CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Evidence Development & Coverage

Advisory Committee

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Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

Panelists

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Committee Acting Vice Chair
Aloysius B. Cuyjet, MD, MPH

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Marcel Salive, MD, MPH
Guofen (Evelyn) Yan, PhD

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Theodore C. Lystig, PhD

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William T. Carpenter, Jr., MD
Bradley Gaynes, MD, MPH
Carlos A. Zarate, Jr., MD

Invited Guest Speakers
Matthew Rudorfer, MD
Madhukar Trivedi, MD

CMS Liaison
Tamara Syrek Jensen, JD

Executive Secretary
Maria Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:21 a.m., Wednesday, April 27, 2016.)

MS. ELLIS: Good morning and welcome, acting chairperson, acting vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Committee called MedCAC. The committee is here today to discuss the recommendations regarding the definition of treatment-resistant depression, TRD, and provide advice to CMS on the use of the definition of TRD in the context of coverage with evidence development and treatment outcomes.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their

employer's financial interests. Each member will be asked to disclose any financial conflicts of interest during their introduction.

We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or has another formal financial interest in any company, including an Internet or e-commerce organization that develops, manufactures, distributes and/or markets, consulting, evidence reviews or analyses, or other services related to treatment-resistant depression. This includes direct financial investment, consulting fees and significant institutional support. If you have not already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today with a very tight agenda, and therefore, cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when

there are two minutes remaining and then turn red when your time is up.

Please note that there is a chair for the next speaker, and please proceed to that

chair when it is your turn.

We ask that all speakers addressing the panel please speak directly into the mic, and state your name.

For the record, voting members present today for today's meeting are Dr. Harry Burke, Dr. Aloysius Cuyjet, Dr. Salvador Cruz-Flores, Dr. Roger Lewis, Dr. Gail Melkus, Dr. Daniel Ollendorf, Dr. Thaddeus Pope, Dr. Marcel Salive, and Dr. Guofen Yan. A quorum is present and no one has been recused because of conflicts of interest.

The entire panel, including nonvoting members, will participate in the voting. The voting results will be available on our website following the meeting.

I ask that all panel members please speak directly into your mic. This meeting is being webcast via CMS in addition to the transcriptionist. By your attendance, you are giving consent to the use and distribution of

your name, likeliness and voice during the meeting. You are also giving consent to the use and distribution of any personally identifiable information that you or others may

disclose about you during today's meeting. Please do not disclose personal health information.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take heed that their conversations about this topic at hand take place in the open forum of the meeting. We are aware that members of the audience, including the media, are anxious to speak with the panel about these proceedings. However, CMS and the committee will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch.

If you require a taxicab, there are telephone numbers for local cab companies at the desk outside of the auditorium.

Please remember to discard your trash

in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MedCAC meeting are only permitted in the following areas of CMS central site: The

main lobby, the auditorium, the lower level lobby and the cafeteria. Any person found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now, I would like to turn the meeting over to Tamara Syrek Jensen.

MS. JENSEN: I just wanted to publicly thank the panel for coming today on this very important topic, but in an effort to get us back on time, I'm just going to end with that, and I also want to thank everyone who showed up today as well. Thank you.

DR. BACH: Same for me, thank you all for attending and thank you, panel, for your participation, we look forward to an active discussion. I'm going to get started with Linda, do you want to go up and read, Linda Gousis, who is going to read the questions today.

MS. GOUSIS: Good morning. I'm Linda

Gousis, a technical adviser in the Division of Medical and Surgical Services in the Coverage and Analysis Group. Our role here today is to read the purpose of the MedCAC and to read the

questions into the record, so let's begin.

The purpose of the meeting today is to obtain the MedCAC recommendations regarding, one, the definition of treatment-resistant depression, abbreviated TRD. Two, advise CMS on the use of the definition of TRD in the context of clinical studies, coverage and evidence development, and treatment outcomes.

Voting question number one. How confident are you that there is a standard definition of TRD that can be applied to Medicare beneficiaries in clinical studies of therapies for this disease? Use the following scale identifying your level of confidence, with a score of one being low or no confidence, and five representing high confidence.

Voting question number two. If intermediate confidence, greater than or equal to 2.5, is noted for question one, please vote by yes or no as to whether the following are important defining characteristics of TRD that

are to be considered in clinical research: A, the number, duration, dosage and/or classes of antidepressants attempted. B, the use of augmentation/combination pharmacological

therapy. C, type of depressive episode, unipolar, bipolar, psychotic, atypical, other. D, the use of nonpharmacological treatments such as electroconvulsive therapy. E, the use of psychotherapy. F, score changes on standardized and validated depression rating instruments, for example the Hamilton Depression Rating Scale. G, suicidal ideation and suicide attempts. H, other.

Voting question number three: If intermediate confidence greater than or equal to 2.5 is noted in question one, how confident are you that this definition can be applied to Medicare beneficiaries: A, in primary care settings. B, in general psychiatric settings. C, in specialty psychiatric settings. Use the following scale identifying your level of confidence, with a score of one being low or no confidence, and five representing high confidence.

Voting question number four: How

confident are you that each of the below is a reliable, valid and meaningful health outcome for Medicare beneficiaries in a clinical study on TRD? A, improvement or decline in function.

B, improvement or decline in quality of life. C, decrease in suicide ideation. D, decrease in suicidal attempts. E, other. Use the following scale identifying your level of confidence, with a score of one being low or no confidence, and five representing high confidence.

Question number four discussion items. For each characteristic in question number four that receives intermediate confidence greater than or equal to 2.5, please discuss the a priori parameters that define successful or failed treatment. Again, the characteristics looked at in question four were, A, improvement or decline in function; B, improvement or decline in quality of life; C, decrease in suicidal ideation; D, decrease in suicidal attempts; E, other.

Voting question number five. How confident are you that the strategies below when applied to Medicare beneficiaries

represent meaningful and realistic study designs in research investigations performed to evaluate interventions for TRD? A, randomized sham-controlled double blind trials. B,

randomized sham-controlled single blinded trials. C, randomized controlled unblinded trials. D, randomized crossover studies. E, nonrandomized crossover studies. F, pre/post study design. G, other. Again, use the following scale identifying your level of confidence, with a score of one being low or no confidence, and five representing high confidence.

And that concludes the questions. Thank you.

DR. BACH: Thank you very much. I'd like to now have the panel introduce themselves, go down the row and with each of us introduces ourselves, and state what our conflicts are as well.

I'm Peter Bach, acting chair today, although I'm the vice chair of MedCAC, and have no conflicts.

DR. CUYJET: I'm Al Cuyjet, I am acting vice chair, and I have no conflicts.

DR. BURKE: I'm Harry Burke, I'm not acting anything, and I have no conflicts to disclose, and the views I express are my own and not representing the federal government or

Uniformed Services University.

DR. CRUZ-FLORES: I'm Sal Cruz-Flores, I have no conflicts to disclose.

DR. LEWIS: Roger Lewis, Harbor-UCLA and Los Angeles County. I have no conflicts to disclose.

DR. MELKUS: Gail Melkus, professor in nursing research. I have no conflicts to disclose.

DR. OLLENDORF: Dan Ollendorf, Institute for Clinical and Economic Review. No conflicts.

DR. POPE: Thaddeus Pope. I have no conflicts to disclose.

DR. SALIVE: Marcel Salive, I'm with the National Institutes of Health representing myself, and I have no conflicts to disclose.

DR. YAN: I'm Guofen Yan from the University of Virginia. I'm a statistician involved in design of clinical research studies.

DR. LYSTIG: I'm Ted Lystig from Medtronic, I'm an employee and shareholder there, and I'm the industry representative.

DR. CARPENTER: I'm Bill Carpenter, a

psychiatrist and professor of psychiatry at the University of Maryland School of Medicine and Maryland Psychiatric Research Center, and also part time at NIMH. And I have conflicts in that I provide occasional consultation with clinical trials and industry, but none of them involve the subject matter today.

DR. GAYNES: I'm Brad Gaynes, a professor of psychiatry at the University of North Carolina, and I have no financial conflicts to disclose.

DR. ZARATE: I'm Carlos Zarate from the National Institute of Mental Health, I'm the chief of neurobiology and treatment of mood disorders. As it pertains today, I don't have a conflict of interest. Other disclosures are that I am a U.S. federal employee, I have a patent pending in depression with the U.S. Government.

DR. BACH: Thank you very much. The first part of the morning is two formal

presentations of 45 minutes each. On your agenda you will see the speakers listed, although they are actually going to present in reverse order, so if we could ask Dr. Madhukar

Trivedi to come up, Dr. Trivedi is a professor of psychiatry, the Betty Jo Hay Distinguished Chair in Mental Health, and director of the Center for Depression Research and Clinical Care at UT Southwestern. Thank you very much for coming today.

DR. TRIVEDI: Good morning. Thank you very much and I'm excited to be here, this is an important topic. And just a quick sort of, my personal view on this, we have for the longest time, I think depression was treated as if it is an episodic illness that can be easily treated. I think the last 15 years of research has convinced us that this is a very complicated, very heterogeneous disorder, and it is much more complicated to treat, leaving a lot of patients at least not improving with the current treatments we have. So this topic of treatment resistance is very important, and hopefully we will get into all the details.

I have consulted with various industry

sponsors on antidepressant treatment development, both pharmaceutical as well as devices, although I'm not really going to talk about treatment per se today. I'm really

addressing the issue of what is treatment resistance and what can we, how best should we think about defining it.

So, I'm going to address the issue of how big is the problem, is this a small proportion of patients with major depressive disorder, bipolar disorder, is it a larger proportion. What are the impacts, what is the impact, both in terms of health care costs, suicide ideation, suicide attempts, suicides, and what are these ways people have really tried to grapple with this idea for definitions? There is actually some debate and discussion to be had about the effect of the definition, and hopefully I will try and clarify it towards the end of the preparation.

So, depression is very difficult to diagnose. As I mentioned earlier, we do not have a blood test, and therefore I think that is an intense part of the debate. Blood tests are not available for major depressive disorder

or any form of depressive disorder overall, leave alone for subtypes or, for that matter, treatment-resistant. And so therefore, we have to be thinking about how best to diagnose

patients based on symptom history, treatment history, as well as other pertinent information in terms of medication use, substance use, et cetera, all of the factors will have to be thought about as we start defining what is treatment-resistant depression.

We do know that only about a third of patients will get to remission with the first antidepressant medication, numerous studies have shown that. I'll also describe a little bit from a large trial that was funded by the National Institute of Mental Health several years back. About 29 to 46 percent of patients will not respond to pharmacological therapy, even after adequate dose and duration, which is a key issue that one must think about when you want to define treatment resistance.

Just to put words on that, there are many mental disorders where we define severity or poor prognosis based on the disease itself or on pathology or on biopsy, et cetera. In

treatment-resistant depression, unfortunately,

some of this is difficult, as you can imagine,

because somebody has to have failed to do well

on several treatments before you define them

treatment-resistant. You cannot actually generally end up being able to define it earlier, and therefore this idea of whether people have gotten adequate dose and duration of each treatment becomes key in defining treatment-resistant depression.

The bottom line is still clear, that even after a patient has been tried on multiple treatments, medications, augmentations with medication, psychotherapy, exercise, any treatments that have been accepted by the field, even after having tried several of these at adequate dose and duration, there are a sizable proportion of patients who remain symptomatic and do not have full recovery in the short term. Again, in the long term these numbers are actually likely to be higher. We suffer in our field from not having large-scale long-term followup data in order for us to know, but even in this group of patients who belong to the non-25 percent who do well from

time to time, if you look at their outcome in the long term, the numbers are actually worse.

So, there is no accepted, universally accepted definition. Part of it is, I think,

that more recognition increasingly, that this is a much more difficult to treat disease. So that 20 years back, only if you had failed many treatments and also ECT, you would start to find that treatment-resistant. I think we are beginning to recognize that if you wait that long, you are missing a whole chunk or group of patients for whom two, four, six treatment steps may not be accruing additional benefits, so therefore we have to devise a new concept of how we want to define treatment-resistant.

Most current definitions still continue to talk about it as that, treatment-resistant depression is a group of patients who have failed to do well on multiple treatments that have been given with adequate dose and duration. However, with the results coming out from several trials, including the STAR*D trial which I'll talk about, we are beginning to recognize that after the first two treatment steps, the benefits to the patient you get in

terms of third, fourth, fifth treatment trials are very small, and therefore after the first two treatment steps, whether we should be calling that treatment-resistant depression or

not is an area of question and debate, and I'll try to address what different groups have tried to talk about in terms of this definition.

There is no debate about whether after somebody has not done well in five or six treatments, or ten or 20 treatments, that this is treatment-resistant obviously, but that is sort of not very clever for us to really call it treatment-resistant, because if somebody's not done well on 20 treatments, anybody's grandmother can define that as treatment-resistant depression. So the question is, how well and how soon and how precise can we early on, in order to make a difference in people's lives, both in terms of health care costs, in terms of suicide ideation, et cetera, is I think where we have to be going as a field.

And as I mentioned, keep on mentioning, two key elements remain, adequate dose and duration, that has to be defined, and partly that is because there's a sizable

proportion of patients when given an antidepressant, that do not actually follow through on that, and so we have to first define that before you call someone treatment-

resistant. You also have to obviously do a differential diagnosis, ruling out other comorbid conditions, other factors that may be associated with poorer outcomes following a given antidepressive treatment.

So, this question of dose, duration and adherence to treatment remains a big puzzle or issue, before we start defining a group of patients that have a severe enough disease that current treatments may not be the best. And that is: Inadequate dosing is often a big problem; early discontinuation, partially because patients recognize they have side effects; and there is not enough patient education; there's not enough collaborative care being delivered; and therefore, patients are less educated about the need to continue or at least go to the next treatment step; atypical pharmacokinetics, maybe patients who have rapid metabolizers with certain drugs or slow metabolizers, et cetera; those with

determined adverse events, and therefore their adherence to treatment; and then misdiagnosis, especially if there is a misdiagnosis in the setting of other chronic medical diseases,

substance abuse disorders, et cetera, remains also an issue that needs to be address before somebody's depression should be thought of as resistant to treatment.

