to pull up the years, and I'm sure my staff is going to do that shortly.

But to summarize what I was trying to address this morning one more time -- and yes, I'm going to refer to slides that are in your packet. So if you look back to the slides that were presented by Marjorie Shulman yesterday morning, just wanted to make sure that you're aware that all the definitions are in that presentation.

So Slide 11 has a description of Class II and Class -- Slide 11, I'm sorry. This is from the morning presentation, not the afternoon presentation. There were two -- right. There were two -- okay.

DR. BROTT: Does everyone have the morning packet so you can follow along? The second slide has Ms. Shulman's name on it.

DR. EYDELMAN: Can you pull them up, actually?

DR. BROTT: Dr. Goodman, do you have it?

DR. EYDELMAN: Perhaps, actually, better than my paraphrasing, I can ask -- you can pull them up? Okay.

All right, so here is, once again, the definition of Class II, and the next slide talks about the special controls. And then the following slide has a definition of Class III, to suggest there's a background. I know that wasn't the question, but I want to make sure that everybody knows what these definitions are.

And then -- Dr. Ross, let me just finish, if I may. And then, if you can go back to Slide 4, actually.

Marjorie, is that the best slide?

MS. SHULMAN: I'm sorry, Marjorie Shulman.

For the timeframe, is that the question?

DR. EYDELMAN: No, just go through the actual what happens, how it gets reclassified, then I will --

MS. SHULMAN: For what happens now. If --

DR. BROTT: What will happen -- Dr. Duff has made the recommendation that ECT for depression remains Class III. What are the implications for that and with respect to what will happen and over what time period?

MS. SHULMAN: Okay. Marjorie Shulman.

We would put a proposed regulation in the Federal Register saying that this remains a Class III device and we'll be calling for PMAs. There would be a certain amount of time, probably 30 months, for the companies to submit the complete 510(k). If the 510(k) application --

DR. BROTT: Is it a 510(k) or a PMA?

MS. SHULMAN: I mean PMA, sorry. I'm on the 510(k) staff, I forget. To submit the PMA.

If the PMA is fileable, meaning it has all the needed information to be reviewed, the company can remain on the market. It does not have to be approved. And at that time if the PMA is not submitted or it's not fileable, they would have to come off the market.

DR. BROTT: Dr. Park, could you tell us, estimate, what type of

clinical information would have to be submitted for a PMA for depression?

DR. EYDELMAN: No.

DR. PARK: No.

(Laughter.)

DR. EYDELMAN: It's a comprehensive question. It's not an easy one to question --

DR. BROTT: Certainly, it is. Do you wish to try to answer it because that was the question of the Panel.

DR. EYDELMAN: The PMA has to provide sufficient safety and effectiveness information to warrant its approval. So what kind of a clinical trial would be required in that submission, if that's your question, I don't think we're ready to answer that question.

DR. BROTT: Dr. Ross.

DR. ROSS: Actually, two questions, I guess.

So when you talk about special controls in a Class II device, that would include the kind of things we were just discussing, like the checklist, regarding the effects of the instrument; is that right?

DR. EYDELMAN: The informed consent can be either for Class II or Class III. As a matter of fact, the IMT example that we used is a Class III device, and that is incorporated in the patient labeling of a PMA.

DR. ROSS: But, I mean, just in terms of the terminology, special controls could include that kind of checklist --

DR. EYDELMAN: Yes.

DR. ROSS: -- is that right? Okay.

And then when you say a clinical trial would be required, in other words, what you're saying is the previous evidence would not be sufficient on its own, and you would require, and as I understand it, for a device it's one single definitive clinical trial; is that right?

DR. EYDELMAN: It is usually one single trial. I did not say that it would have to be of new data. I said it would have to demonstrate safety and effectiveness.

It is up to the Panel to recommend whether a retrospective analysis should be entertained by FDA, in other words, whether it's something from historical data, something "paper PMA," in other words, gathering -- if there's a way to pull together information known in the literature about ECT devices in a scientific manner to assess its safety and effectiveness.

So for a particular device -- now, if a PMA goes to a particular device in question, that could be entertained if that's the Panel's recommendation. So we're interested in your recommendation, but we're not ready to commit to what it will require.

DR. ROSS: Thanks very much for answering that question.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: So from the way this question is formatted,

could you have a Class III for depression but a Class II for schizophrenia, for example?

DR. EYDELMAN: Yes.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: I want to make sure my assumptions and interpretation are correct.

So if the Panel says, recommends, that for major depression, ECT should remain a Class III device, that means that we do not feel that there's sufficient evidence for its efficacy or effectiveness or safety and that special controls are insufficient to ensure, particularly, safety?

So it's -- to make a sure way for anyone to say that ECT should remain a Class III device for major depression means that they are not convinced that existing data support efficacy or effectiveness.

DR. BROTT: Dr. Park.

And, Dr. Eydelman, can you answer Dr. Goodman?

MS. SHULMAN: Marjorie Shulman.

DR. EYDELMAN: I defer to --

MS. SHULMAN: I'm just going to say that the first part is not necessarily true. It's not that we're not saying that it's not effective. We're saying that there are risks associated with it and the special controls, that list by themselves, such as guidance documents, tracking, and postmarket surveillance, labeling, cannot mitigate those risks.

DR. EYDELMAN: If I can just paraphrase. This is Dr. Eydelman.

What we're trying to say, is there sufficient information about all ECT devices such that we can write special controls that will be able to control each ECT device that's going to come on the market from now on? As opposed to PMA, its assurance of safety and effectiveness of each device on its own. Does that help?

DR. GOODMAN: By indication? Intended use, by intended use?

DR. EYDELMAN: Yes.

And just to clarify, in some other device arenas, we've even split by whether it was primary intervention or secondary, whether it's end stage or not, so -- yes, you can be as specific as you want in the indication.

DR. BROTT: Another question.

There are devices that are Class III that are approved as Class III and then another device that is a predicate device but is yet Class III; in other words, it's very similar. For them to be approved, they have to do a PMA, correct?

DR. EYDELMAN: Okay, predicate only applies to Class II.

DR. BROTT: Fine. A similar device for the similar part of the body, okay?

DR. EYDELMAN: The definition of Class III means that for each device of that type, they need to come in with a PMA.

DR. BROTT: Right.

DR. EYDELMAN: But I have answer to your previous question of recent reclassification from III to II. It's PTCA catheters and spinal cages are the most recent examples.

DR. BROTT: And were they reclassified?

DR. EYDELMAN: From III to II.

DR. BROTT: Okay.

DR. EYDELMAN: That was your question, I believe.

DR. BROTT: Right. On this one, what I'm wondering is we have two machines; they are Class III. They've been grandfathered in as Class III, and how would this impact those as opposed to future?

DR. EYDELMAN: Okay. Let me recap what I was trying to -- I'm going to be redundant, but just because there's so much confusion, I'm going to try to say it one more time.

DR. BROTT: That's a pejorative term, okay.

DR. EYDELMAN: Thank you for that clarification.

For Class -- if FDA decides to classify ECT as Class III devices, the PMA would be called for. What that means is for both the devices, for any device that wants to be marketed in the United States, a PMA application would have to be submitted and approved by the FDA in order for it to be on the market. Now, any device. That includes the devices that are currently on the market and the devices that will come in the future.