Depression is often chronic and patients may not adhere. So the chronic nature of the depression in the Collaborative Depression Study, it was a long-running large NIH-funded study, there are patients who were followed up to 12 years, and you can see that only 27 percent of patients did not have even a single asymptomatic week during that study. So this population really clearly helps us understand that there is a large portion of the population that does not do well, and doesn't do well at all actually in this study, and that has to be addressed and not be seen as some, you know, as a normal outcome of disease.

So the prevalence of treatment-resistant depression remains something that people always question, so even in primary care

most often, when somebody thinks about treatment-resistant depression, we all think of these patients as being seen in psychiatrist's or psychologist's offices and that is not

always true. So, this is in a primary care population in the UK, and you can see of this 2,439 patients who responded, 37 percent had minimal or greater depressive symptoms even after 12 months of antidepressant medication treatment. So there is, again, a group of patients even in primary care that remain symptomatic despite treatment.

This is from a Canadian study. Here this was partly based on case reports filled out by physicians in over a thousand patients, they defined it as failure to respond to two antidepressants, and they had, 27 percent of patients had treatment-resistant depression. The features of these are, again, very common and similar to what other studies have shown, patients who have not responded to several treatments end up being those who have early age at onset, those who have had chronic episodes of depression, those who have had early like trauma, those patients who have

associated significant comorbid medical conditions, associated significant anxiety symptoms, are the kinds of patients that remain resistant to current treatments.

So, risk factors for treatment-resistant depression, as I mentioned, actually I've listed some of them already, include comorbid anxiety disorder, suicide risk, and another common feature is bipolarity. Bipolar disorder actually, in saying treatment-resistant, is an important issue that needs to be addressed, and a differential diagnosis that requires understanding of the unipolar depression and bipolar depression is also worth paying attention to, that needs to be seriously considered, and then the same things I mentioned earlier with onset, et cetera.

Health care costs for treatment-resistant depression have been very, are easily seen to be significantly higher than the health care costs for patients who do not have treatment-resistant depression. And in this large economic study based on a very large cohort, you can see about 24,000 patients were defined as treatment-resistant depression, and

their costs were quite significantly higher than those who were not resistant.

Health care costs for TRD and others, this is a study showing that even after you

adjust for other factors, about 30 percent of the cost is, or the cost is about 30 percent higher for people with treatment-resistant depression than for nondepressed, or nonresistant depression.

So health care costs are higher for patients who have treatment-resistant depression and there are many factors, obviously the cost of the treatment itself, but the cost to society is something that we have to be paying attention to, so you can see this data showing about $4,000 in terms of lost productivity associated with treatment-resistant depression and the annual health care costs of $5,000.

Same thing, repeatedly seen, that the more treatment-resistant the patient's illness is, the higher the health care costs, both direct as well as indirect costs, are routinely seen.

The one other important factor that we

have not really paid attention to as a field enough is the rates of suicide in this population. Suicide rate is clearly something that we have to be considering for patients who

have treatment-resistant depression. As we saw in the Collaborative Study, there is a sizable proportion of patients who do not ever have a symptomatic link, that means that there is a longer duration of exposure for them to have suicide ideation, suicide attempts, and unfortunately suicides, and recent data shows that suicide rates are not decreasing, if anything they are increasing in the United States.

So, about 17 percent here of patients with TRD reported prior suicide attempts; again, that is a very large burden for both the patient, the families and society, coming from treatment-resistant depression.

So, how do we define treatment-resistant? As I started the conversation, there is some debate, and let me sort of also clarify this debate first, and then I'll give you what other people, different groups have really used to define treatment resistance.

The debate actually is not whether or not treatment-resistant depression exists, that is clear. I don't think, and I showed you the data and I can show you more.

The debate actually in the field these days is whether we should wait for five, six treatment failures, whether we should wait for failure on different things like electroconvulsive therapy or other treatment before we declare treatment-resistant depression or, like we do in general medical illness, should we start thinking about segregating patients for whom the risk for treatment resistance is earlier on, so that our interventions can actually be matched to patients. That is what we have not done, and I think the debate really primarily revolves around how best to start thinking about it, and I'm not going to sort of tip the scale in terms of my opinion, but I think that is really the issue in the field.

And so, people have used medication failure methods, they have used, defined the category of whether the patient has treatment-resistant depression or not, yes or no, or

there's degrees of failure as well that other people have done, that is the staging model, and there are many groups that have attempted to do this by fine-tuning the methods.

I think John Rush and Michael Thase described this in the early '90s, and strategically most other groups have really sort of modified that a little bit but really the basic principles still apply, and I'll go through that and then give you some idea of the other methods people have used.

So this is the original method that Thase and Rush used to define. This is really using SSRI and tricyclic antidepressants, and those were the primary antidepressant medications available at that time. And then as other treatments started coming along like the selective serotonin reuptake inhibitors, they also modified the condition a little bit. So the first step in it, first was Stage 0, any medication trial determined to be inadequate; Stage I is if they have one antidepressant trial of one major class; Stage II is failure on two adequate trials, two distinctly different classes. Originally in the '90s and

then even in the early 2000s, they and others actually meant this to include an SSRI here, and an SNRI here would be something that you can count.

Recent data are really beginning to question whether there is that big difference between the second step, SSRI and SNRI, suggesting that it is really not that precise, but the point being one adequate treatment trial, two adequate treatment trials, and then really thinking about adding a tricyclic antidepressant although, again, the data supporting the sort of strength of this evidence as a third step over some other treatments, there are very few studies talking about it.

And then the fourth treatment stage failure is monoamine oxidase inhibitors. This makes pharmacological and logical sense, not necessarily all based on pristine well-controlled clinical trials with randomized patients to treat, after treatments, if you add monoamine oxidase it is worse than something else.

So therefore, this really was meant as

a guide and that definition, or that approach to defining treatment-resistant depression in general still really holds. People have misunderstood by calling this only resistant

when these patients have had four treatment failures, but if you really carefully understand this, they are actually talking about treatment resistance starting where we are, and then you are to decide how severe the treatment-resistant form of this depression is, so that a patient here can and should be seen as resistant, but there might be people for whom tricyclics are able to be recommended.

The Mass General approach is very similar to it, although they focus a lot more on the adequacy of the dose and duration of the treatment exposure, and actually there are two major approaches that document the level of resistance. One is, the Mass General Hospital has a questionnaire called ATRQ, which stands for Antidepressant Treatment. And then the other is, the Columbia group has used a questionnaire for a very long time, again defining the exact clarity of how well the antidepressant was delivered in the patient's

22 past. That talks about dose, duration and

23 adequacy of the treatment trial, really

24 defining whether somebody had one, two, three,

25 four treatment failures. How best then to

define the addition of an augmentation agent that is not itself an antidepressant treatment, medication or psychotherapy, et cetera, is something that both the MGH approach and the Columbia approach tried to accomplish.

The European method really, again, builds on the same things, a nonresponder to six to eight weeks of traditional antidepressant treatments, but they include any of these, including SSRI, ECT, and then there is a staging of treatment resistance that is one treatment trial, two, three, four treatment trials approach. And then if it is for over 12 months, they call it chronic resistant depression. This is the European method of defining treatment-resistant depression, again similar models, similar logic, but this method tends to actually also emphasize the duration for which somebody has remained resistant.

The Maudsley method is slightly more sophisticated in terms of trying to figure out

scoring based on the kinds of treatment exposures patients have had, all trying to try to figure out if it is really III, Stage 3 treatment resistance or 3.5 treatment

resistance, but again, not any profound difference in terms of the principles used.

So, the question and the debate that I was talking about is, should this staging that was brought out by Michael Thase and John Rush in the early '90s continue to be the same approach, or should we start thinking about whether at the end of two or three treatment steps with current antidepressants we have now arrived at a point where the patient's history defines them as a group of patients who are at high risk, or higher risk for resistant depression, and therefore requiring or needing special attention by the assessments, treatment, et cetera.

I'm not going to go into the questionnaire, but this is the kind of thing, just to give you an idea, of the questionnaires that are used in order to define exactly the nature and the position of the antidepressant treatment trials.

So, bottom line is at the end of the day, our goal, in order to ensure that somebody has been getting adequate treatment before they, sort of in the early stages so that we

can then pay extra attention or special attention to patients with treatment-resistant depression, would require that these four steps be part of that as a treatment is started. So any given antidepressant treatment trial is started with medication, psychotherapy, it doesn't matter what treatment, should be fully optimized in order to, A, give the patient the best chance of success, and prospectively, eventually what we end up with is a subgroup that requires additional attention, we have actually good enough confidence that they have had good trials.

And if the optimized treatment does not meet to our expectations, then we should think about whether they should be switched, whether a combination should be used, or an augmentation agent to be used. For the purposes of this discussion and overall in general in the literature, when somebody talks about combinations, it's two antidepressants

that individually have been seen as antidepressants in their action, augmentation is an augmentation agent that itself is often not seen as an antidepressant but when added to

the antidepressant medication and psychotherapy, augments that effect, and lithium comes to mind as a classic augmentation agent.

So, a few words on the STAR*D trial and then I'll stop. And so the sequence for the treatment alternatives to relieve depression was large, in fact the largest clinical trial still conducted in terms of efficacy for antidepressant treatments, it was designed to answer this kind of real life question, it was done in real practice, primary care and specialty care settings, 4,000 patients. The patients were really entered into the study with the assumption that they would really try to address the question, if the first treatment does not work, what is the second best treatment; if the second doesn't work, what is the third best treatment; if the third doesn't work, what is the fourth best treatment?

This was done, started in the late '90s and finished in 2006, had been primarily with medications and psychotherapy, or only medications and psychotherapy, and what we

found is that at the end of first step, remission rates are about 30 percent, at the end of second step, remission rates are close to 25 to 30 percent, but the remission rates of third and fourth treatment steps dramatically drop, and that was the question of whether you should start thinking about the group of patients at this point as people we should be thinking about differently.

There was some distinction in the STAR*D trial, and let me take a minute to walk you through this. If patients, this was citalopram, if patients had not done well on citalopram they could be switched to a second antidepressant medication or psychotherapy, so there were three antidepressant medications and psychotherapy, or they could be augmented with an augmentation agent, two augmentation agents, or psychotherapy, and similarly for third and fourth treatment steps.

And as you can see, for these patients

who ended up being augmented with just a second treatment, they did slightly better than those who got switched, with a very major caveat for you to remember. That is, this was done in an

equipoise randomized design so the patients had a choice to make at that point. And so therefore, this group of patients would have agreed to go to an augmentation primarily because they were able to tolerate this treatment or at least were willing to go along with it, and were wanting to try a second thing added to the first. This group of patients may have actually primarily said I am done with this treatment, give me something totally different, and therefore these groups are slightly different in their clinical status, so we shouldn't automatically jump to the conclusion that augmentation is always better, but at least in this group of patients for whom augmentation was chosen, their remission rates are higher.

The long-term outlook for depression treatment is why I think this topic is that important, I think this is not only the short-term outcome that we should be thinking

about, the long-term outcomes for this disorder are very troublesome.

So this is for people who got well on the first treatment step, then you did a

one-year naturalistic followup. You can see a large proportion, even those who are in remission, about 30 percent of these patients, 33 percent of these patients actually relapsed. If the patient entered this long-term phase without achieving full remission then the relapse rates were even higher, and then the succeeding steps, this is the most amazing, that at the end of second or at the end of four treatment steps, they were in remission at the beginning of the long-term phase, and still the relapse rates were significantly high. So that means that the treatment of depression really should not actually be seen as a very short lasting episodic illness, but that we should be monitoring the long-term course and probably thinking about additional treatment approaches.

There is also the other issue, and that is, the clinical practice has moved a little farther ahead from the data we had, so if you look at rates of combination

antidepressants in the United States, this is also Mark Olfson's data, between 1996 and 2005-06, the rate of use of combination antidepressants in the United States doubled,

so we have to follow that up with a study trying to address the question as if you started the patients on two combinations at the beginning and compared that to monotherapy, would that produce better outcomes so to speak, stave off resistance in these patients if you were aggressive to begin with.

Remember, the options were, again, using traditional antidepressant medications, and so here what we did was we compared bupropion and escitalopram, and venlafaxine and mirtazapine, to escitalopram alone, to find out whether a combination arm can produce higher remission rates if you start patients on it. So it is, again, we want to emphasize that the pharmacotherapy they used was traditional, it was nothing that was novel or different, and you find that remission rates are no different for people who are started on a combination as opposed to those who are started on a monotherapy, so at least with these

antidepressant medications you are not actually reducing or improving the chances of success compared to a monotherapy.

So, let me end by saying it is common

and costly, and it does account for a fair, for a high risk of morbidity and mortality for patients with treatment-resistant depression, and options are -- fortunately, that wasn't part of my presentation, but I think few options are available. Thank you very much.

(Applause.)

DR. BACH: Thank you very much, Dr. Trivedi. I'm going to next call on Dr. Matthew Rudorfer, who's a program chief at the National Institute of Mental Health.

DR. RUDORFER: Good morning. It's a pleasure to be with you this morning. This is actually my first MedCAC meeting and I've already learned three new acronyms. I have no disclosures to report, and the opinions I voice are my own, though I think for the most part they will be reflected in the evidence.

And to begin, I just want to note, our discussion today will be focused on treatments of proven efficacy and effectiveness, but it is

important to note that people continue to use a variety of interventions that are not proven and not tested, and one of my favorites, puppy licking your face is a common augmentation

agent, but I have no clinical trials to present.

Now, I'm sorry for the busyness of this slide, but it tells a good story in one picture. This is to focus us on where we are right now in the treatment of late life depression, this is from Chip Reynolds and his colleagues at Pittsburgh. They write:

"In general, the pharmacologic treatment of nonpsychotic major depressive disorder in old age is only partially successful, with approximately 50 percent of older depressed adults improving with initial antidepressant monotherapy. If an initial antidepressant trial fails, the clinician has two pharmacologic options," just as we heard about in STAR*D, "switch or augment on the one hand, or combine antidepressant therapies. About 50 percent of patients who do not improve after initial antidepressant therapy will respond to either switch or augment.

"If the clinician treats vigorously and if the patient and clinician persevere, up to 90 percent of older depressed patients will respond to pharmacologic treatment.

Furthermore, electroconvulsive therapy or ECT is a safe and effective nonpharmacologic strategy for nonpsychotic major depression that fails to respond to pharmacotherapy.

"Getting well and staying well is the goal; thus, clinicians should treat to remission, not merely to response."

So what I thought I would do with my time is present an overview of the study of depression with a skewing towards treatment resistance, a skewing towards older folks, and a skewing towards some of the methodologic challenges that complicate the interpretation of the data and will inform how we proceed from this point on.

So I would like to start at the beginning, and I'm told that on Security Boulevard the beginning of time is defined as 1965, with the birth of Medicare and Medicaid. Now across the pond in the UK, some exciting thing were happening also. The Beatles

released their second full length feature, Help, but we won't go there, but in the world of clinical research, this remains one of my favorite clinical trials, not to be replicated.

This Report to the Medical Research Council published in the British Medical Journal in '65, reported 250 hospitalized patients. These were not treatment-resistant, this was pretty much standard moderately depressed patients, many in primary care, and they were randomly assigned to four weeks of inpatient treatment with one of these interventions, one of the two standard pharmacotherapies at the time, an intravenous tricyclic, phenelzine or Nardil, placebo, or ECT.

Now it's particularly fascinating here, first of all, I just wanted to note, because this is one phenomenon that has been lost to time, studies in inpatient samples are mostly a thing of the past, and of course for many folks today, hospitalization is not cost effective, it is much less frequently done than back in the '60s, say through '80s, and of course the hospital stay today would be measured in days and not weeks. The advantage

of a study done in an inpatient stay is that on the one hand it's a kind of screening for severity, if you will, if someone is sick enough to require to be in the hospital for

weeks, that usually indicates that their level of depression and level of dysfunction is quite severe, and existing treatments could often be safely discontinued and new treatments started and given enough time to see if they will work. Also, the idea of randomly assigning people to ECT or any other active intervention is exceedingly hard to find in the decades since this was done.

Now for reasons that were not explained, in this first four-week phase of the study, men and women were analyzed separately. There was a notable placebo response. Now again, these were folks admitted to the hospital, which certainly probably contributes to that. The MAO inhibitor had some efficacy in the men, and for reasons that baffled the authors, it really didn't work at all in the women. Imipramine, really the prototype antidepressant of the era, was nicely effective in the men, a little less so in the women. And

of course ECT blew everybody, blew the other treatments out of the water.

What is especially striking, and I thought it's worth noting here, because you

remember what Dr. Trivedi mentioned a few minutes ago, that again, these were not treatment-resistant patients, it's both a sign of the potency of ECT and a reminder that it's not necessary for many people to wait until they fail 20 treatments to think that maybe one needs to go beyond the usual pharmacotherapy.

The other point I'd make about STAR*D which Dr. Trivedi so nicely described for us, is that it really has a major impact to the field in introducing the concept of the stepwise treatment algorithm, that is, as opposed to taking each patient and trying to match them individually with an existing treatment, the idea was to go through a logical series of steps allowing adequate time and dosing at each, and then having preplanned branch points.

I'm sorry, I realize this is quite illegible, but I'll point out the key highlights. Ben Mulsant at Toronto reanalyzed

a couple of subsequent large clinical trials in late life depression, also using a similar kind of treatment algorithm. He had the IMPACT study with three steps, and PROSPECT went to

six steps. And in IMPACT, rate of response which was defined as 50 percent reduction in depression score after 12 months, the step care approach using this kind of algorithm showed a 45 percent response rate compared to usual care with only 19 percent. And PROSPECT, the results are a little less dramatic but also significant in favor of using this kind of STAR*D like algorithm as opposed to usual care.

Subsequently, these are practice guidelines which I just want to call your attention to, one or two interesting things. This is U.S. guidelines, and Canadian next to them. Here's an item, what to do in case of partial response to initial antidepressant? The U.S. says combine or augment with another agent and the Canadians say switch, and I just thought that was interesting in that as we saw with STAR*D, that's still an unsettled question and remains open to further study, and often is still a matter of clinical judgment.

Agent to consider for combination or augmentation, both guidelines agree that bupropion and lithium are good choices, this now admittedly was from 2001, and the U.S. was

still talking about nortriptyline, the tricyclic, and the Canadians five years later had dropped the tricyclics altogether and moved on to mirtazapine. I think that remains an interesting question for further consideration, that is, should we totally rule out the older classes of pharmacologic agents in treatment-resistant patients.

Mulsant came up with his own synthesis of the current literature which looks like a kind of streamlined STAR*D, and I think that is pretty typical of today's clinical approach.

Now, I just want to mention something about the different types of clinical trials because as I think you've gathered already, not all trials are the same, and I find it particularly helpful in understanding the literature to appreciate the differences in methodology which often can greatly influence the outcomes. So by efficacy, that's so-called regulatory trials, and this is an overstatement

for yesterday, but these are the standard FDA type active drug versus placebo studies and these are, remain essential for proving that a treatment actually works. The dilemma which

even the FDA now acknowledges is that generalizing from that to actual clinical samples can be a challenge when many of these trials are done in young physically healthy white people, formerly men only, and don't resemble the actual patients being treated.

And so that led to the concept of the effectiveness trials, which STAR*D is a perfect example of, where inclusion and exclusion criteria would be typically less stringent, people with comorbid conditions, making taking other meds for other illnesses would not be excluded as they would be in an efficacy trial, and the important point there is that that has to build on efficacy, because by the effectiveness stage it's pretty much too late to see if something works, but if you want to see if it actually works, you do want that more homogeneous sample, but they work nicely sequentially like that.

And I'll say something about where

we're heading with clinical trials and I say well, the ultimate goal of personalized treatment, I think, remains a little bit beyond our grasp at the present time.

Now, former NIH Director Tom Insel has moved on to GoogleHealth, so you know he knows the future. Now, he had this very nice description of experimental therapeutics as an approach to clinical trials, essentially introducing a translational aspect to clinical trials. That is, instead of just, here's a treatment, let's see how the depression rating changes, introducing a step in between to see that the intervention is actually engaging the target that's presumed to be the focus of the treatment, and that that engagement is actually contributing to the clinical effect. In other words, trying to get at that kind of black box in between giving a medication and doing a rating, and this is still a new concept and this is what we are now requiring of all NIMH clinical trials, so I hope that will inform us going forward.

Dr. Trivedi mentioned the, some aspects of trials, I'll just skim over lightly,

but I think that in reviewing the literature, there are a number of aspects beyond what kind of jumps out at one that are important to consider. So that, the way people are

recruited to trials is not always obvious, but in recent years it's been noted that the placebo response rate in many trials seems to be creeping upward, and why could that be? One possible reason that's been put forward is that increasingly subjects are recruited not through clinical channels but maybe through advertising, and are some of those folks less seriously ill to begin with and are less likely to respond to an active treatment, more likely to respond to a placebo, those are open questions.

The comorbid conditions is certainly very important because while comorbidities are allowed in effectiveness trials, you want to know about them so you can properly account for them, and I think the main message here is there are many aspects of subjects in clinical trials that you don't know unless you ask, and in many trials if you're just kind of glancing at an abstract quickly, you might not

appreciate that the interrogation of the subjects might have been more or less comprehensive, and that can really influence how much you know about the people being

studied.

Similarly, all trials are not the same in terms of the treatment that is in the control condition. You know you might be studying a new treatment or combination of treatments for depression, but as we'll see in a minute, even issues like the nature of placebo, the field has been arguing about probably going back to 1965, if you think about it, a group taking, say a tricyclic antidepressant and another group taking a placebo, it wouldn't take -- well, as Dr. Trivedi would point out, anybody's grandmother could probably tell the difference between a tricyclic filled with adverse effects and an inert placebo, so the field could argue for many years whether we need active placebos, and that really never caught on.

Ratings we know are important. The Hamilton rating is one of those instruments that pronounced, it's pronounced dead and passe

about every other year, and we're still talking about it. It still, it remains the gold standard. Its primary problem is that it has a lot of focus on somatic symptoms and if we get

into the DSM at all today, you will soon see that when we look at, say DSM-V criteria for major depression and the proverbial five of nine symptoms, not everybody with major depression has the same symptom cluster and there are folks who really have little in the way of somatic symptoms, and on the other hand, sometimes an immediate effect of a drug-like sedation can have a disproportionate effect on a Hamilton symptom without getting at the core features of the depression.

As we saw with the STAR*D trial, the QIDS has now become a standard alternative, and especially in European studies, the Montgomery-Asberg, MADRS has been very popular and is said to better reflect the changes induced by treatment over time. Now in the efficacy trial era, the Hamilton score was the be all and end all, and now of course we're looking at other outcomes as well as you see here, suicidal ideation and behavior, and all

important functioning, which is obviously key to relieving resistant depression, quality of life, and the interaction of mental health and physical health.

Now, just one more point in terms of trial design, in screening tools such as the Patient Health Questionnaire Nine, which is very common now in primary care, and rating instruments such as Hamilton, are not substitutes for complete history and diagnostic assessment, and I think that's really key because there are the occasional trials that can still slip into the literature where if you look at the inclusion criteria it might say all patients meeting the PHQ-9 criteria for major depression, which is perfectly true but totally inadequate, because you don't know anything else if all that happened was a research assistant stood with a checklist of DSM criteria. And so major depression can be a final common pathway of many conditions, it can be associated with all sorts of other mental and physical health issues, and even the very basic, as Dr. Trivedi pointed out, the very basic distinction between unipolar and bipolar

depression can sometimes be missed, and sometimes takes some digging because if a person, say, has bipolar II disorder, they might well seek treatment for their depressive

episode and fail to mention anything about hypomania unless they're actually closely asked about it.

And similarly, we all are familiar that many relatively serious conditions such as OCD can be fairly silent if a patient or a would-be subject in a trial for an antidepressant is not asked about it, so a full diagnostic inquiry certainly is the state of the art.

Moving along, along those same lines, we know that there are some useful subtypes of depression, and then there are some subtypes that haven't quite lived up to their reputation, so psychotic depression is one of them. Again here, in many cases this will be obvious but if a person has, say, delusional ideas and is not verbalizing them, that can be easily missed. I'm thinking of a woman I once asked to sign a consent form for an ECT trial and after she signed, I asked her what it was

she had just agreed to and she said, well, she just signed a confession to the police because she must have done something terrible.

So, this study shown here, STOP-PD and

the followup, STOP-PD-2, is specifically using combination of an antipsychotic and an antidepressant. The real question is, how long do people need to stay on their antipsychotic and again, as you can imagine, folks in a trial like this you would not want in the typical treatment-resistant depression study that we're talking about, because it is very unlikely that you could expect them to respond to monotherapy with an antidepressant agent.

Now, a couple words about the switch in augmentation issues we've been discussing this morning. I think it's safe to say that on the whole, there's a certain amount of evidence for several approaches and so, this is different doses of quetiapine, atypical antipsychotic. These are depression scores going down in this six-week trial comparative to continuation of an only partially effective antidepressant. And a longer study with aripiprazole similarly shows that adding that

in an atypical to a partially effective antidepressant was, certainly was effective. What we still lack is that personalization aspect to be able to predict for whom is this

an appropriate intervention, why not add lithium instead, and we really don't know at this point.

This was a nice recent meta-analysis showing a total of 18 randomized clinical trials showing the effectiveness of atypical antipsychotics as adjunctive agents to partially effective antidepressants. What I think is particularly interesting here, it does show how even though clinical trials can sometimes seem far removed from the clinic, they can provide very practical information, and that was the finding that low dose atypicals actually were not effective, that it required full standard antipsychotic dosing, which might not have otherwise seemed obvious.

Psychostimulants are, for many years have been one of the kind of go-to treatments for older people, especially with many physical health challenges where docs are often reluctant to add an antidepressant maybe to a

22 complicated medication regimen. And there is
23 certainly some evidence in the literature, I
24 put this here really just to show with this
25 relatively recent publication that we're still

talking about case series and really not well designed clinical trials. So again, there are a lot of treatments out there with really very varying levels of evidence.

A new publication by Jan Fawcett and John Rush and colleagues, pramipexole, the dopamine agonist, this is also a case series, they did manage to collect 42 patients, so this we still need to take with a grain of salt, this is not a controlled trial. What I thought was interesting here on their idea of who responded, they talk about depressive episodes that are associated with severe anhedonia, lack of motivation, inability to initiate behaviors and unreactive moods, those are likely candidates. In one sense it's a bit of a throwback to the idea of trying to match patients with treatments, it's interesting that this is not a typical antidepressant. So I mean, I think that's certainly in need of further definitive study, but that's an

interesting idea, I think, because it's something that the field has really been looking for for some time.

I just want to quickly skim over the

devices, because we could spend a whole day or longer on this, and maybe you have, or will. I think it's safe to say that ECT, which here, this is a unilateral electrode placement which they undoubtedly did not use in that 1965 study, so that we do have more modern approaches to this old treatment method. ECT remains the gold standard for treatment-resistant depression and there's a reason it hasn't gone away after all these years, because nothing really has been able to replace it.

As we're well aware, other device-based interventions are at varying levels of evidence, so vagus nerve stimulation is on the market and the field continues to discuss this, the acute results were disappointing but there seems to be a later stage efficacy for some patients. Again, the nature of that response and for whom, I think remains an unsettled question.

Similarly, rTMS is on the market. It

was actually initially approved specifically for early stage treatment resistance, so that has been loosened. It was initially defined as indicated just for folks who had failed one

antidepressant trial, and now that's with the addition of multiple devices, that's been expanded. An interesting fact here is that as I'll show you in a minute, the best large scale trials were by their very nature efficacy trials, meaning they used rTMS as monotherapy and the results, while significant, were less than startling, and leaving us with the question, well, but in real life circumstances, wouldn't you combine this with medication, or increasingly even, people are trying to combine it with cognitive therapy and so I think that, again, there are many open questions there.

They have deep brain stimulation, there are certainly, there are ongoing studies so far with mixed results in the literature.

So ECT, just to make the point that in geriatric depression in particular, ECT is long felt to have a place in the armamentarium. Sarah Lisanby published this review, a 75 percent remission rate which we're not used to

seeing in psychiatry, and an effect size greater than pharmacotherapy. Now to be fair, this was not based on random treatment assignment like in that early British study, so

people are carefully selected for likely response to ECT. A longstanding question was how to keep people well after they responded to ECT, and I think this remains an active question for many newer treatments under study, which seem to have a short duration of effect, and we've supported studies showing the effectiveness in some people of various forms of pharmacotherapy and continuation of ECT, so even here there is a substantial relapse rate in the first year after response, so more work is certainly needed.