For the devices that are already on the market, we will do

something like grandfathering that, i.e., allowing them X amount of time, perhaps up to 30 months, to put together their PMA applications and submit it and not do a regulatory action.

In other words, we would not deem them adulterated and misbranded if it's three months after the decision was made that they need a PMA. We would give them some time during which time they would be allowed to continue to market the device while they're putting together the application. I hope --

DR. BROTT: I have a question for a psychiatrist with regard to depression. Within the profession of psychiatry today, what would ethically acceptable clinical studies of ECT and depression be like in general terms?

Dr. Goodman.

DR. GOODMAN: Well, first I don't think that they're necessary, at least for demonstrating efficacy. If we were starting from scratch, they would be sham-controlled and include some of the other safety assessments we talked about.

Can I just go back to -- I want to make sure I understand what the implications are of our decision here. So let's assume we leave ECT Class III for unipolar depression, PMAs are called for and those require, based on your question to me, a large-scale study, say, involving 150 patients --

DR. BROTT: No, no. Just -- I can clarify right there.

They would not necessarily require anything in addition to what

we have today. The companies could just submit what they have. Now, the Panel may not agree that that's sufficient, and practically speaking, I would imagine that other studies would be considered. But it probably would require additional studies. That's my opinion; it's not in the law. We've heard the law.

DR. EYDELMAN: Actually, let me clarify that. That's not totally correct. They would require to submit data that would demonstrate safety and effectiveness of their particular device.

DR. GOODMAN: So, again, let me kind of just stay with that assumption.

DR. BROTT: Absolutely.

DR. GOODMAN: I just want to take it --

DR. BROTT: Absolutely.

DR. GOODMAN: -- to a complete conclusion.

And assuming that that led to a design of a trial that required 150 patients per group and a sham design, it is conceivable, then, that no manufacturer would be able to afford that and at some point after the period of, say, 30 months expired, existing ECT devices could be taken off the market?

DR. BROTT: That's correct.

Dr. Eydelman, would you agree?

DR. EYDELMAN: In order to stay on the market, the applicants

would have to submit the application. After 30 months they wouldn't be taken off the market, but after 30 months, they would have to submit the application and hopefully -- there is some time after which that could happen, let's get --

DR. BROTT: Ms. Shulman, any comments?

MS. SHULMAN: No, I totally agree with what Dr. Eydelman said and all. I just wanted to add, when you wanted an example, there's contact lenses and for extended wear, overnight, they're Class III; for daily wear, Class II. Same device, different indication.

DR. BROTT: Yeah, but -- okay. Thank you.

Dr. Ross.

DR. ROSS: So I would support the indication for depression continuing as Class II. My --

DR. BROTT: No, it's currently Class III.

DR. ROSS: Sorry. Being changed to Class II.

My concern about having to do a clinical trial is not just a practical one. First of all, I do think the old evidence, while not done in the way studies would be done now, is really overwhelming and the clinical experience of people who are involved with ECTs is generally overwhelming, but what I'd be concerned about is would we have equipoise to do the kind of randomized study that you would need to do?

I think, based on the existing knowledge, it would be hard to

design a trial in which you would give sham ECT.

DR. BROTT: That was my question to Dr. Goodman.

DR. ROSS: That would be a concern of mine.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: So just a point of clarification.

So a PMA would be required from both manufacturers, from each manufacturer who currently makes the machine, right? They couldn't combine the PMA?

DR. EYDELMAN: Correct.

But having said that, that does not mean that each -- that the requirement would be a randomized clinical trial of 150 patients. That's the discrepancy that I hear the confusion on.

DR. STEBBINS: Right, right, right.

DR. EYDELMAN: It could be that we say yes for the current -- I'm just throwing this out -- for the current manufacturers, we do want their assessment, but we'll believe that perhaps going back and trying to see if we can find historical information with that particular device, that that would -- for us to consider that for assessment of safety and efficacy. That's --

DR. BROTT: Now, this is the point I was trying to make, that the evidence that we've heard today, you and the profession of psychiatry has found that evidence sufficient to make this part of your practice guidelines. That evidence may also be in the PMA and may or may not convince that

panel to recommend to the FDA clearance under the Class III designation.

The FDA, then, does not have to take the advice of the Panel. They make the ultimate determination. Do you agree with that, Dr. Eydelman?

DR. EYDELMAN: Definitely.

DR. BROTT: Dr. McDonald.

DR. McDONALD: The evidence that ECT is effective is through NIMH trials. It's not through sham control trials. In the '80s there were two very large NIMH trials, have over 250 patients or close to 250 patients in them. In patients who are treatment resistant, who have treatment resistant depression, you get an 80 to 90 percent remission rate. Not response rate, but remission. People's symptoms go away.

These trials have followed people out for six months, and the group that got pharmacology only, their cognitive status returned to baseline.

And there are good trials that show ECT is extremely effective in depressed patients that match the clinical literature. I don't think we need to do a sham control trial, and I actually think we need to make -- there are some areas we've discussed today making it Class II which would make it safe for use in the public and very effective treatment.

If we have a 33-month waiting period for people to conduct the clinical trial is nothing. There's no way you're going to get a clinical trial with an ECT group --

DR. EYDELMAN: Okay.

DR. McDONALD: -- done in 33 months.

DR. BROTT: Dr. Goodman -- excuse me, McDonald.

If the evidence is overwhelming, then the PMA will be approved.

DR. McDONALD: But there's good reason to make it a Class II and put some controls on it.

DR. BROTT: That's, of course, for this Panel to decide.

I just wanted you to know that if the evidence is overwhelming for effectiveness and the panel is like this Panel and they agree that it's as you have stated, the PMA will be recommended for approval.

DR. EYDELMAN: And just one more clarification.

If the PMA is being -- the idea is that the PMA will be submitted, but the device is under an IDE that would warrant them another extension. So I just wanted to clarify that.

First of all, it does not mean that a new trial needs to be done --

DR. McDONALD: Correct, correct.

DR. EYDELMAN: -- because the device is on the market.

But second point of clarification, should somebody require -- should a new clinical trial be required for any of the indications, and let's say the call is for 30 months, if -- I'm just making up the dates for the point of

discussion -- if at that point the sponsor is still actively collecting information, they would get an extension until they can grant that it was legally under an IDE.

DR. McDONALD: I think, to go back to your point, it's ours to make a decision today --

DR. BROTT: Correct.

DR. McDONALD: -- not to wait and put it off for another 33 months; we have patients who depend on this procedure. And to take it off the market, hold it up for 33 months in a procedure --

DR. BROTT: No, no, no, no, no.

DR. McDONALD: Put it in a state where there's a question about continuing the treatment, I think, is a mistake. I think -- well.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Yeah, I just think we need to clarify. We've been given the definition so many times that we all need to integrate it into our minds.

We aren't going to be shutting down ECT. We're not going to be taking a device off the market. I think some of our statements at this point are a little bit not quite accurate in what -- from I've heard and been educated on in the multiple trainings and talks that we've been given. To me, our primary request at this time isn't -- maybe effectiveness is one piece, but we can say it's effective, we all agree it's effective. The data is that it's

effective.

The primary difference, in my mind, that's left, since we all agree with the effectiveness data, is whether we can mitigate the risks. And if we cannot mitigate the risks, it needs to remain a Class III. If we can mitigate the risks, it goes to a Class II.

Now, am I incorrect in that definition?