This was just a recent study quantitating the speed of remission of ECT, which again, in some cases would call for its use. This was specifically in older folks, but this kind of result would call for its use earlier in the algorithm than one might think of otherwise, so that an older patient, for instance, who is close to refusing to either eat or drink and might be at very serious

danger of physical harm, one does not need to say well, we need to go through these eight steps of the algorithm before we get to ECT.

And a recently completed NIMH

supported trial, Prolonging Remission in Depressed Elderly studied a novel form of personalized continuation ECT whereby depending on weekly Hamilton ratings, a patient who had responded acutely to ECT could get one or two maintenance treatments that week or skip that week altogether if they remained in good shape, trying to use the lowest effective dose, if you will.

And another older slide but unfortunately still relevant, this showed the distribution of ECT across the country, so high ECT rates are in black and no ECT reported is in white, so this is the picture worth a thousand words and if anything, this is a 20-year-old survey and I think it's safe to say if anything, there'd be more white on the map today. And I think less often appreciated is that especially as we talk about specialized treatments, and even cognitive therapy could be included, that it can be surprisingly hard to

find really well qualified, well trained practitioners, especially once we get away from the major metropolitan areas.

I mentioned rTMS. This was the

Forsythe trial, or Mark George, that NIMH supported. So a remission rate of 14 percent with active rTMS and five percent in sham was significant and again, obviously that one could say is less than exciting, and to be fair this was rTMS monotherapy. But the other interesting thing here that might be particularly important going forward was Dr. George and his colleagues spent a lot of time developing a sham version of rTMS, which has now become pretty well standardized in the field, and the idea being that one could hook up the patient to the device, put the electrode on the scalp and have it actually heat up, vibrate, make noise, and for all the world seem like the real thing, only there's a metal plate blocking the magnetic waves from actually going into the brain, so that it's an ideal kind of sham device which we're not used to seeing in psychiatry, because all these years it's really been difficult to do with ECT.

There were about a dozen British studies a generation ago but that's, would be very problematic today, because sham ECT would require giving people general anesthesia and

then not actually giving them a useful intervention, so I think ethically we would frown on that today.

Among the issues of diagnosis, one phenomenon in older folks that's very easy to miss is the idea of complicated grief. And as you may know, the DSM committee struggled a lot with the so-called bereavement exclusion in depression, which is no longer with us, the point being that if a bereaved person has depression, they should be treated for depression. A lot of work that we've supported, many done by Kathy Shear and her group at Columbia, has identified complicated grief, really unusually prolonged disabling grief which is especially prevalent in older women in their samples, and it's as if there's depression to be sure, but with an overlay of what seems to be something akin to post-traumatic stress disorder. And so they've developed a psychotherapy that essentially took

elements of both, took cognitive therapy and added some prolonged exposure components as might be seen in treatment of PTSD, and have developed a very effective psychotherapeutic

intervention.

This JAMA paper from 2014, they actually with a complicated group compared it to interpersonal therapy, which was very brave of them, there's a specialized psychotherapy for depression, but the response rate was double for the complicated grief therapy cohort.

And they just finished an AMA supported Forsythe trial adding in a pharmacotherapy option, so as you can see, these are cognitive grief psychotherapy and citalopram alone or combined, and we're expecting those results soon.

My point here is that what is still unclear is whether folks who would be studied in this kind of trial would be included in a treatment-resistant depression study and if so, would that influence the results one way or another. Again, I think it's fair to say that depression remains a very heterogeneous

condition and it is sometimes very tempting to overlook that in the interest of filling the cells in a study, but sometimes we can wind up diluting otherwise good results.

The last item I want to cover, then, takes off from there in terms of the larger issue of where exactly does psychotherapy fit in the issue of treatment-resistant depression, and I think different approaches have been taken with different and sometimes slightly conflicting results.

This review in 2010 was very frank in terms of the utility of psychotherapy managing treatment-resistant depression; the evidence is sparse and results are mixed, and I think that was very accurate. We tried to hone in on that with a couple of very specific studies.

REVAMP used a modified form of cognitive behavioral therapy called CBASP, cognitive behavioral analysis system, which was designed to treat chronic depression, and this was an interesting design of optimizing pharmacotherapy in people with depression and then if folks did not adequately respond, augmenting with either CBASP, this novel CBT

22 treatment, or just supportive psychotherapy,

23 and unfortunately the results were

24 disappointing. These were the nonresponders

25 and the partial responders, this being the

Hamilton depression score on the Y axis, and essentially you see these groups of three bars representing meds only, meds plus CBT, meds plus supportive therapy, and basically they're all the same. In other words, augmenting, optimized medication with psychotherapy, even this highly specialized form of CBT, did not seem to make a difference.

Now back in Britain, they're looking at the effect of adding a (illegible) to behavioral, no, not just that. I don't know how they came up with CoBalT unless they were just looking for a word that they could use CBT in, but this was actually, Dr. Trivedi showed one of their design slides just showing the high incidence of treatment-resistant depression in primary care, and so they rounded up many practices to contribute to this study to see if augmentation of antidepressants with CBT could be effective, and I think what was particularly nice here, going back to one of

Dr. Trivedi's early caveats, they have up to five years followup, which is very hard to find and very impressive.

They did admittedly have a lot of

blank space in between, but nonetheless here, this is four-year followup and they said well, the, everybody seemed to improve though nobody was perfect, but people who wound up on that combination fared better over time. And I just like this, they often have interesting turns of phrases across the pond and I just like this, good value for money, that's a very direct observation, that this was a very cost effective intervention that kept people well for three to five years.

On the other hand, this study published in 2014 by a very stellar group of investigators has proven somewhat problematic. It's so problematic that in between the time I submitted the slide and today, they retracted the paper, but then they contributed a revised version of it. There was apparently some problem with the pain analysis, but the results are unchanged. Here in contrast to that CoBalT study where partial responders were augmented

with CBT, here from the get-go folks with depression were randomized to either meds alone or meds plus cognitive therapy. And again, just at the outset, these are very serious

investigators led by Steve Hollon, who is certainly a leading investigator in CBT for depression, so you know that the treatment was very well provided.

As a function of severity, these less severe folks, more severe. The lighter blue line, which is a little bit higher showing greater improvement, was really not much different in the less severe group. In the more severe group, the addition of CBT from the outset did seem to make a difference.

Now just looking at the severe group, who as a whole did well with combined treatment, here we have the less chronically ill, and you can see here the kind of results that really were expected more or less across the board. These are folks treated just with meds, these are folks treated with a combination of meds plus CBT, and you can see recovery rates on the Y axis going notably higher with the combination group. On the

other hand, the more chronically ill didn't make a difference.

So they were left with this unexpected finding that augmenting antidepressants from

day one with CBT seemed to be helpful, but only for some people, in the more severe but less chronically ill patients, and to state the obvious, that will require further study and replication, but I think it's a good illustration for us of how the field is not yet at the point of very clear-cut definitive findings.

Michael Thase did publish a very laudatory editorial, but to be fair, that was before the data problems were found.

DR. BACH: Dr. Rudorfer, take about five more minutes, please.

DR. RUDORFER: So to wrap up, let me just point a little bit towards the future. You're probably all familiar with ketamine so I won't go into that, a very nice acute treatment response often seen within an hour, can last anywhere from a day to a week or so, and again, I think there the issues are sustaining that improvement.

I just want to point out one thing as I wrap up and that is, increasingly the field is looking at components of mental disorders, including depression, as possible on one hand

building blocks of pathophysiology, and on the other important to us today as targets of treatment. And so here just looking at the anhedonia item on the, in this case the MADRS scale, anhedonia being obviously a key component of serious depression, you can see the response to ketamine.

Similarly, suicidal ideation as a target of treatment unto itself has been gaining traction in some studies, ketamine in red, wish to live going up, wish to die going down.

And an experimental intervention, magnetic seizure therapy, which I thought was interesting just in terms of is that depression per se, but remission of suicidal ideation being the target of the treatment, you could read this in last month's JAMA Psychiatry.

And one of the newest medications on the market, vortioxetine, has what appears to be unique data in terms of a positive effect on

cognitive symptoms associated with depression, and they have been in discussions with the FDA seeking to expand their labeling, although I think that's taken a turn for the negative.

And so, we are trying to support this type of going back to basics, back to the building blocks of mental disorders, away from focusing narrowly just on DSM categories with our RDoC project, which you can read about on our website, and on that note, I thank you for your attention.

(Applause.)

DR. BACH: Thank you very much. I appreciate the speakers' carefully designed presentations and also for being on time. So, we're going to take a 15-minute break, we're going to start again at 10:13.

(Recess.)

DR. BACH: The next section of the meeting is we have some scheduled comments, we have eight speakers who are scheduled, beginning with Dr. Aaronson. I'll ask that Dr. Aaronson proceed to the speaker and the next speaker have a chair, who is Dr. Sackeim, if you could come and wait in the chair.

One side note. Out on the desk there is a list of people who would like to sign up to make open public comments which we will do immediately after this, it's a brief period of

15 minutes. No one has signed up, which is of course fine, don't feel pressured, but if you would like to make a comment we'll leave the list open, you need to fill out the disclosure form that is next to it. If you'd like to do that, please do that in the next half hour. Anyway, so thank you very much, Dr. Aaronson, you have seven minutes.

DR. AARONSON: Thank you. I'm Scott Aaronson, I'm director of clinical research programs at Sheppard Pratt Health System in Baltimore, and a clinical associate professor of psychiatry at the University of Maryland. I have these disclosures, and I'll proceed to talk.

Depression is a very serious disorder with significant morbidity and mortality, it's a leading cause of disability in the U.S. and six out of ten Medicare beneficiaries under the age of 65 are diagnosed with mental disorder, with mood disorders being the second leading

cause of disability in Medicare recipients under the age of 65.

Depression is one of the best predictors of the onset of stroke, diabetes and

heart disease, and anytime it's comorbid with any medical condition it worsens the prognosis as well as the expense quite dramatically. People with depression are three times more likely to have heart attacks and it's a stronger indication, actually, than hypertension. As well, a number of chronic conditions like asthma and other autoimmune diseases have a much higher likelihood in people with mood disorders.

Every 13 minutes an American dies by suicide, so we're counting up to 40,000-plus deaths per year by suicide, and 90 percent of these people who committed suicide have a diagnosable psychiatric condition at the time of their death, and about half of those people who commit suicide are suffering from major depressive disorder. Mortality rates in Medicare beneficiaries with depression are similar to the overall population, but the age of death is about 11 years younger.

The expenditures for patients with depression get added on to the medical expenditures and while you see that folks with depression, you see the actual mental health

expenditures are relatively small, they dramatically increase the total medical expenditures.

And in general, if somebody shows up at a primary care clinician's office with two complaints of physical problems, they are twice as likely to have depression. For each additional medical complaint they've had, you actually can sum up and say for three complaints they're three times more likely to have depression, and even when you get up to nine complaints, they are nine times more likely to have depression.

CMS recognized this in 2011 and decided to cover annual screening for depression, and this is an important step forward and we need to continue to have access for these patients throughout the continuum of care and for people with treatment-resistant depression.

I think that staging depression should

not be different than the staging of, in oncology for cancers, where the more aggressive, toxic or expensive treatments are reserved for the more severely ill. I think

that's fairly easily translatable within psychiatry.

Most of my research is in fact in treatment-resistant depression using a variety of different agents, as well as different somatic equipment, and I just want to give you some perspective about where the field is with regard to treatment-resistant depression. As an investigator for a number of different studies, we're very used to routinely staging patients and most of the protocols that I do these days actually require pretty specific staging that, we have to evaluate the records of all patients coming into a study and determine their level of treatment resistance. We log basically every adequate trial of an agent both in current and past episodes, and we calculate the severity of their illness based on the number of adequate medical and somatic therapies, and some trials as well include calculating psychotherapy.

Increasingly, some of the studies, as the prior speakers have mentioned, are including suicide as a marker, which with some of the more recent agents like NNDA and

ketamine become a particular target for symptoms. From the clinician point of view, another one of my roles at Sheppard Pratt, which is a very large psychiatric teaching hospital, 330 beds and several hundred psychiatrists, I'm the psychopharmacologist of last resort. My colleagues know what treatment-resistant illness is and I don't get calls to see people who don't have treatment-resistant illness, the clinicians are never in doubt when they want an expert opinion. Patients too are very well aware when they have a treatment-resistant illness. It's actually easier for me to do studies that require me to find people with treatment-resistant illness than to just find standard people with depression who have not already been exposed to a number of agents.

As well, my retention of patients in TRD studies is superior to that in just my routine studies because these people are

desperate, they want care. My retention rate for a study that was a five-year study looking at people with an implantable device, our retention rate was 90 percent over five years,

so we need to be able to offer these people something.

I'm actually part of a triad of psychiatrists who will be presenting. My colleagues Dr. Sackeim and Dr. Conway will be addressing the more specific questions from the panel, and I also want to mention that the patient perspective will also be addressed in greater detail by Charlie Donovan. Thank you.

(Applause.)

DR. BACH: Thank you very much for your comments. Our next speaker is Dr. Harold Sackeim, professor in the Departments of Psychiatry and Radiology and the College of Physicians and Surgeons at Columbia, and emeritus chief, Department of Biological Psychiatry, New York State Psychiatric Institute.

DR. SACKEIM: It's a pleasure to be here. Could we have the slides? I see them, but you don't. That will induce treatment-

resistant depression. There we go. Thank you.

In terms of disclosures, I consult to a number of companies that work with brain stimulation devices as well as pharmaceuticals

and I'm the inventor of two forms of brain stimulation that are used primarily in treatment-resistant depression.

The most common instrument used to assess treatment resistance across the world is the antidepressant treatment history form, which is an instrument we created in the late '90s, early '90s actually, and I want to highlight some features of it so you get the sense of how reliably and validly we can assess treatment resistance. This is certainly critical to the definition of what treatment-resistant depression is.

In clinical practice and in the world we're going to see patients who have a treatment history and so we're going to have to retrospectively evaluate whether or not their trials were adequate. That is opposed to prospective assessment which occurs for instance in studies like STAR*D, where we see the patients de novo and we grow treatment

resistance.

The ATHF relies on multiple sources of information, it has explicit criteria as you'll see in a second for the dose and duration of

interventions. Interventions that count are only those that account for treatment resistance which have established evidence regarding their efficacy in the treatment of depression.

In making these judgments with the ATHF one accounts for adherence and the outcome of the trial, so patients who do not adhere to treatment are not considered resistant in that trial, and patients who for instance benefit significantly and then the regimen is changed and they relapse, the original trial is not considered one that was failed.

Each trial is rated on a one to five potency scale, with a threshold of three being what is considered to be an adequate or failed trial, and different criteria, different ratings are used for unipolar and bipolar depression, psychotic and nonpsychotic depression and so on, individualizing to some extent the evaluation of treatment resistance.

To give you a sense, the evidence in the field is quite strong that patients with psychotic depression require combined treatment with an antipsychotic and an antidepressant,

antidepressants alone are not effective in that condition, so if a psychotically depressed patient only receives an antidepressant, that would not be considered an adequately failed trial.

To highlight just the example of, let's say nortriptyline, a tricyclic antidepressant, blood levels take precedence over oral dose at any time, if you take the drug for less than four weeks you get the lowest score regardless of the dosage you take, or the blood level, the blood levels of 50 and above ng/ml reach the threshold of three for an adequate trial, and to get to the top score of five, you have to have augmentation with a drug like lithium.

Now, the ATHF has been applied in a host of contexts and I'll just share with you very briefly a few examples. The first area was in regards to ECT. ECT has always been thought to be in many ways indifferent to the

treatment stream of patients. It is our treatment, so to speak, of last resort, and treatment resistance now by the FDA is the leading indication for the use of ECT.

Nonetheless, until 1990 or so, we had no data on the impact of treatment resistance on ECT outcome.

These are from a randomized double blinded control trial at Columbia in which patients were assigned to four types of ECT, three types of right unilateral ECT, one type of bilateral, and you can see that the forms of treatment differed in their efficacy, these are the response rates for this treatment. But across the types of ECT, those who were medication-resistant by the ATHF did less well than those who were not. In fact with the most potent forms of treatment, high dose right unilateral treatment, you get an almost 90 percent response rate in the nonresistant, and that drops to about 50 percent in the resistant. This explains both that treatment resistance even impacts on the efficacy of ECT, as well as the fact that ECT nonetheless among treatment-resistant patients is remarkably

effective.

Now, this phenomenon has been sustained in a meta-analysis, these are studies that have been done across the world, and what

we can see is that degree of treatment resistance is associated with an impact on clinical outcome, so that this is now becoming an established phenomenon.

Treatment resistance not only predicts whether or not you get well with ECT but if you do get well, if you do remit, whether you're going to stay well. These data are from the first study of treatment resistance in depression basically, and we were looking at a survival curve here of likelihood of not relapsing over a year period following remission with ECT, and we're comparing non-treatment-resistant patients at that time to TCA-resistant patients, and you can see this big difference in propensity in relapse. This in fact has been replicated in a number of studies.

Here's another study from Columbia, in fact that 2000 study that you saw the acute data from, and this is inadequate pharmacology

before ECT, adequate pharmacology. So the treatment-resistant patient is both less likely to benefit from ECT and more likely to relapse if they do benefit, giving you a sense of the

magnitude of the problem that we face, and the fact that the assessment of treatments obviously has important predictive validity.

Some general observations. Typically patients receive twice as many antidepressant trials as those that are deemed to be adequate, that there's a good deal of pseudoresistance, and that's particularly true in the older patient population where they have greater intolerance to medications. Various studies have looked at what about treatment resistance predicts outcomes, whether we count the total number of trials patients have had, the potency score of each trial, or the number of adequate trials. It's the number of adequate trials that consistently has been predictive of future outcomes.

And as you see in these data, patient resistance is predictive of both immediate outcome and relapse rates, so it has an impact on the long-term outcomes of patients. In the

ECT studies about two-thirds of the patients were over the age of 65 and a large number were disabled, so it's obviously relevant to the Medicare population.

To illustrate from another form of brain stimulation, this is repetitive transcranial magnetic stimulation and these were the data that led the FDA to approve TMS for treatment of depression. It was a post hoc analysis that was reported in a paper by Lisanby in Neuropsychopharmacology in which the patient group was broken up into those who had one adequate antidepressant trial which they failed prior to entering the study, or more than one.

DR. BACH: Please wrap up.

DR. SACKEIM: Sure. The difference with sham and active treatment was absent in those with more than one, and in one there was a significant effect. This predictive value of treatment resistance was replicated in our NIMH study that I co-directed.

Finally, a point that I'd make is if we look prospectively at treatment resistance, these are STAR*D data that Dr. Trivedi had

shown earlier where we're looking at acute revision rates at the different levels of STAR*D, likelihood of remaining well for a year following STAR*D, and if we compute something

important, the probability of sustained benefit, both remitting acutely and remaining well, you can see in Level 1 that about a quarter of patients have a sustained benefit.

DR. BACH: Dr. Sackeim, could you wrap up, please?

DR. SACKEIM: Yes. But at the Level 3 and above, it sharply is reduced. Thank you.

(Applause.)

DR. BACH: Thank you very much. Next up is Dr. Charles Conway, professor of psychiatry and director of the Washington University Treatment-Resistant Depression Center at the Washington University School of Medicine.

DR. CONWAY: First of all, I would like to thank Dr. Bach and the members of the panel for having this very important MedCAC conference on the issue of treatment-resistant depression. As Dr. Bach mentioned in my introduction, I'm a professor of psychiatry at

Washington University School of Medicine, I run the Washington University Treatment-Resistant Depression Center. My life's work is devoted to those who have treatment-resistant

depression, so I feel very passionately about this cause.

My disclosures, I do have some research funded by the National Institute of Mental Health and I have had research that's been funded by multiple private foundations. I am here, I'm paying for myself to be here, so there's no one supporting me coming here.

This is a slide, there's a lot of information on this one slide that I think is very important. This is a slide that is an empirical model of treatment resistance that the three psychiatrists, Dr. Aaronson, Sackeim and myself put together. This is a model in which we present a workable empirically based model of treatment resistance based largely on the STAR*D trial and as Dr. Trivedi mentioned in his opening talk, to some extent at this point in our knowledge of treatment-resistant depression, we can say with some certainty that there is a turning point, typically as was

observed in the STAR*D trial, right at the level of two adequate dose duration failures.

What I think is important, and Dr. Sackeim just brought up this point, was

that after you fail two adequate dose duration trials, not only is your probability of responding to a third trial poor, but your probability of sustaining a response drops significantly, such that at this point here, you can safely say that individuals who fail a third adequate dose duration trial with antidepressants have about a five percent chance of being well at one year. So in other words, this is pretty clearly a point of treatment resistance we would offer to you, the panel, that the empirical evidence clearly supports, that this is a point at which we need to begin thinking about novel treatments.

One of the things that Dr. Sackeim and others have demonstrated is that stimulation therapies and other types of therapies actually seem to have better staying power than do medications in terms of this resistant population. These are the types of treatments that we need to think about supporting in our

research operational definition of treatment-resistant depression.

Now where -- if you look at -- this is similar to a model of cancer treatments with a

Stage I and a Stage II. The treatments, as Dr. Aaronson pointed out, the more invasive treatments, things that involve implanting devices into people, should probably be saved for those who have more severe treatment-resistant depression, similar to the cancer model where more severe cancers would get more severe treatment. Okay.

What I'm going to do in the next six slides is go through each of the individual questions that the panel asks, and give a consensus of our group, and the field in general, I think, supports the evidence that I'm about to present.

So the first question was from the panel, should the number, in defining treatment-resistant depression, should the number of dose, duration and class of antidepressants be included? The answer would be yes, yes, yes, no. The number of dose and duration, that's information that's provided in

the STAR*D trial and that information pretty definitively indicates that there is a point where you can just determine treatment resistance. Antidepressant class, probably

not, because the current evidence suggests that different antidepressants are equally effective in depression, with perhaps some exception of MAOI inhibitors.

Augmentation strategies and combination strategies, as the STAR*D data demonstrates, they do also represent antidepressants, adequate antidepressant measures, or should be included in a characterization of treatment-resistant depression trials.

The type of depression, obviously this topic could be, you could give a 45-minute talk on it, but the answer is yes, the type of depression is very important. For all intents and purposes we have, the most studies that have been done so far and the most evidence that is present is for unipolar depression, that was what the STAR*D trial did. The other types of depression such as psychotic depression, bipolar depression, as the slide

indicates, the treatment for those is very different and because of that, we're proposing in our treatment-resistant depression operational definition that this should be only

for treatment-resistant unipolar depression. The other types of depression are equally severe and have their own issues, but I think for the purposes of this operational definition we need to focus on unipolar depression.

Should ECT be a mandatory part of an operational definition of TRD? The answer, we believe, is no, you should not have to have ECT, no one should be required to have ECT in order to meet the operational definition of treatment-resistant depression despite the fact, as Dr. Sackeim pointed out, it is a critical part of our treatment for TRD.

Psychotherapy, yes, as was pointed out by Dr. Rudorfer's talk and others, psychotherapy does play a central role in managing treatment-resistant depression and should be included as another treatment trial in terms of determining efficacy.

In terms of should we use standardized scales to treat and to measure response to

treatment-resistant depression, the answer would be yes. The scales, there's a whole diversity of scales, the Hamilton, the MADRS and others that were mentioned, but we believe

that you should, there should be a minimum score but that we see a lot of patients with long-term mild to moderate depression so it's not a single one size fits all.

Suicide is a huge issue in TRD as was pointed out by other speakers. Last week the CDC issued a statement indicating that over the last ten years the suicide rate has grown one percent in the first five years of that ten-year study, two percent for each year in the second five years of that study, so a significant proportion of those patients who are committing suicide have treatment-resistant depression, so I think the critical importance of this is huge.

So, where should we study treatment-resistant depression? We would argue that the best place to study treatment-resistant depression is probably in psychiatric clinics, and the best place we believe to study treatment-resistant depression is in clinics

with expertise in treatment-resistant depression, or centers of excellence, similar to models that have been used in other areas that CMS has done research in. We've

established centers that have expertise in treatment-resistant depression and there are many of these centers throughout the country that have been involved in treatment-resistant depression studies for years.

And finally, my last slide, in terms of what is the best way to study treatment-resistant depression, well, the answer depends on what you want to, what you're trying to get at in terms of the study. In most studies we prefer to use sham control, double blinded placebo, prospective trials, but there are other good methods of studying treatment-resistant depression.

In closing, I would like to make this remark to the panel. This issue, the decision that you're going to be making this afternoon I think is very very critical and it's going to affect thousands, tens of thousands of people's lives going forward, and I think some of the people who are going to follow me up here are

going to speak eloquently about how treatment resistance has affected their lives and lives of family members. This is a very real illness and we need, as a field and as a country, I

think we need to do more for these people, and what we're doing right now I think is inadequate. I thank you for your time and attention.

(Applause.)

DR. BACH: Thank you very much. Dr. Stephanie Fox-Rawlings is next. She's a senior fellow at the National Center for Health Research. You don't have any slides; is that correct?

DR. FOX-RAWLINGS: No. Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings, I was previously a neuroscientist at the Children's National Medical Center and I'm now a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data to provide objective health information to patients, policy-makers and providers. We do not accept funding from the drug or medical device industry and I have no conflicts of

interest.

A standard definition for TRD would be beneficial to patients, prescribers, researchers and insurance companies. A

Medicare definition for TRD could have a widespread impact. Unfortunately, definitions for TRD in clinical trials are diverse and some do not make sense. For example, the definition used by some studies of TMS and other devices is a failure of just one prior treatment. One treatment failure is not uncommon and should not be considered treatment-resistant. A definition that balances the need for identifying most patients without being overly broad can improve our knowledge of which treatments tend to work and for whom.

Providing a better definition for TRD would reduce the number of patients incorrectly given the diagnosis. A recent review by Marzek found that most patients diagnosed with TRD may not be. This could be due to inaccurate or incomplete diagnosis or insufficient treatment duration or dosage. It can also be caused by limited access to affordable or effective mental health services.

About a third of misdiagnoses are due to nonadherence to treatment. This could be caused by cost, social environmental conditions or side effects. Stricter guidelines for TRD

would help to control these confounding variables, helping to identify whether a treatment works or not. It's important to reduce barriers to compliance because after multiple treatment failures, patients are less likely to achieve remission and more likely to try treatments with more severe side effects or less clear best efficacy.

A definition for TRD would also need to address the issue of how to define remission and to describe what constitutes a physician's inadequate treatment trial. It would further need to include the number of treatments, trials and their types. Inclusion of specific types of therapy in the definition may increase the likelihood that they are attempted. Many patients defined as having TRD may never have tried cognitive behavioral therapy although it can be effective. Patients may not know where to find a therapist or have heard of it, or prefer medication.

If Medicare defines TRD as a condition for people who have tried and failed several types of therapy, including cognitive behavioral therapy, it could influence patients

to try it. A recent review of TRD studies found that only about 15 percent of patients reported suicide ideation and 17 percent had a previous suicide attempt. Either TRD was not appropriately defined for these studies or a definition requiring either suicide ideation or attempts would inappropriately exclude many TRD patients.

To be useful for clinical trials a definition for TRD needs to take into account that depression waxes and wanes for most patients. Randomized studies with placebo and sham treatments are essential for differentiating between treatment efficacy, depression's cyclic nature and a strong placebo effect. Medicare analysis of the efficacy of a particular treatment needs to include randomized, blinded and placebo or sham controlled studies. Clinical trials should include men and women as well as sufficient numbers of racial minorities and patients over

65.

Many treatments have not been analyzed to ensure that they are both safe and effective for patients 65 and older. Metabolism, eating

habits and activity levels change with age and can affect the way a treatment works. Similarly, some treatments do not work as well for certain minority groups or for both men and women due to cultural or biological reasons.

Clinical trials should focus on clinically meaningful improvements in patients' lives. They should include improvement in the ability to function and quality of life. For those that have suicide ideation or suicide attempts a decrease would be beneficial, but this is not relevant to the population as a whole.

In conclusion, a clear, well constructed TRD definition for Medicare would benefit patients. Treatments should be evaluated in terms of improving daily life functioning and quality of life. Decisions concerning the appropriate treatments for TRD should include well controlled randomized trials including men, women, minorities and

patients over 65. Thank you for your time and consideration of our views.