MS. SHULMAN: You are absolutely correct. If you can write special controls to mitigate the risks --

DR. PAULSEN: Right.

MS. SHULMAN: -- it can be a Class II if you can --

DR. PAULSEN: I have not heard any way we can mitigate the 77 to 80 percent cognitive risk --

DR. KIM: Can we get a definition of mitigate, please?

UNIDENTIFIED SPEAKER: Yes.

DR. PAULSEN: Okay, thank you.

But that -- I think we're way off course, so let's focus on --

DR. BROTT: I don't think we're way off course.

DR. PAULSEN: Yes, it's effective.

DR. BROTT: Let's watch our language.

DR. PAULSEN: Yes, it's -- I'm sorry. I apologize to the Panel. It's just that we want to get focused here and that the question is can we mitigate the risks that we have listed, those 20-odd lists, can they be

mitigated? It sounds like most of them can to the point that we didn't even want to put them on the checklist. If we can't do all of them, it needs to stay at a Class III. That's my understanding and Dr. Kim --

DR. KIM: I think we need to know what mitigate means, though, because -- I need to understand the statutory definition, and my understanding is what Dr. Paulsen just said isn't what we're asked to do, so it would help us.

DR. PARK: This is Larry Park from FDA. I would defer the statutory definition of mitigation, sufficient mitigation of risk, to Dr. Eydelman.

(Laughter.)

DR. EYDELMAN: Okay, hopefully my voice is back. I was trying to get some wind.

So I'm just trying to come up with a different way to say it. Mitigation means that we know enough about these type of devices that we can write controls that will adequately address, sufficiently address the risks for this whole device type, that we don't need to see specific information for every -- well, specific unique information like in a clinical trial for the future ECT device.

In other words, can we write the controls, knowing what we know today, that would assure us that the next ECT device that comes in tomorrow will be adequate, will be able to go to the market without

conducting a clinical trial and without demonstrating that that particular device is safe and efficacious for its intended use.

DR. BROTT: Dr. Good.

DR. GOOD: So let's -- let me be hypothetical here.

So if we decided to make this a Level II device, we could put things in like ECT for depression, the specific indication would be indicated only in cases of refractory depression, failed two medications. I'm just being hypothetical here. Or people who were -- who needed acute treatment because of life-threatening depression, something like that could be built in to a Class II device.

I'm just giving a couple examples. Is that correct?

DR. EYDELMAN: Could you repeat that, please?

DR. GOOD: So I'm just saying hypothetically, say we decide we, hypothetically, we want to classify ECT as a Class II device for major depression, just that category. Could we put stipulations in saying that it could be used -- now, maybe this is practicing medicine -- but maybe put stipulations, could be only used for major depression that had failed medical treatment and/or there was a need for an acute treatment because it was a life-threatening situation, either a suicide risk or a person could die because of catatonia?

I'm just thinking of, you know, throwing some things out.

DR. EYDELMAN: Yes.

So, again, this goes back to the example that was provided for contact lenses. Depending, for example, for the length of time -- so this would be very similar. We can say this is Class II for a patient population with depression that had failed A, B, C, and D.

DR. BROTT: So let's get back to the question of depression. Dr. Duff has recommended that the classification for Class III remain. I think we were clear on the implications of that recommendation, so could we have comments from the Panel members on that recommendation of Dr. Duff?

Dr. Kim.

Actually, you know, we need to hear from -- this is very important. We need to hear from as many of us as possible on this point and right -- pardon me? Yeah, that's not actually a bad idea. Could we start with Mr. Mueller?

MR. MUELLER: Yes, David Mueller.

I disagree with the proposal. I believe it should be Class II, especially as we were just discussing, for depression. It has the most data. Everyone here, the whole Panel agreed earlier that it is efficacious, and I believe that the controls we have discussed adequately minimize the risks.

Now, minimize doesn't mean eliminate. It means it helps minimize the risks, and people go in with their eyes open, so to speak. They know what the risks are. Therefore, I think it should be Class II.

DR. BROTT: Ms. McElveen.

MS. STOKES McELVEEN: Francine Stokes McElveen.

As to depression, my concern is that while there is evidence of effectiveness, it's only to the extent of acute effects and the -- we only know about the effect short-term, really. You're talking immediate to perhaps maybe one month out. That, to me, poses a concern.

When we look at mitigating factors, I don't think you can mitigate depression in this instance. The use of the equipment would not mitigate because we know that there are -- there's going to be an adverse event that will occur as a result of using the equipment, and once you've used that, we know, in many instances, there's going to be a second or maybe other repeated use of the equipment. We don't know the long-term results of that. I think it should remain in Class III.

DR. BROTT: Ms. Carras.

MS. CARRAS: I have to agree with Ms. McElveen that we don't know the long-term effects, and I believe the sponsor and other folks who have done the studies have had quite a few decades to prove safety and effectiveness, and if the Panel can't agree that -- come to a consensus that we can mitigate the risks, then I say there's not enough evidence for that. I think it should remain Class III.

DR. BROTT: Dr. Ellenberg.

DR. ELLENBERG: Thank you.

My sense is that it should remain Class III from the point of

view of the demonstration of efficacy, which is essential to our discussions here. I won't comment on the issue of whether or not the controls can mitigate. It's not something I really can -- have the expertise to comment on.

So the -- if I can read a little bit into what Dr. Park said yesterday, the final slide of the five sham studies, the final med analysis, the only slide of results shown yesterday showed an estimate of about 7 points increase in HAM-D score among those that --

DR. BROTT: Dr. Park, you haven't been questioned, I don't think.

DR. PARK: Sorry.

DR. ELLENBERG: Oh, he may be pulling up that slide.

DR. PARK: I was going to pull up the slide.

DR. BROTT: We didn't request that at this point.

DR. ELLENBERG: The variability in that or the confidence we have in whether or not there is a 7 point increase is huge, and we don't know why, whether it was sample size or the inherent variability in the process.

We have not seen who is benefitting in terms of severity of disease. The category of patients are all those that are refractory to current medications or other approaches to getting rid of depression, but we don't know whether that series of clinical trials demonstrates this high variability because it's based on severity of disease. So I'm not ready to say, based on what we've seen, that this drug -- excuse me, ECT has an overall effectiveness

that is clear and unquestionable.

With that in mind, my sense of the cost/benefit ratio for ECT, I find difficult to relate to the risks, and so I would, just because it's primarily because of efficacy, I would like to see it remain in Phase III, and that would force us, I think I'm hearing, either new evidence or a reassessment of the old evidence in order to keep it on the market.

And I'm fairly convinced that this should not have a deleterious effect on the access to ECT unless this new evidence fails to convince the FDA that it is either non-efficacious or it's too dangerous. And if that happens, that doesn't seem to me to be a bad thing. So I would vote for keeping it as Class III.

DR. BROTT: Dr. Ross.

DR. ROSS: Well, I must say I'm speaking partly as a clinician who has seen remarkable positive effects with it and who's also seen a lot of patients with the side effects including the memory dysfunction, but those are really the minority of patients.

And looking up the definition of mitigate, it's not to eliminate, but it's to lessen in force or intensity or moderate, and it does seem to me that, based on what we've heard so far, the device is efficacious, and I believe we can, at least, moderate the known risks by an appropriate informed consent and checklist procedures we've discussed.

So I think I would be in favor of moving it to Class II.

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DR. BROTT: Dr. Anderson.

DR. ANDERSON: I would agree with Dr. Ross. I think that we've seen evidence that it's very efficacious, and I do agree that, based on the definition of mitigate, that we have steps in place that we can take to mitigate the risk of memory dysfunction and the other risks.

DR. BROTT: Dr. Gordon.

DR. GORDON: I feel strongly it should retain Class III status. I do most of my work in ophthalmology, and I'm very familiar with the research on extended contact lenses and daily wear lenses, which are also --

DR. BROTT: Could you come a little closer to the microphone?

DR. GORDON: Oh. I'm very familiar with extended wear and lenses which are in Class III.

I'm voting for Class III for reasons of a lack of long-term data on efficacy and safety. The indications are all chronic conditions that are mostly lifelong, and for us to not have data in hand to -- reasonable assurance of efficacy and safety long-term, I think, is a major failure.

I do not believe that the consent process proposed adequately mitigate the memory losses. In our binder, Page 89, is a summary going over about three pages of autobiographical memory loss. The summary suggests that 25 percent of the -- and all the studies that are in this range of autobiographical memory loss. And I think our Patient Representative has underscored how much psychological distress is caused by this.

I think we don't weight this adequately, nor have we measured it adequately before having outcome measures that quantitate this. In the Sackeim study, I think published in like '03, '08, the right unilateral group had the least autobiographical memory loss, but it's still around 25 percent. To me, that's very big, and it's an important hit. I don't think consent and being informed about it really and truly mitigate it. So I'm for Class III.

DR. BROTT: Dr. Good.

DR. GOOD: Well, this is a tough one.

At this point, I'm leaning towards leaving it Class III for some of the reasons that my colleagues have already mentioned.

I am concerned about lack of long-term efficacy. I'm struck by the difference between clinical practice from my psychiatric colleagues who've seen tremendous improvement in individual patients and the lack in the literature of real support for that, except for some very, very old studies.

So I'm a little bit concerned, though, because we heard from the public docket there were some people have felt that it's been lifesaving for them, and we've also heard public docket that it's been a life-changing event in the opposite direction, mostly because of the memory.

So I'm a little bit concerned about possibly putting some people who might be actively suicidal at risk for taking it away because my colleagues in psychiatry say these people really do benefit. I can't see it in the hard data, but they tell me that. And you guys see it; there are some studies. We

haven't really seen those studies, though. It seems more anecdotal to me.

I'm willing to let somebody else respond to that. There's a couple of hands up.

DR. BROTT: We'll --

DR. GOOD: Okay.

DR. BROTT: -- get around.

DR. GOOD: So I think at this stage, I don't really see the long-term efficacy in large numbers of people, and I see a lot of people who feel they've been hurt, and I think there's strong evidence of memory loss. So at this point, I'm leaning that way. If it went to Class II, there would have to be very strict restrictions, in my opinion.

DR. BROTT: Dr. Peavy.

DR. PEAVY: My sense at this point is that it should remain at III. One of the reasons is because I feel that there are brain changes that we just don't understand, and I think that that could be affecting people in some important ways that we cannot detect at this point.

That being said, I have concerns about the people that feel like they depend on it. The feelings that -- subjective feelings that people have expressed are very poignant, and if there is some way that we could deal with that while keeping it at Class III, then I would be happier about that. I guess I feel that if we do keep it at Class III, it probably will not be taken away but there is that chance.

I also feel like the people that are actually using ECT here are sort of the cream of the crop. They know, they care about people, my impression, they know how to -- they know what things to pay attention to. I feel that there are practitioners out there that are not at that same level or don't have the same level of caring, and I'm concerned about that.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: I'm in favor of maintaining it at Class III at this point mostly because of the lack of long-term data on the side effects of memory loss and the potential for dose effect that seems to be more memory loss associated with three times treat versus two, and then if you extend that into maintenance ECT, what does that mean in the long term and we just -- we have no data on that at all.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: I would support keeping it at Class III. I think the data is lacking in how we can better mitigate the risks.

DR. BROTT: Dr. Duff.

DR. DUFF: I maintain my position of keeping it at Class III largely because I don't think any of the recommendations that we've made will mitigate the cognitive changes associated with it. Monitoring cognition, however you want to define monitoring in having them check off a box, I don't think is going to do anything.

DR. BROTT: Dr. Winokur.

DR. WINOKUR: I have a lot to say, you may need to cut me off, but I'm in favor of switching to Class II. I don't support maintenance of Class III.

My first point with respect to the efficacy data, we heard from the FDA presentation and review on at least three instances or examples of efficacy from the kind of data that they reviewed. Efficacy, granted, you know, more short-term timeframe with respect to sham, placebo, and also strikingly compared to other antidepressants. We looked at data where there's no overlap showing superiority to ECT.

Now, in my opinion of limitation of the studies, which are, to a large extent, older, is that it was not clear to what extent the depressed patients included represented treatment-refractory depressed patients, but we've heard from Dr. McDonald that there have been some newer studies, albeit not in the format that the FDA has as their priority to review, that have focused on the treatment-refractory subset of depressed patients.

What I want to emphasize is that the recent data and experience with treatment-refractory populations, including both depression and bipolar and also schizophrenia, I'll mention briefly, have increasingly been making us aware of what a particularly challenging population that is to get a good or positive response.

The STAR*D trial is one example where the remission rate went down from close to 40 percent after Stage 1 and 2 to 13 percent beyond two

unsuccessful trials.

In my clinical work, in my opinion, the majority of what we're seeing in clinical psychiatry are treatment-refractory depressed patients because the PCPs are taking care of the majority of patients who respond readily.

So we have a real challenge with patients who are not responding readily, and what else we can do. We know that with severe depression, there's a 15 percent death by suicide, there's morbidity and mortality. There are also brain changes that have been now convincingly shown in patients with both unipolar and bipolar depression related to the illness to the extent that those studies have clarified.

So I think a combination of both the FDA's analysis of the data that fit their parameters for what they chose to evaluate, some newer studies that Dr. McDonald can recite much more accurately than I can, and clinical experience hang together to make it clear that efficacy is well established.

I'm not so concerned about the long-term efficacy because I don't think -- again, I'm not an ECT provider. I don't think, clinically, we're largely using ECT as monotherapy in a longitudinal perspective. We're typically intervening with ECT in terribly sick, ill patients, thankfully in many cases getting a response, and then coming behind that with pharmacotherapy which may include maintenance ECT, but it gets to be a different situation.

So a fellow named Gary Sachs, who is a prominent bipolar

expert, has used a paradigm of sequential versus urgent care treatment paradigms, and with sequential care, you have a patient who has an illness and they're not urgently ill, and you start with a treatment that has the lowest side effect impact and then build up from there.

And a good example is hypertension where you might start with diet and exercise, add a little diuretic, and so on. But if you have a patient with malignant hypertension, you have to prioritize a treatment that's going to be effective, and you understand that there may be a greater side effect liability, so it's really a risk/benefit analysis, not just risk by itself.

I think that we have heard ways to mitigate risk that, to me, are meaningful by more careful selection of patients to be included by improvement of the informed consent process and by more systematic monitoring of cognitive problems so that the treatment approach can be modified. That's what we do clinically. I think the top ECT programs do that.

If that was set up as the standard, I think, to me, that would be a meaningful way to, you know, modify the approach or mitigate the risk in a meaningful way.