(Applause.)

DR. BACH: Thank you very much. Next

up is Charlie Donovan, and Mr. Donovan, you do not have slides either?

MR. DONOVAN: No. My name is Charles Donovan and I am a mortgage banker in St. Louis, Missouri, employed by Mortgage Solutions of St. Louis. LivaNova paid for the travel expenses that enabled me to be here today. I have no other disclosures. I appreciate the opportunity to speak to the panel.

As the panel deliberates today on an operational definition of treatment-resistant depression, an estimated 120 people will commit suicide and tomorrow another 120 people will commit suicide, and according to an alarming report issued last week by the Centers for Disease Control and Prevention, 41,000 people in the United States commit suicide annually. Many of these suicides are the result of the hopelessness that comes with TRD.

I feel like I'm in a unique position

to speak to you about treatment-resistant depression. 12 years ago I wrote a book on this very specific topic of treatment-resistant depression. The book entitled Out of the Black

Hole chronicles my personal struggle with the disease, the seemingly endless search for a solution, and my emergence from TRD thanks to the pioneering treatment of vagus nerve stimulation. Since that time I have received countless letters and emails from desperate TRD patients seeking a solution to this terrible disease. In their communications to me virtually all of them say the exact same thing, that they had read their own very personal story in my book.

I struggled with how to share with the panel what life is like to live with major or resistant depression, so I needed only to consult the book that I had written 12 years ago. I could only read a few pages. I was shocked and appalled by the very words I had written. It took me back through my journey into the black hole of depression. It was about as ugly a story as one would ever want to read. Unfortunately, it is a story shared by

many TRD patients. Speaking to the panel about this today is not easy for me.

Nobody rings a bell when depression starts. For me it began in my teens. Over the

ensuing years the episodes came back with greater frequency and severity. I suffered my first major depressive episode as a senior studying in the business school at Georgetown University, ironically not far from where we are today. Day after day, month after month, I suffered from absolutely debilitating depression. I greatly feared that I would be unable to graduate. Eventually I did recover but it was a battle.

After graduation I moved to New York to begin a career on Wall Street. Within a few months the depression returned and I started on a 20-year merry-go-round of antidepressants, augmentation strategies, tranquilizers and psychotropic drugs. I have always had access to the very best that our health care system had to offer, including highly skilled and experienced psychiatrists and psychotherapists. I have been so fortunate to have been under the guidance and expertise of some of the leading

clinicians in the country.

We tried absolutely every treatment modality possible, but nothing worked. By age 39 I had tried 15 different medications, ECT,

seen eight different psychiatrists, had countless psychotherapy sessions, and been hospitalized four to five different times. I just gave up on living. I was unable to work, I isolated myself from friends and family, I suffered from terrible agoraphobia. I could not concentrate enough to read a book, follow the plot of a movie or television program. There was no happiness or joy. Isolation, social withdrawal, despair and helplessness, these are all common symptoms of TRD.

I'll just deviate from my statement. The previous presenters talked about the costs and expenditures related to TRD. I have to believe the cost, the direct cost to treat me during those 20 years was in the hundreds of thousands of dollars.

In 2001 by a stroke of incredible good luck, I found out about a novel treatment for TRD that was undergoing early studies, vagus nerve stimulation. Mostly out of sheer

desperation, I considered entering a double blind placebo controlled clinical trial. The research psychiatrist, who happens to be here today, said to me that there was an inkling

that there might possibly be something to this novel treatment, and I said to myself, inkling, I'll try it, I was so desperate to try something new, I had nothing to lose.

The day before the procedure I simply told the clinical researchers that I wanted to die on the operating table. You cannot sink any lower than that without committing suicide. The therapy ultimately completely changed my life. In 2005, vagus nerve stimulation received FDA approval for TRD. Eleven years after FDA approval, TRD patients still do not have access to this potentially remarkable life-saving, life-altering procedure.

Many of us who write memoirs about a disease or a challenge they have overcome conclude their story that they are grateful for what they have learned from their experience. As I conclude I can tell you, I am not in any way grateful for my horrific experience with TRD. TRD patients often suffer in silence. I

hope that I have given these patients a voice here at today's meeting. The health care system has failed this desperate patient population for many years. I strongly urge the

panel to do everything in its power to rectify this terrible injustice. The determination of a reasonable definition of TRD is a beginning for the development and the approval of new treatments for resistant depression. Thank you.

(Applause.)

DR. BACH: Next up is Andrew Sperling, the director of advocacy, National Alliance on Mental Illness.

MR. SPERLING: Thank you, I have no slides. It's difficult to follow that very moving statement. Thank you for that courageous step just to be here today.

So I'm Andrew Sperling with the National Alliance on Mental Illness. NAMI is the largest grassroots organization representing and advocating on behalf of people with severe mental illness, including treatment-resistant depression. You heard certainly from Dr. Trivedi and Dr. Rudorfer and

many other witnesses the enormous public health burden associated with treatment-resistant depression, the enormous risk of suicide. Few people know this, but mortality from suicide

now in the United States exceeds mortality from both breast cancer and prostate cancer. The public health world is not just the treatment of the disorder but the enormous risks that people with treatment-resistant depression have just getting comorbid chronic medical conditions, and because of their depression are unable to manage those comorbid chronic conditions, and it actually leads to early mortality from those disorders as well.

The diagnostics are an enormous challenge and I think Dr. Rudorfer, Dr. Trivedi talked about that, we have to move beyond the current diagnostics and move toward RDoC, that's why the important work the NMIH is doing has to go forward. We have to get beyond measuring the severity of symptoms if we're going to move forward in really developing disease modifying therapies for this very serious disorder.

What is critical and our main takeaway

from our presentation today is that CMS and this MedCAC panel do nothing to limit access to any FDA-approved therapy for treatment-resistant depression, and do not develop any

strict criteria that would apply to any particular therapy before patients can access those therapies.

Let me briefly go through the questions that are presented to this MedCAC panel. Number one, in terms of defining treatment-resistant depression, I think Dr. Trivedi and Dr. Rudorfer have provided strong evidence that there are well established definitions of treatment-resistant depression out there, and I even question whether it's CMS's job as a payer to define what treatment-resistant depression is. The research needs to drive that question, which is precisely why the important work that NMIH is doing on RDoC to develop newer and better diagnostic criteria has to move forward, and CMS as a payer establishing a static definition of treatment-resistant depression is not the way to go. You need to allow the science to evolve and advance on that particular question.

Number two, the defining characteristics, all of those listed in the question should apply. Unipolar versus bipolar, augmentation therapy used with

psychotherapy, suicidal ideation, suicidal depression, all these characteristics should apply because it is really a very heterogeneous population, particularly within the Medicare population.

Which brings us to question number three, how to apply this definition to Medicare. You have to recognize the heterogeneity of people, Medicare beneficiaries with treatment-resistant depression. People think of Medicare being the elderly, the senior citizen health care program. There are more than six million non-elderly people with disabilities that qualify for Medicare as a result of getting on SSDI. This particular cohort is more likely to have treatment-resistant depression because they've met a definition of disability that they are so disabled they can't work in any job in the American economy in what's called substantial gainful activity, a little over a thousand

dollars a month. So you're more likely to find a concentration of people with treatment-resistant depression that got onto SSDI in that population, and you have to recognize that they

are going to be seen largely in this specialty behavior health care setting, very very different in how this is diagnosed and treated in the elderly population where it's more likely to be with a geriatrician or a primary care doctor who first diagnoses it, and they're unlikely to end up with that specialty behavioral health setting over time.

Number four, what are the reliable and valid outcomes for Medicare beneficiaries? I think all the things listed there, both function and quality of life, suicidal ideation and attempts, the outcomes we get from this population I think we've heard over and over again from Dr. Rudorfer, Dr. Trivedi and others, are pretty grim. Suicide, greater risk of poorly managed comorbid medical conditions, we need a whole slew of outcomes that CMS ought to be looking at in terms of what we think outcomes ought to be in advancing on treatment-resistant depression.

And then finally, the realistic study design. Obviously, randomized control trials remain the gold standard but we have to advance beyond, because many randomized control trials

have exclusionary criteria that will lead the most severely ill patients out of a certain randomized control trial. So previous history of suicidal ideation or suicidal attempts, it's very difficult to study treatment-resistant depression when you say if you've had any suicidal ideation or any previous attempted suicide you're excluded from a randomized control trial. You are not going to get the answers to the questions you need for real treatment-resistant depression using exclusionary criteria, so you should be very careful with that.

And then in conclusion, again, this panel, CMS should not be using this in any way to limit access or place barriers in front of existing FDA-approved therapies for treatment-resistant depression. These patients and their families are desperate for answers, desperate for advancements, and CMS needs to keep that in mind. Thank you very much.

(Applause.)

DR. BACH: Thank you very much. Next up is Eric Scharf, who is the advocacy advisor for the Depression and Bipolar Support

Alliance.

MR. SCHARF: Thank you, it's good to be here today. Again, my name is Eric Scharf, I work as a volunteer with the Depression and Bipolar Support Alliance. In terms of disclosures, they did pay my way, reimburse me for travel today. I have a written statement. There's also been a more in-depth statement provided to you also from our national office.

Unlike any organization of its kind, DBSA is created and led by individuals who themselves have a mood disorder diagnosis with our bylaws, which stipulate that over half of our governing board of directors and the paid professional staff must be people who have or had depression or bipolar disorder. Therefore, this first person lived experience informs everything we do.

I personally live with TRD and receive Social Security disability benefits. Prior to my TRD diagnosis I was the owner of an

association management and consulting firm.

During my career I had served as executive

director of four different membership

associations and worked with many others.

During that time I worked at a professional level, I often described my current situation as going from eight cylinders to four cylinders, often just not having the energy to focus on the work like I did previously.

I have tried countless medications with little or no success. Today, though, with the help of my Social Security benefits, which has provided me with some sense of financial stability, and new life skills and the medication that helps me to treat some of the symptoms that I experience, I'm able to lead a life of meaning, but lacking in the level of energy and excitement that I once felt, and so it's a very frustrating situation to be in.

DBSA's position is wellness for people with mood disorders, and we believe that an open and collaborative approach to treatment that accounts for the whole person where she or he is right now, is what allows people to achieve what they personally define as

wellness. Our collaborators include a scientific advisory board made up of the nation's leading clinical and research experts on mood disorders. We are nationally

recognized for peer support training services and we add those with a lifetime experience of mental health conditions into the fabric of care as providers of education and support.

Ultimately, we at DBSA believe that our balanced person centered wellness oriented approach is what has allowed us to educate, empower, support and inspire individuals to achieve the lives they want to lead for our now 30 years in existence. Moreover, these three decades of peer led work have enabled DBSA to coalesce a strong base of active participants. In fact, through the more than 700 in-person peer support groups provided by DBSA's network of 300 chapters throughout the country, along with our printed and virtual education resources and wellness materials, DBSA reaches over three million people per year.

As the foregoing hopefully illustrates, DBSA's three decades of representation of and engagement with people

who have mood disorders has put DBSA in a unique position to assist MedCAC as they seek to define treatment-resistant depression, and provide guidance on how to conduct studies for

treatment options.

Overall, we believe that meaningful innovation in treatment will be aided by understanding first and foremost how those receiving the treatment define success, rather than simply relying upon the assessments of clinicians and researchers. Along these lines, the following are the five most important areas that DBSA asks you to consider when providing guidance:

One, efforts to improve definitions and measurement of success from the perspective of those who live with TRD, much like some of the folks who've spoken already. For the people who live with TRD, the past 25 years has seen anemic progress in the development of meaningful new treatments. Innovation has been incremental. People are constantly, are consequently frustrated by and losing hope for a solution. Modest improvements in clinical outcomes are simply no longer enough.

Of course the first priority for treatment is ensuring that a person living with TRD is -- excuse me for a second -- is provided a pathway out of crisis and onto stability.

However, all too often this baseline stability is ultimately the end goal established for successful long-term care. Stable or better is not always synonymous with well. DBSA believes that every person deserves the opportunity not just to survive but to thrive, and to do that we need to ensure true wellness as the end goal for TRD treatment.

Consider this: The successful treatment for cancer targets is the removal of every cancerous cell, the achievement is complete remission. We, DBSA believes that measure of treatment efficacy needs to evolve. Changing measurement tools to include wellness outcomes as defined by people with TRD would greatly improve treatments. For example, MedCAC could recommend elevating the importance of existing clinical measurement tools that address function, such as the Sheehan disability scale, or that address wellness, such as the WHO-5 scales. Both are useful in

allowing not only for the mood-related improvements necessary by achieving complete wellness, but also the interpersonal and relational aspects of an individual's

experience with TRD.

Three, DBSA's participants with TRD look to MedCAC to increase consideration of the whole health implications of interventions with TRD symptoms. The weight of TRD negatively affects people with co-occurring conditions, which are frequent and diverse, ranging from diabetes to cardiovascular conditions to cancer. Treating both TRD and any co-occurring conditions, recognizing and allowing for their complex interrelationships is imperative to achieving optimal symptom outcomes.

DBSA urges MedCAC to consider implications of chronic versus episodic experiences. Success should not be defined by controlling this week's, month's or even year's episode, but by reducing the severity and eliminating the reoccurrence of symptoms over the entire lifetime. This is not often a defined objective for clinicians or researchers but is of vital importance to people

experiencing TRD as well as their families.

Finally, DBSA notes that payers, including the Centers for Medicare and Medicaid Services, hesitates to include novel treatments

for depression. The current measures and criteria for determining that a new treatment is safe and effective do not answer payers' questions about whether a new treatment offers benefit over existing treatments, and whether these added benefits justify an added cost. Because payers tend to resist coverage for new treatments, an inadvertent disincentive for research and development exists.

DBSA supports your initiative around TRD. We sincerely hope that with the committee's work we will promote an environment that supports the development of better treatment options, encourages exploration on the steps that need to be taken in order to break out from the current dynamics of incremental slow improvements to one of exciting breakthroughs. Part of this depends upon a transformation of the way we currently measure success. We urge the committee to look for guidance from those living with, to then

focus the scientific discoveries towards the things that matter the most to all of us.

Thank you for your attention.

(Applause.)

DR. BACH: Thank you very much. Next up is Dr. Bryan Olin, he's the vice president of quality and regulatory affairs for Cyberonics, Inc.