The final example I'm going to point out, in a different therapeutic area, clozapine was initially identified as the first new antipsychotic treatment that we had for treatment of refractory patients with schizophrenia. And even in the face of the risk of agranulocytosis, the one percent of patients on clozapine, the FDA decided to approve clozapine

for use in the U.S. based on results of a really pioneering study that was done by Kane and Meltzer and colleagues in patients that were clearly shown to be very hardcore treatment or refractory schizophrenic, which I believe is analogous to the majority of patients getting ECT.

What I wanted to point out is that the number of schizophrenic patients in that trial who responded based on a pre-specified response criteria was 30 percent, and that was enough to convince the FDA that this drug needed to be available to the public. The comparison group, chlorpromazine, you know, gold standard antipsychotic, had a four percent response rate in the group that was randomized to chlorpromazine. So only 30 percent of patients responded to clozapine, but in this category of treatment of refractory, it's so important for us to have options that show therapeutic promise that just figuring out ways to mitigate the risk of clozapine was clearly something that was justified based on the benefit part.

So I think the risk/benefit is really the crucial issue here.

DR. BROTT: Dr. Kim.

DR. KIM: And please stop me if I go on too long because I do have several points I'd like to make.

I want to say, at the outset, I'm not a member of the APA or a physician who does ECT. I am, however, a practicing psychiatrist who has referred patients to ECT, so you have that background. And I've tried to look at the data as dispassionately as I can in spite of that.

I think that there are a couple issues that I'd like to point out. One is the repeated mentions of lack of --

DR. BROTT: Just as an introduction, so we can focus our own thinking, what's your position on the recommendation?

DR. KIM: Oh, I'm sorry. I feel fairly strongly that this should be reclassified to Class II and that the special and general controls are sufficient to mitigate the risk in relation to the effectiveness that -- and the importance of having the treatment.

So just a couple of points. First, that there is repeated mention of lack of long-term efficacy. As Dr. Winokur points out, you know, psychiatrists don't refer patients to ECT for long-term benefit. It's because we're in a situation where we need to change the trajectory of the disease, and that's what ECT is good for. So I'm very disturbed that there's a heavy weighting of the lack of long-term efficacy, number one.

Number two, the lack of efficacy, opinion seems to be based on the systematic review on the meta-analysis data. As I understand those papers, after the immediate post-sham period, those trials have relatively little control over what happened to those patients.

So pretty much, there's going to be an expected lack of difference between sham and intervention groups because once they're done with ECT, they return to the community. And so I think that that should be a very important factor in interpreting those studies.

Now, second point is the issue of mitigation, and I wanted to make this point when Dr. Paulsen brought up the very important point of we should understand what mitigation is. As I understand the statutory definition, it says that what we're asked to think about is mitigation, is there enough information, sufficient information, so we can mitigate such that that two types of controls are sufficient to provide reasonable assurance of safety and effectiveness? Now, note that they include both safety and effectiveness. It's not just can we get rid of all risks or can we get some intuitive sense that this is safe enough. That's not what we're asked to do. What we're asked to do is, in relation to the effectiveness, the benefits, is the known information in the literature sufficient for us to say well, this is what we can generally expect, and having read it, we think it's sufficient to allow competent adults take account of that risk for themselves?

Now, it seems to me if you consider the fact that the efficacy data, in my view, for acute treatment, which is the reason why we use ECT, is very strong even from the -- sorry to use technical language -- crappy old studies, right? So I think that's clear. So the question really becomes what's the magnitude and the public health importance which is the effectiveness side.

Now, you saw that 21 percent of people in this country have a lifetime prevalence of mood disorders, and we know from STAR*D study that a high proportion of those people are going to have refractory depression.

This is now an everyday occurrence.

To me, the estimate of 100,000 people who get ECT is a surprisingly low number, and I think that should tell us that these are not done willy-nilly. It's done after very careful discussions with patients, and that's why, in spite of the incredibly high number of people who have refractory depression, we get so few people who get ECT. And I think that has not been brought out sufficiently.

So when you add that together, really the question of mitigation isn't whether in the abstract or in some intuitive sense can we kind of make us feel comfortable that there is now a low enough risk, but rather in light of the importance of having the effectiveness, can we mitigate it knowing that there's always going to be uncertainties and knowing that is it sufficient to allow competent adults to take on that risk.

For that reason, I think that -- let me just add one other thing about the risk. I kept hearing that we don't have long-term data about cognitive impairment and memory and so forth. I think what we do have are very difficult to interpret data about retrograde amnesia, and I think there's sufficient evidence that people get truly impaired because of that. However -- or impairment of that memory.

But the cognitive function data that was presented, it's firmly convincing for most of the -- let's make a distinction between loss of memory, which is the concrete loss of what you stored before, versus cognitive

function, which is what you can actually perform. The evidence that was presented by FDA is that the functioning aspect actually returns to baseline or improves. So I think it's wrong to say that we don't have sufficient data long-term about the functioning aspect of cognition.

So given all that, I feel like the very thorough review that was given to us is sufficient information to say that given the risks and benefits, is this something that we think that competent adults in this country, suffering from a life-threatening illness, should take on? I say yes. And we should leave it in Class II.

DR. BROTT: Dr. McDonald.

DR. McDONALD: I would argue for moving to Class II, and I appreciate --

DR. EYDELMAN: I'm sorry. I was just wondering --

DR. BROTT: Dr. Eydelman.

DR. EYDELMAN: Sorry. I was just wondering if I could make a comment in light of Dr. Kim's -- well, the comments he just made.

You're absolutely right that mitigation does not mean elimination of the risk. However, it does mean, Class II does mean that the benefits outweighs the risk, and I wanted Ms. Shulman, if you don't mind, just to read that from the --

DR. BROTT: Ms. Shulman, are you prepared to read it?

MS. SHULMAN: Hi, Marjorie Shulman.

Under 21 C.F.R. 860.70 there is a determination of safety and effectiveness.

DR. BROTT: Excuse me, Ms. Shulman. Could you come a little closer to the microphone and go from 78 to 33 and a third?

MS. SHULMAN: All right, sorry. Under 21 C.F.R. --

DR. BROTT: A little bit slower, please.

MS. SHULMAN: Under 21 C.F.R. 860.70, there is a determination of -- explanation of determination of safety and effectiveness, and it's very long, so I'm just going to try and just summarize it while I'm up here.

But it says in determining the safety and effectiveness of a device for purposes of classification, establishment of performance standards for Class II devices and premarket approval of Class III devices, the Commissioner and the classification panels will consider the following among other relevant factors: the persons for whose use the device is represented or intended; the conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use; the probable benefit to health from the use of the device weighing against any probable injury or illness from such device; and the reliability of a device.

It does go on for a lot longer, but that's the --

DR. BROTT: Fine, thank you.

MS. SHULMAN: -- definition of safety and effectiveness.

DR. BROTT: Dr. McDonald.

DR. McDONALD: Thank you.

I very much appreciate what people have said, and I realize this is a hard decision for people to make. I would argue for it being Class II. I think the controls that we've set out will actually make ECT better, and I think it will help mitigate the risks.

There are -- if you think about the average patient who comes to ECT, and some people came to the podium yesterday and talked about their experiences, this is not a decision people make lightly. In fact, I think most people who practice ECT would say that it's put off for years, and after they get better, they wonder why didn't I do this before I lost my job and before I lost my marriage?