DR. OLIN: Thank you for having me here. As mentioned, I'm the vice president of quality and regulatory for Cyberonics, a division of LivaNova, and as such I am an employee and shareholder of the company.

What I'm going to start talking about today is addressing question four, which has to do with the outcomes measures to really assess the degree to which patients improve under treatment. And the question deals with, it provides a number of different outcome measures, and I'll mention that all those outcome measures that are provided within that question have been successfully used in both preapproval trials for drugs that are now covered, or approved by FDA and covered by CMS for treatment-resistant depression, as well as

trials for devices that were approved and in some cases covered by CMS.

These are all validated measures, they have all been well characterized throughout the

literature, and as you know, as you probably saw this morning in several of the physicians' presentations, they were featured prominently in many of these trials.

From the standpoint of the quality of life and patient functioning measures, I've listed several of those below there, MADRS, Hamilton depression rating scales, and a couple of those are actually patient-rated scales as well, which provides kind of the unique perspective of the patient's self-assessment of their improvement as they're moving through the treatment continuum.

I also note that a couple of the questions, or one of the concepts was looking at suicidal ideation, and two of those particular scales and many others like them, the Hamilton, the MADRS, and also the IDS as well, count as an item imbedded in there that speaks to suicidal ideation, so that's allowed us to actually measure longitudinally over time

how that, how the patients progress with respect to that.

And then finally, CMS's and HHS's own databases allow us to extract and have some

sense of suicide attempts around psychiatric hospitalizations, medical hospitalizations, as well as utilizations, and these will all help give us a good sense of how that patient is doing on these treatments.

The second thing, what I would like to kind of conclude with is also, as we transition now from the speakers discussing or providing their perspective into the MedCAC panel deliberation, I'd like to provide you with some background on a similar situation in which the MedCAC met over a decade ago to consider a situation that had a lot of striking parallels to the question that we're covering today, and that was namely the MedCAC's consideration of the use of bariatric surgery in morbidly obese populations, and they shared a lot of striking similarities there in terms of what that MedCAC panel had to discuss.

They had to grapple with uncertainties around definitions. They had to grapple around

a population that had, a lot of the evidence base had a limited experience in the traditional Medicare population. Many of those patients in that evidence base were in their

30s, their 40s, their 50s. They were entering Medicare through disability as opposed to age. There were, the same types of morbidities were present in that patient population, choice issues, hypertension, metabolic disorders. Those are also present in the TRD population that we're discussing today. Likewise in terms of how you measure success in outcome, that was very patient-dependent as well too in those considerations, and there's a staged approach to care.

So there have, MedCACs before have had to grapple with these types of difficulties, and were able to be able to successfully do that, to find a way to come up and allow coverage of appropriate therapies for patients with this disorder.

Further showing some of the similarities between these populations, one of the measures that has been used many times to assess patient functioning and quality of life

is the SF-36, and what you see here is a direct comparison of the obesity population, patients that are subjected to bariatric surgery, and in the lighter blue bar or, I'm sorry, the darker

blue bar, patients from an early pilot study on patients with TRD that were treated with VNS therapy. And what you notice is strikingly, in a lot of the physical function domains of the SF-36, these patient populations are very comparable. But very clearly when you get to the mental health functioning, the patients with TRD are much more lower functioning and much more severely ill. So again, very similar patient populations until it comes to the mental health aspects of this.

So, this is a bit of a, sort of more details on the specific comparisons here, but again, I think, you know, the really important things are around, again, the difficulties of coming up with a common definition, and I think as we've seen today throughout the discussions that each of the physicians have had, there's some common themes around duration, around severity, around the number of prior treatments that have been failed that are very very

consistent threads in the definition of TRD, and there were similar threads within bariatric surgery.

Likewise, there's very clear ways to

measure them. There are a variety of different ways to measure selection of the ones that are most appropriate from an evidence development, and I provided some on the previous slide.

I discussed the population issues and morbidity issues, I'll conclude with the treatment issues. Again, bariatric surgery in morbidly obese patients, just as with TRD that we're considering today, it's very important to consider an individualized approach to treatment, and to make sure that the appropriate treatments are available for that individualized approach to take place. And again, I think that is really crucial, and the other aspect is, both have a staged approach to care and both in that staged approach to care, as discussed by Dr. Rudorfer and others, had to do with looking at the individual benefit-risk for that patient at that point in time in their disease direction.

What I would like to conclude with is,

as a few people have discussed, a pressing need to really look at one of those specific treatments for patients with treatment-resistant depression, and that's vagus nerve

stimulation. In the context of the definition we're discussing today, the FDA approved indication features many of the items, if not all of the items that were discussed through prior speakers today in terms of failed medications, prior severity, the chronicity of disease, it's well proven and tried throughout clinical trials. There have been a variety of randomized trials that have been conducted on this, whereas even in some of the prior MedCACs the decisions, coverage decisions were made without any RCTs and without the same level of evidence base.

And what I would conclude with is, based on this discussion, we can, this panel can provide patients with this additional option while simultaneously developing evidence that can help answer some of the open questions. There are appropriate study designs to be able to address this. There are appropriate means by which we can classify

patients with TRD or not. As others have talked about, there are and there exist experienced centers to do this, similar to the TAVR situation that CMS has approved, to make

sure people get the proper treatment.

And finally, I just talked about recommended outcome measures; those exist and each of those can answer the open questions that remain about this, and provide a roadmap for future therapies. Thank you very much.

(Applause.)

DR. BACH: Thank you very much, Dr. Olin. That concludes our scheduled public comments. Despite us leaving the sign-up list open longer, apparently the rest of you have no interest in speaking to your government, so no one signed up, which means first, we're going to break for lunch early. Everything on the agenda is now 15 minutes earlier.

Let me just say, thank you to the ten speakers this morning for your organization, for your thoughtfulness, for your focus. I think you've done a great service to the panel and to the topic collectively and individually, and everyone enjoy your lunch.

(Luncheon recess.)

DR. BACH: Could I ask those of you who presented this morning, including all ten of you, there's actually chairs in the front

row, or close to the microphone would be great.

We are going to spend about the next hour, but the time as needed, discussing with the presenters some of the issues we're focusing on. After that, we're going to have a discussion amongst ourselves, still in public, and then proceed to voting. So in the spirit of openness, although questions will be asked to specific ones of you in most cases or maybe all cases, I generally have the view that if somebody has, some of the presenters has something to say that is on point to the question, I invite you to also answer after the person who has been asked has offered an answer. I don't want that to become kind of out of control, and so we'll manage that and I ask you to stay concise and on the question at hand.

But I think we can get started and so I guess I'll open the floor to the panel. Anyone can ask, anyone from the panel can ask a

question of any of the presenters, and of course as a presenter, you are free to pass if you don't want to offer an answer. Please, Roger. And panelists, please reintroduce

yourself when you ask a question, mostly for the recording.

Roger, hold on one second. I don't think -- can you hear? No. I think we have an AV problem. Oh, you have to turn it on.

DR. LEWIS: Okay, take two. My name is Roger Lewis, my question's directed to the first two presenters primarily. It has to do with the incorporation and a possible definition of treatment-resistant depression that includes an adequate trial of a pharmacologic agent, specifically in an elderly population that may have a decreased ability to tolerate that agent. So it strikes me that using an intention to treat philosophy, that if a patient is unable to tolerate the usual dose of a medication, that it's not clear to me that from a clinical perspective it makes sense to discount that in counting the number of failed trials. Would you like to comment on that?

DR. BACH: Before you start, can you

clarify what you mean by discount?

DR. LEWIS: So if one considers a possible definition that counts the number of failed trials, it was my understanding that a

trial in which the patient failed to be able to tolerate the minimum dose that might be used in the other patients, that that trial would not be counted, and to me that seems to violate an intention to treat principle that might affect the definitions as applied to an elderly population.

DR. TRIVEDI: So, the short answer is yes, the intention to treat analysis should be included in these trials, so therefore if you're doing an efficacy trial you should include intent to treat analysis to address the side effects as well as improvements. For the purposes of defining whether somebody has had an adequate exposure to an antidepressant so as to have had an adequate trial, this definition is really designed for that, and in that case if you have a patient who is unable to tolerate three antidepressants one after the other after taking the first drug, and if you wanted to call that an adequate trial, it would have

actually kind of, doesn't match the way we think of treatment with this. So it is conceivable that the patient has that physiology that gets you there, but then you

have to redefine for that patient how to call it, but if you don't have adequate exposure, you don't have exposure to treatment for it to work, because it's not designed as an intent to treat analysis, that's not the purpose of the finding.

DR. LEWIS: May I ask a follow-up?

DR. BACH: Absolutely.

DR. LEWIS: So, I understand completely the philosophy from a pharmacokinetic or pharmacodynamics point of view, but I'm trying to envision the operational application of one of these criteria, and I see, I envision any future definition of treatment-resistant depression as being a potential gateway to coverage for alternative treatments, and if an elderly patient, for example, were unable to tolerate three medications in a row, as a nonspecialist it seems reasonable to me that the clinician may want to have access to a different mode of

therapy.

DR. BACH: Yes, please, if you'd just come to the microphone, and again, could you also state your name simply for the recording?

DR. SACKEIM: Harold Sackeim, Columbia University. When we developed the plan for evaluating treatment and actually built the question, did it matter whether the patient met dosage-duration criteria, was that particularly predictive, or did it matter that the patient got exposed to the drug, so is it more important that you count the number of total trials that the patient or just those that were adequate, and that's been looked at several times in the literature in terms of predicting, what does it tell us what's going to happen with the next treatment, and it's only the number of adequate trials that has the greatest power in predicting the next treatment.

Now in terms of -- so that's the scientific justification. The practical or clinical approach, of course if somebody, an elderly patient has difficulty tolerating a number of trials, you're going to go to something else to treat them. That's not going

to restrict, necessarily, what's available for their treatment, but we wouldn't necessarily consider them treatment-resistant.

DR. CARPENTER: Could I just ask --

Harold, don't leave for a moment. May I follow up on that for a second?

DR. BACH: Please state your name, if you will.

DR. CARPENTER: Will Carpenter. For people who have not had an adequate trial, do we know how likely they are to be responders? So, it's not the strongest predictor, but is it a weak predictor, moderate predictor?

DR. SACKEIM: Across brain stimulation and pharmacologic treatments, patients who have not had an adequate trial do far better than patients who have failed one, and certainly patients who have failed two or more trials. So in a number of recent studies, for instance, the inclusion criteria for the CMS trials, the two major ones in the United States, allowed in patients who were intolerant to medication or who had proved their resistance to medication, they allowed both in, and those who were intolerant did better.

DR. BACH: I don't know if there's another question. I actually think that follow-up answer also addressed your question, Roger, and let me try and put a point on it and

please, anyone correct me if I've got this wrong. That there is, resistance to treatment is, if you, an indirect measure of the disease, and intolerance of treatment is, if you will, a fairly direct measure of the patient's ability to sort of take the medication. And so that categorization needs to comport with what you just said, which is that condition, obviously there's two different ways of getting into a trial but the outcomes are different. So you're faced with the term treatment-resistant but as we've discussed before, we don't know what that means in the context of answering these questions.

DR. CUYJET: Al Cuyjet. I have a question related to, I'll put my intern's hat on for a moment. I know we talk about treatment-resistant hypertension, but in the Medicare population if you look at the incidence and prevalence of high blood pressure, diabetes, lung disease, glaucoma and

the chronic conditions, and now we're going to add in a couple other medications to the mix where pharmacy is already an issue, I just have a general question in terms of psychotropic

interactions, side effects, and is there a general experience how you fit that into the mix looking at the patient as the whole entity? It's problematic, so --

SPEAKER: It sounds like maybe what you're saying might be, and correct me if I'm wrong, you might have some concerns about drug interactions with these pharmacologic recommendations with depression; is that kind of what you're saying?

DR. CUYJET: Kind of, yeah, but is there anyone else of the experts with a response?

DR. RUDORFER: I'm Matt Rudorfer from NIMH. I think the move from the tricyclics to SSRIs was probably helpful in that regard in that the SSRIs can be easier to tolerate with fewer side effects. I think it's fair to say that many clinicians will look to drugs like citalopram, which was the stage one in STAR*D, as having relatively few drug-caused

interactions, and usually mixes well with meds for physical illnesses.

I think at the same time, research has shown that specialized forms of psychotherapy,

the ECT and personal therapies we spoke some about this morning, have merit as first line treatment for many people with depression and again, that would avoid the issue of adding more drugs, and of course as we've been saying, at the most rear end of the spectrum historically, that's been one of the roles of ECT in terms of a nonpharmacologic intervention which is done under controlled conditions, so that even the frail elderly can be safely treated.

DR. CONWAY: Chuck Conway from Washington University, St. Louis. I think along the same lines, one of the big issues with regard to polypharmacy is that some of the treatment-resistant population that we've studied, many of these patients have been on a series of medications, in fact oftentimes from the same class. So you see, for example, someone that's been on (inaudible) and in our database there are over 150 patients with

treatment-resistant depression. What's happening to the people in the community is that they're getting the same medication classes over and over again with the same

outcome of failure, failure, failure, so I think the evidence that was presented today, and perhaps this wasn't emphasized enough, we were talking more about treatment-resistant depression rather than treatments for it.

But there is evidence, pretty good evidence that some of the more novel treatments like stimulation treatments, perhaps the NMG antagonist treatments, and also the vagus nerve stimulation, the effect of these drugs, these devices is much more long lasting, and in some ways I think the issue of compliance with treatments and the issue of interaction with drugs is removed from the equation.

So I would argue that there's evidence that there does come a point where we have to use something other than the existing treatments, and that's where I think there are advantages to these novel treatments, many of the novel treatments are very clean and very safe.

DR. BACH: Doctor, if I can ask, and if I'm misremembering or misapplying a statement to you that someone else made, I apologize. I thought I heard at least this

morning that the number of different treatments was a factor in considering treatments and the categories of those treatments, we're talking about pharmacologic, should not be considered.

DR. CONWAY: Well, I think the general consensus is that there is no definitive evidence that one antidepressant class is superior to another, but I think the general practice in treating depression is if you try a medication, for example if you treat an SNRI and it failed, the patient didn't respond at all, the next drug you would try would be something like a serotonin reuptake inhibitor like duloxetine or something like that, but a different neurotransmitter system would be targeted, that's sort of the standard of care.