In psychiatry, we don't have a huge armamentarium. We have a lot of medications that either work on serotonin or serotonin and norepinephrine. This is a novel treatment that pulls in 80 to 90 percent of people and causes a complete remission of their symptoms.

These are people who have been suffering, and they know the risks, many of them. We've heard about people that did not know the risks, but many people have gone on the Internet, they've thought about this, they've talked to their doctors for months before they come to ECT, and they're willing to take that risk. They understand what the risk is; they're

willing to take the risk.

There is very good acute evidence, and I would say there is long term. I'm not sure I missed something on the communication in the airport trying to watch the webcast yesterday, but there are studies of hundreds of patients that show, placed on pharmacotherapy, placed on lithium and nortriptyline, 86 percent of people will stay well for six months. That seems like a long-term benefit. If you put them on placebo, 80 percent will relapse. That seems like a clear long-term benefit of ECT plus medication.

We use maintenance medications on our patients and patients stay well. The latest large study that looked at patients given randomized maintenance ECT or maintenance pharmacotherapy after they got well with ECT, 50 percent of people stay well.

These are treatments that work. They work in a group of patients for which we have few other choices. We can mitigate the risk by pointing out -- some of the things that have been pointed out, I think, will really help ECT and help mitigate this risk, and I think it's important that we classify it as Class II and use the controls that we've discussed.

DR. BROTT: Thank you.

Dr. Goodman.

DR. GOODMAN: Yeah. I feel very strongly that ECT should be reclassified as a Class II device for the treatment of depression. I won't repeat all the previous comments, but I do want to underscore a few of them.

One of them that was just mentioned by Dr. McDonald is there is no equivalent, there is no alternative to ECT for the kinds of patients for which it's used. For the acutely suicidal, treatment-resistant depression -- patient with treatment-resistant depression who does not respond to other treatments, it is literally lifesaving, and so to eliminate this option would be literally eliminating a lifeline to many patients.

Now, one of the problems, it's not -- I think there is a disconnect between the published data and the clinical impressions you're hearing from psychiatrists like myself. I don't quite understand it, but I'll venture a hypothesis.

Oftentimes there are clinical trials impeccably done, randomized clinical trials, and we learn a lot when it moves from that controlled state to what is often referred to as effectiveness studies, when they try to generalize it and it doesn't perform as well. That has not been the case in ECT.

In the case of ECT, I have often used the expression that ECT is the gold standard for the treatment of depression in teaching residents. And that's been my impression, continued to be my impression, and when -- I pride myself as being a pharmacologist, and I consider it a personal failure when I can't manage a case with psychopharmacology alone -- I know, at a certain point, that I need to refer that person to ECT to save their lives.

I think that's what happened is that some years ago, maybe 20

or 25 years ago, there was such uptake and realization, such a strong wealth of clinical impression that ECT is so efficacious that we've skipped the step somewhere along the way of doing the trials that normally would convince a group like this that we have adequate safeguards, we have adequate evidence for efficacy and safety.

When I spent my two years at NIMH on the extramural side, I don't think that reviewers of program staff would even entertain an application to perform a study of sham-controlled ECT because it's a given. But I think what we've seen in the last two days is when you scrutinize the available studies and use the conventional standards, it doesn't look as strong as those of us who, in clinical practice, know it to be.

I think that it would be a mistake to even take the risk of leaving it as a Class III and the possibility that it may be removed from market.

DR. BROTT: Dr. Domino.

DR. DOMINO: I'm in favor of reclassifying it as Class II for the indication of depression. I do think the special controls, some of which we haven't discussed, might be helpful, and those include postmarket surveillance and patient registries as an option.

And I also wonder if the indication shouldn't be severe depression, refractory to medical management, rather than all -- depression of all comers.

DR. BROTT: Thank you.

We have nine Panel members who have expressed an opinion that the classification should remain in Class III and nine Panel members who have expressed the opinion that we should classify the -- pardon me?

UNIDENTIFIED SPEAKERS: Eight. Eight. It was eight.

DR. BROTT: I thought it was nine to nine.

DR. EYDELMAN: We'll look at the transcript when it's done.

DR. BROTT: We'll get an accurate vote in a moment.

DR. EYDELMAN: This is not a vote.

DR. BROTT: Pardon me?

DR. EYDELMAN: This is not a vote.

DR. BROTT: No, I understand it's not a vote, but I think the numbers are pertinent.

Ordinarily, I wouldn't offer an opinion, but I'm going to offer an opinion today. I'm a practicing neurologist, I attend on the floor, and my habit is to go through guidelines for the different diseases that we meet in neurology, and I would do the same for psychiatry.

And I've been struck, by doing this over the years, the holes in the evidence that we have for the things that we believe to be effective and the things that we see to be effective. In the practice of medicine, we do this every day, and so it's not a shock to me to see the disconnect that has been referred to by the people on this Panel who take care of the patients.

And I personally am convinced, by my own homework, my own review of the evidence and the presentation of the FDA, that ECT is effective treatment for depression. And I take Dr. Winokur's comments very much to heart with regard to the time to treat acutely and the time to give the patient the treatment they need right away when we do know that pharmacotherapy takes time. And so I believe that this medication is effective for this indication, I'm convinced.

What I do worry about is going forward. We have devices and we've heard about Class I, Class II, Class III. My own simple understanding is Class I is not very risky, not risky at all; Class II, a little risky; Class III, risky. It's got some risks. I deal with a Class III, which is the carotid stent.

We just had a Panel meeting, 2,500 patients, the risk of a stroke from surgery for this was 1.8 percent or something in that region for the surgical group, risky. We've heard a lot of information, we've reviewed a lot of information that this procedure is associated with risk. So I have a little problem with classifying this procedure as a Class II procedure going forward and perhaps for the next decade or decades.

What about the process? I do have experience -- I held the IDE for tPA as treatment for stroke. I'm currently a sponsor of an IDE. I've been on this Panel now for some period of time, familiar with the 510(k) process and the PMA process.

I'm confident that were these procedures to go through the

PMA process, that they will meet the conditions of the PMA process, and I'm very confident. So I don't see that the reclassification would decrease the access of psychiatric patients to this procedure. And for that reason, the degree of risk, the level of the evidence, and the long-term, I would like to put confidence in the FDA in a Class III in seeing these processes go forward.

At this point we need a break. We'll come back at three o'clock.

(Off the record.)

(On the record.)

DR. BROTT: Again, we want to have as much participation as we can. But as we provide our comments and recommendations, it would be helpful to be succinct with regard to our responses, as each of us thinks is appropriate. And the next question is 5(b).

Lieutenant Commander Cunningham.

LCDR CUNNINGHAM: Yes, the same question applies to part (b).

Please provide your overall recommendation for the classification (Class II or III) of the ECT device for schizophrenia.

DR. BROTT: And let's start with Dr. Domino.

DR. DOMINO: I propose leaving it as Class III for schizophrenia. That's based on my assessment of what the FDA presented in terms of effectiveness and looking at the benefit/risk ratio.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Propose reclassifying as Class II for similar reasons as I stated before for the case of depression. Although probably the need is not quite as wide and there may be some other alternatives mentioned, clozapine, as an alternative to treatment-resistant schizophrenia, nevertheless, there's some patients for whom it is a critical and sometimes lifesaving intervention.

DR. BROTT: Dr. McDonald.

DR. McDONALD: Dr. McDonald. I would propose making it Class II, I think, and the same mitigating factors, and I think we can use the same controls. Schizophrenia has been shown to be responsive to ECT, particularly in treatment-resistant cases and particularly when combined with medications such as clozapine. So I would propose Class II.

DR. BROTT: Dr. Kim.

DR. KIM: Based on what was presented, I thought the data for schizophrenia were much weaker and not as extensive, and based on that, I think that for this indication it should remain in Class III. May I ask one question, however?

DR. BROTT: Yes.

DR. KIM: I am a little bit -- I was curious about the way we're answering this particular question, 5, is so different from the way we discussed all the other questions. In other words, for the other questions we

had a chance to listen to people's different views and so forth, and here it's almost as though, just from a sociopsychological perspective, we're sort of putting our foot forward and then we've -- it just seems like it's very different. I'm kind of curious why we're doing it differently for this question.

DR. BROTT: I think you're correct. From my own point view as Chair, this question was placed last as well. It could've been placed third or first or second. And I think that it was placed last for a good reason because this is the most important part of what we've done, and it's the end of a one-and-a-half-day and now nearly two-day process in which we've been able to express previously many of the things that each of us expressed as we went through with the vote.

I did it this way to try to make sure that each of us would have the opportunity to express our opinions, which I think were done rather eloquently. And so while I grant you that the process has been different, I do think that it's been a good process, myself.

Dr. Winokur.

DR. WINOKUR: Well, I'm more ambivalent about this one. I think the data for efficacy in schizophrenia are weaker, but the FDA did show us some data for accelerating onset of response, and again, assuming that this is in a particularly hardcore group of patients with schizophrenia who would've been involved in a study where ECT was added.

So for this indication, based on a combination of some data

supporting efficacy and a lot of clinical experience that matches with that and the same mitigating approaches that we talked before, I would favor Class II.

DR. BROTT: Thank you. Dr. Duff.

DR. DUFF: Yeah, I vote to retain Class III. I think there's even less that we know about the benefits and risks associated with ECT treatment for patients with schizophrenia.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Perhaps you should pass me. I missed this question.

DR. BROTT: Lieutenant Commander Cunningham, can you repeat the question?

LCDR CUNNINGHAM: Yes. Please provide your overall recommendation --

DR. BROTT: Hang on just a moment.

LCDR CUNNINGHAM: Yes.

DR. BROTT: Ready?

LCDR CUNNINGHAM: Please provide your overall recommendation for the classification (Class II or III) of the ECT device for schizophrenia.

DR. PAULSEN: So I'll maintain the Class III. Thanks.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: Yeah, I think I'd recommend keeping it in

Class III, mostly because of the questions on efficacy.

DR. BROTT: Dr. Peavy.

DR. PEAVY: I recommend Class III for similar reasons.

DR. BROTT: Dr. Good.

DR. GOOD: Yes, I definitely feel Class III on this, based on the fact that it's not clearly better than sham in some of the studies that were presented. And also it's not clearly better than medication. So I would go Class III.

DR. BROTT: Dr. Gordon.

DR. GORDON: Class III, likewise, for the same reasons.

DR. BROTT: Dr. Anderson.

DR. ANDERSON: I have more difficulty coming to a decision on this one, again, because of the lack of evidence. I think to err on the side of caution, I would recommend that it stay at Class III.

DR. BROTT: Dr. Ross.

DR. ROSS: Class III.

DR. ELLENBERG: Jonas Ellenberg. Class III.

DR. BROTT: Dr. Ellenberg.

DR. ELLENBERG: Jonas Ellenberg. Class III.

DR. BROTT: Ms. Carras.

MS. CARRAS: Class III.

DR. BROTT: Ms. -- I've got to get your name correct -- McElvin?

MS. STOKES McELVEEN: McElveen.

DR. BROTT: McElveen.

MS. STOKES McELVEEN: Class III.

DR. BROTT: Mr. Mueller.

MR. MUELLER: Class II, following the eminent Dr. Gordon and Dr. McDonald.

DR. BROTT: Dr. Eydelman, with regard to the question as to the overall recommendation for the classification of ECT, the ECT device for schizophrenia, the Panel is not unanimous, but the majority favors maintaining the device in Class III.

DR. EYDELMAN: Thank you.

DR. BROTT: Next is bipolar manic states. And let's start with Dr. Stebbins.

DR. STEBBINS: I would vote to maintain Class III on this.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Class III.

DR. BROTT: Dr. Good.

DR. GOOD: Class III.

DR. BROTT: Dr. Duff.

DR. DUFF: Class III.

DR. BROTT: Dr. Gordon.

DR. GORDON: Class III.

DR. BROTT: I guess you know it's Dr. Winokur.

(Laughter.)

DR. WINOKUR: Class III.

DR. BROTT: Dr. Anderson.

DR. ANDERSON: Class III.

DR. BROTT: Dr. Kim.

DR. KIM: For this indication, I would favor reclassifying to Class II. May I just make one point why I --

DR. BROTT: Absolutely.

DR. KIM: Bipolar mania, it's very, very difficult to do clinical trials in this condition because it's a very temporally sensitive situation; therefore, it's not surprising to me that there aren't many studies. However, one, the usually good medications for mania are not effective. This can be a lifesaving procedure. So I am concerned for the same reasons I indicated. So for that reason I would reclassify this as Class II.

DR. BROTT: Dr. Ross.

DR. ROSS: Well, I think this is more difficult, but I think I agree with Dr. Kim and would stick with Class II.

DR. BROTT: Dr. McDonald.

DR. McDONALD: Class II, for those same reasons. Particularly mixed states of mania are very difficult to treat and often cannot respond to medication. And there is good efficacy from a number of studies.

DR. BROTT: Dr. Ellenberg.

DR. ELLENBERG: Class III.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Class II. Again, similar reasons to Dr. Kim, needed as an alternative where there are few options for very severely ill and treatment-resistant patients, and I think it might not be that feasible to conduct the kind of studies that might be recommended.

DR. BROTT: Ms. Carras.

MS. CARRAS: Class III because I have the utmost confidence in the ability of clinicians and researchers to come up with appropriate studies that could provide that evidence.

DR. BROTT: Dr. Domino.

DR. DOMINO: Class III.

DR. BROTT: Ms. McElveen.

MS. STOKES McELVEEN: Class III.

DR. BROTT: Mr. Mueller.

MR. MUELLER: Class II.

DR. BROTT: Oh, excuse me. Dr. Peavy.

DR. PEAVY: Class III.

DR. BROTT: Lieutenant Commander Cunningham.

LCDR CUNNINGHAM: Please provide your overall recommendation for the classification (Class II or III) of the ECT device for

schizoaffective disorder.

DR. BROTT: Let's just start with Dr. Domino.

DR. DOMINO: Class III.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Class II.

DR. BROTT: Dr. McDonald.

DR. McDONALD: Class II.

DR. BROTT: Dr. Kim. Now let me just stop there for -- go ahead.

DR. KIM: Class III.

DR. BROTT: Class III? Okay. Were there any comments that you wanted to make in terms of the process as we go forward? Are we okay?

DR. KIM: Thank you for asking, Mr. Chairman. I'm fine, thank you.

(Laughter.)

DR. BROTT: Okay. Dr. Winokur.

DR. WINOKUR: Class III.

DR. BROTT: Dr. Duff.

DR. DUFF: Class III.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Class III.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: Class III.

DR. BROTT: Dr. Peavy.

DR. PEAVY: Class III.

DR. BROTT: Dr. Good.

DR. GOOD: Class III.

DR. BROTT: Dr. Gordon.

DR. GORDON: Class III.

DR. BROTT: Dr. Anderson.

DR. ANDERSON: Class III.

DR. BROTT: Dr. Ross.

DR. ROSS: Class III.

DR. BROTT: Dr. Ellenberg.

DR. ELLENBERG: Class III.

DR. BROTT: Ms. Carras.

MS. CARRAS: Class III.

DR. BROTT: Ms. McElveen.

MS. STOKES McELVEEN: Class III.

DR. BROTT: Mr. Mueller.

MR. MUELLER: Class II.

DR. BROTT: Lieutenant Commander -- oh, Dr. Eydelman, with regard to schizoaffective disorder, the consensus of the Panel is that the classification of Class III be maintained, but the opinion is not unanimous.

DR. EYDELMAN: Thank you.

DR. BROTT: Lieutenant Commander Cunningham.

LCDR CUNNINGHAM: Please provide your overall recommendation for the classification (Class II or III) of the ECT device for schizophreniform disorder.

DR. BROTT: Mr. Mueller.

MR. MUELLER: Class II.

DR. BROTT: Ms. McElveen.

MS. STOKES McELVEEN: Class III.

DR. BROTT: Ms. Carras.

MS. CARRAS: Class III.

DR. BROTT: Dr. Ellenberg.

DR. ELLENBERG: Class III.

DR. BROTT: Dr. Ross.

DR. ROSS: Class III.

DR. BROTT: Dr. Anderson.

DR. ANDERSON: Class III.

DR. BROTT: Dr. Gordon.

DR. GORDON: Class III.

DR. BROTT: Dr. Good.

DR. GOOD: Class III.

DR. BROTT: Dr. Peavy.

DR. PEAVY: Class III.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: Class III.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Class III.

DR. BROTT: Dr. Duff.

DR. DUFF: Class III.

DR. BROTT: Dr. Winokur.

DR. WINOKUR: Class III.

DR. BROTT: Dr. Kim.

DR. KIM: Class III.

DR. BROTT: Dr. McDonald.

DR. McDONALD: Class III.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Class III.

DR. BROTT: Dr. Domino.

DR. DOMINO: Class III.

DR. BROTT: Dr. Eydelman, with regard to the classification of ECT devices for schizophreniform disorders, the Panel is in consensus and near unanimity that the classification of Class III be maintained.

DR. EYDELMAN: Thank you.

DR. BROTT: Lieutenant Commander Cunningham.

LCDR CUNNINGHAM: Please provide your overall recommendation for the classification (Class II or III) of the ECT device for catatonia.

DR. BROTT: Dr. Stebbins.

DR. STEBBINS: Class III.

DR. BROTT: Dr. Peavy.

DR. PEAVY: Class III.

DR. BROTT: Dr. Good.

DR. GOOD: This is a little more difficult for me, but I'm going to say Class III.

DR. BROTT: Dr. Gordon.

DR. GORDON: Class III.

DR. BROTT: Dr. Anderson.

DR. ANDERSON: This is a more difficult one because the data are not as strong, but I feel, since this is a lifesaving treatment in some of these extreme cases and there are so few alternatives, I vote Class II.

DR. BROTT: Dr. Ross.

DR. ROSS: Class II, for the same reasons.

DR. BROTT: Dr. Ellenberg.

DR. ELLENBERG: Class III.

DR. BROTT: Ms. Carras.

MS. CARRAS: I don't know enough about catatonia. I would

have to say it seems like we've heard that this is one of the cases where it is even more clear that it is felt to be lifesaving. So in this case it may be that it could be mitigated and be put into Class II.

DR. BROTT: Ms. McElveen.

MS. STOKES McELVEEN: Class III.

DR. BROTT: Mr. Mueller.

MR. MUELLER: Class II.

DR. BROTT: Dr. Paulsen.

DR. PAULSEN: Class III.

DR. BROTT: Dr. Duff.

DR. DUFF: Class III. But I would also like to hope that if the FDA decides to make this Class III and this goes towards a PMA, that they'll consider how difficult it will be to collect clinical trial data in this population.

DR. BROTT: Dr. Winokur.

DR. WINOKUR: Class II, for the reasons that Dr. Anderson expressed very eloquently.

DR. BROTT: Dr. Kim.

DR. KIM: Class II, simply because I don't see how you could do -- it would be unethical to do a randomized clinical trial, in my view. This is a lifesaving treatment, and there's really no alternatives for those people who don't respond to benzodiazepines, such that -- okay. Well, that's my reason for suggesting we classify it into Class II.

DR. BROTT: Dr. McDonald.

DR. McDONALD: Class II.

DR. BROTT: Dr. Goodman.

DR. GOODMAN: Yeah, a strong endorsement for Class II.

DR. BROTT: Dr. Domino.

DR. DOMINO: Class II.

DR. BROTT: Dr. Eydelman, with regard to catatonia, the Panel does not have a consensus with regard to classification. While some of the Panel members believe that the classification of Class III should be maintained, others have put forward that the appropriate studies to address this rare or relatively infrequent condition could be limiting, such that the treatment, if effective, might be inappropriately restricted, such that it not be available for these patients.

DR. EYDELMAN: Thank you.

DR. BROTT: We've finished the questions, and before we bring things to an order, I'm wondering if Panel members would like to make any comments. Dr. Kim.

DR. KIM: Mr. Chairman, in spite of my comment about the process, I really appreciated your leadership today.

DR. BROTT: Thank you. Any other comments from the Panel?
Dr. Gordon.

DR. GORDON: As you know, I'm a biostatistician and I

specialize in vision disorders. So I need to ask the Panel, or others, whether you know of any other use of a device that requires general anesthesia and a neuromuscular block two to three times a week for about three to four weeks. To me this is a rather high-risk exposure, and I'm responding to the sense of how important it is to have general anesthesia and neuromuscular block. But two to three times a week in the induction case seems like a lot of exposure to me.

DR. BROTT: Thank you. I think the Panel -- Ms. Carras.

MS. CARRAS: I promise to be quick. I just wanted to say that Dr. Kim spoke repeatedly about -- in terms of mitigating risks, that we need to have this procedure available for competent adults who can accept those risks, and I haven't heard any acknowledgment of the use of ECT involuntarily, and it is something that happens. So, again, if the FDA decides differently from what the Panel has recommended, I hope it will consider the involuntary use of ECT.

DR. BROTT: Thank you. Before we adjourn, just a logistical point before we adjourn. Transportation has been arranged for the Panel members, so kind of stay in this area.

And just prior to our adjournment, Dr. Eydelman, I would like to ask if you have any comments to make on behalf of the FDA.

DR. EYDELMAN: Yes, I would like to take this opportunity to thank an outstanding FDA team for their hard work and dedication, as

demonstrated in preparation for this meeting.

(Applause.)

DR. EYDELMAN: And I also would like to say thank you to all of the Panel members for getting here, first, irrespective of the inclement weather, and for your thoughtful and very productive deliberations. Thank you all.

DR. BROTT: This meeting of the Neurological Devices Panel is adjourned.

(Whereupon, at 3:18 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

January 28, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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