There is some evidence that if you fail one SSRI, a second SSRI does sometimes work, but I think the repetitive giving of the fifth SSRI after one and two haven't worked, that's going on in the community right now in

the geriatric population, and you're right, the polypharmacy issue is a huge one in this population. That's one of the things that the devices, the devices and some of the newer

treatments don't, they take that out of the equation.

DR. BACH: So you would consider somebody who's failed two successive SSRIs as different from someone who's failed two different classes of drugs in terms of whether or not they qualify for treatment resistance?

DR. CONWAY: I would, yes, that would be my recommendation.

DR. BACH: Go ahead, and then Dr. Carpenter.

DR. TRIVEDI: So, two points. One is, I think the issue of polypharmacy and drug interaction for the elderly is the real issue and real difficulty and that should be seen as an issue that we need to be dealing with in the medically frail as well as the elderly with treatment-resistant depression problems.

There is one component of this which we have noticed. Some of these patients after they've had multiple treatments, combinations,

and therefore, it enhances the risk for drug interaction. Going to the second SNRI is more complicated, so for this reason we switch them from one SSRI to the next SSRI, and compare

that to an SNRI which they were able to remain on. There was no difference and so therefore, at least in our study, our hands in that study, going from one SSRI to another, or from a second SSRI to SNRI, was not superior from one SSRI to another SSRI.

What ends up happening is clinically, so to speak, a little more medical logic, that if you have tried an SSRI and another SSRI, it doesn't make sense to go to a third one, but data-wise we don't really have any confounder that tells us to go to something different. So to your answer to your concrete question, category doesn't matter if you've had multiple SSRIs.

DR. BACH: Thank you very much. Dr. Carpenter? Actually, it might be easier if you guys put up your tent cards if you are waiting to ask a question, but go ahead.

DR. CARPENTER: So, I think that answers the question whether or not different

class made any real difference, and at least in the field I work in, a blinded switch to the same drug seems more effective than a blind switch to another drug, there's slight evidence

for that, but I think that answered my question.

The other thing that I wanted to ask, to change the subject, can I go ahead and change the subject of this?

DR. BACH: Absolutely, within the bounds of the topic of the MedCAC.

DR. CARPENTER: Yeah. So this is in the criteria of predicting resistance, cognition impairment is not there, and I wonder, what is the role of impaired cognition in thinking about treatment-resistant depression?

DR. BACH: Is there anyone that wants to answer that?

DR. CARPENTER: Treatment of depression is a big issue in our field now in general. The FDA is struggling with how you think about cognition as an indication of depression and in some circumstances such as schizophrenia, premorbid depression is a

predictor of a longer-term course, i.e. treatment resistance, and I just wondered why that pathology is not among the things behind treatment-resistant depression.

DR. SACKEIM: Harold Sackeim from Columbia, and I thank you for that question. There are many aspects of depression that are reflected in dysfunction and it's quite clear, I think, that major depression and in particular patients with treatment-resistant depression have cognitive deficits. We've been able to show that in, the longer the duration of episodes of bipolar disorder, the more severe effects you see on memory functioning, for instance, but the definition itself of treatment resistance is in many ways independent of the clinical characteristics or the manifestation of the depressive illness itself, which can be quite heterogeneous, there may be suicidal ideation but maybe not, there may be cognitive impairment but maybe not, but fundamentally treatment resistance pertains to the patient's history of failure with particular treatments, lack of benefit from treatments, and that I think makes it crystal

clear, so to speak, what we mean by treatment-resistant depression, and it leaves it open what the manifestations of depression would be itself.

DR. BACH: If I could restate that answer, are you saying that other related conditions do not modify the definition of treatment-resistant depression, they may change the probability of it, but you don't incorporate them into the definition?

DR. SACKEIM: Right, and to the perception that it's a misdiagnosis of depression, it's really an occult medical illness presenting as quote-unquote treatment-resistant depression. But within the diagnostic category of major depressive illness, it's the history of treatment that defines what the treatment-resistant depression is.

DR. BACK: Thank you very much. Dr. Aaronson, and then Dr. Ollendorf will be next.

DR. AARONSON: Scott Aaronson, Sheppard Pratt. Just further along that line of thinking, I think that the development of

new tools to assess severity of depression sort of goes in line with what medications we've got. So, a couple of medications that have come out on the market, there's a new

medication called vortioxetine that a lot of the clinical trials have included doing cognitive testing, because they believe that that medication might help cognitive testing. And as well, some of the device-based systems have included cognitive testing as part of the general screening for these folks, but it really has only come into play as we think we now have different means to improve cognition with ongoing depression. And, you know, cognition is part of, a MADRS scale includes concentration as one of the parameters, so we've got a crude measure there.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Yeah, thank you, Dan Ollendorf. So, I'm thinking about operationalizing the definition as well, I think more clinical research studies will be coming, and any coverage decision will be based on tracking and monitoring issues.

So you talked, several of the clinical

researchers talked about a pseudoresistance. What is your sense of the magnitude of this issue? I'm assuming it's pretty big since adherence is an issue across all medication

classes that alter cognition.

I'm also thinking, and I don't know if there are, if there's stratification that's sufficient enough to try to understand performance in the entire group of nonresistant patients, first the subgroup that is not resistant because they never got to an adequate trial of drug, and obviously you would want to include those who are being successfully treated. So if there's any information on that, that would be important to know as well.

Then the second part of my question is really more to those in the patient community, what are the challenges in actually getting through an adequate trial of an antidepressant, because if you've got disease that's really causing you problems and affecting your life, are you actually able to get through an adequate trial in terms of duration and dose? So, I'd love to hear thoughts on both of those levels.

DR. TRIVEDI: So, the rate of pseudoresistance, actually the data surrounding that are sort of mixed, we don't have large scale long-term follow-up cohorts where we can

officially tell. There is, we have very good evidence that in primary care after people who started antidepressants, only half of them actually get just minimal necessary treatment requirements met for patient's treatment, adequacy of treatment, suggesting that the other half do not potentially have adequate dose integrations and could then come back, the patients may come back in six months and then be seen as having failed to respond to one trial, which is now pseudoresistance. So we do have that kind of indirect data to help give you the scores for the magnitude of pseudoresistance.

DR. CONWAY: And a followup to that point, Chuck Conway from Washington University, I think it's important to, when thinking about your question, that it's what Dr. Trivedi was talking about, the vast majority of people, I think it's estimated that about 90 percent of antidepressants are prescribed by primary care

22 doctors, not psychiatrists. When you get to
23 what we're talking about today, more of the
24 resistant population, those patients, I think,
25 they're not immune from pseudoresistance but I

think this is why when we talked about how this would best be, when operationally defining it, how would it best be studied, I think having centers of excellence or centers of expertise in treatment-resistant depression is really critical, because what centers like the one that I'm part of, we actually dissect very carefully what a patient's history was.

Obviously it's very difficult to prove if a person was compliant with the medication, you can't be at their house making sure they're swallowing their meds, but you can tell by pharmacy records, you can tell by is the patient reporting to their physician at each visit, so I think when you look at an operational definition for research purposes, it does, I think that the pseudoresistance numbers that have been talked about are on the high side when you look at it from a research perspective.

MR. DONOVAN: Charlie Donovan,

patient. When you have TRD you are in a war, it's a battle, and I could just speak for myself. I never missed a medication, followed the directives of my psychiatrist, and I would

do anything, whatever it takes to get better, try as many medications, combinations, augmentation strategies. I mean, you have to put up your fists and realize you are in a fight for your life.

MR. SCHARF: Eric Scharf with DBSA. I assume when you used the term trial you meant trials with different types of drug, not a drug trial per se.

DR. OLLENDORF: That's correct.

MR. SCHARF: And my experience was that I tried many different medications, there's an NIMH publication called Mental Health Medications, I think it was called, and in the back there's a whole list of all the different medications, and I went into my last psychiatrist and just checked off all the different things. I couldn't remember why some worked and some didn't, but I was able to just go through that, and at DBSA meetings, again, I take that out and tell people that's a great

resource to use, but you know, it is challenging with so many different medications out there for people to try.

In my case, you know, I think it was,

again, sort of as he was referring to, you make those efforts. My strength, though, and listening to folks in the support group that I facilitate here in the D.C. area, there are many folks for whom just, they resist the idea of taking the medication, they've tried some and some didn't work so they decided none of them are going to work and, you know, so they face those kinds of challenges, so it's just understanding those kinds of things.

The final thing I'll just say is, I don't know the exact percentage, obviously some CMS expert would have the number, you know, but people who are in the Medicare program obviously are mostly senior citizens, but the mental health component of those I think would still be very high. And so keep that in mind, it's not just senior citizens, but folks from a wide stretch of ages, and I am not a senior citizen yet. So, thank you.

DR. CUYJET: Al Cuyjet. I'm going to

ask a question and then the next question will be asked by Dr. Cruz-Flores.

My question goes back to the initial definition of TRD. Now we've heard unipolar,

bipolar, atypical and psychotic and one presenter, I forget whom, suggested that we restrict the definition to unipolar, others suggested we include other types of depression treatments, because depression comes in an umbrella of the definitions. I'd like feedback from the presenters in terms of what your opinions are in terms of an inclusive or exclusive definition for those four different types of syndromes that are related but are not all the same, or should this definition just include unipolar depression or should it be inclusive of other types?

DR. SACKEIM: Hal Sackeim again, from Columbia. I think some of the confusion comes from the fact that we have evidence that different treatments may be effective for different subtypes and a good example is psychotic depression, which can occur with bipolar or unipolar depression. The evidence is extremely compelling that antidepressants

alone are pretty much ineffective, that you have to combine them with antipsychotics.

In fact in relation to the previous question about tolerability and can people take

the drugs, when we examined psychotic depression in a large multicenter study, only four percent of the patients with that condition met the AHTF criteria for having an adequate medication trial because the dosage of antipsychotic that we used was so high that elderly patients in particular couldn't tolerate that.

Now with the change in medications and the second generation antipsychotics atypical, we see many more patients who are able to tolerate the antipsychotic plus the antidepressant and they're considered now treatment consistent. So it's one thing to say yes, we have one set of criteria for unipolar nonpsychotic depression but when we come to evaluating drugs like lithium or the anticonvulsants, we treat them very differently in a bipolar disorder than a unipolar disorder, so one's criteria for what constitutes treatment resistance should have

differentiation of depressive subtype in line with the evidence for efficacy of particular interventions.

DR. CUYJET: But somebody did say we

should just do unipolar. So, did you want to follow up regarding an opinion regarding the definition?

DR. TRIVEDI: So, I think it's not entirely different but I think in order to describe, clarify and use a targeted definition, at least we have to be thinking about each individually, so the unipolar representing three treatment drugs, four treatment drugs, and you're talking about them in a different construct than psychotic or bipolar depression. So I think we can debate about whether each one of them has then to have its own categories, but each one has to have more studies.

DR. CRUZ-FLORES: I have just a follow-up question to that. There are these different groups and certainly all of them require treatment. What is the size of the problem? I mean, if we're talking about 30,000 people a year that have TRD, what's the

proportion of those that are unipolar versus psychotic versus -- that would give us a better sense of a focus, or perhaps to modernize the groups. That's my follow-up question and then

I have another question.

DR. CONWAY: Chuck Conway from Washington University. I think as Dr. Trivedi said, it gets very complicated when you start talking about bipolar versus unipolar. By far, the majority of patients who have resistant depression are unipolar and the percentage of patients with unipolar who have psychotic depression is very small, the estimate is around eight to 10 percent, and so some type of psychosis can be very subtle. In terms of the percentage of patients who have bipolar-resistant depression, that's even smaller.

That being said, I think where the story gets complicated is that there is a significant subset of patients with bipolar disorder who have treatment-resistant, or who, the majority of time their bipolar extends when their mood is regulated, extends to depression, so two-thirds of their time when their mood is not feeling well they're in depression, and

many of these patients with bipolar disorder

actually do respond to the same novel

treatments as do patients with unipolar

depression, that's what I mean by the story

gets complicated.

So from my standpoint, I think the group that put together the white paper for this conference, we feel that given the current evidence, if we're going to use the model of a series of medication failures as the empirical definition of treatment-resistant depression, I think it should be based on the existing evidence, which is unipolar, but I think that's not to neglect those individuals, because there are many of them with bipolar disorder that the treatment applies to. I worry a little bit about that, because I don't want that population, that population also needs the same level of attention and aggressive treatments.

DR. CRUZ-FLORES: And then my other question, it has to do with, I wonder about the definition, and this is for you or anybody else. If we say, the sense that I gather, and I don't know the whole literature, just what you guys presented, so on the one hand it seems

like it's a big problem, we have the definition that we need to take to trials with how they are dosed and so on, but as I see it, we watch and see these patients, right, so from the

clinician's point of view the evidence says that level of remission for level one is 36 percent, that the remission remaining at four months is about 70 percent, and then for the ones with sustained benefits it's about 25 percent.

You still have here too, which is still part of it, you still have about 30 percent response, and the probability of actually being in remission at 12 months is less than 50 percent, and then it falls to half as many when you look at sustained remission. So the question is, why do we have to wait for two trials? Do you guys have a sense or information or evidence or clinical trials to show that comparing the course of people with one failure and then continuing with whatever else, if there are two trials for those kind of therapies you could see what's effective, because whatever the percentage is, it tends to get much better with ECT or better with some of

the other therapies.

So I just wonder, have you considered this in a population older than 65 and the problems with pharmacologic interaction and so

on, so, any sense, input that can help us?

DR. SACKEIM: Two points. One, the magnitude of the trial level is frightening in terms of the demographics that we're talking about. One out of five Americans will have major depression in their lifetime, that's 20 percent of the population. Our estimates in general and the agreed upon notion is that at least 30 percent of those individuals will have treatment resistance, so we're talking about, you know, conceivably millions of people, not a few, and so the definitions that you propose and ultimately accept are going to be very very important.

Two may be conservative, two failed trials that is, but certainly by the STAR*D data you fall off the cliff after two failed trials, the likelihood of sustained benefit is less than five percent at that point, so that provides an empirical cutting point.

But also we're not testing just, for

instance in epilepsy today, whether one failed trial or two failed trials justifies surgical intervention, and this is the same type of questions that's being asked in depression.

And because it's in part a judgment, there's always some judgment that comes into account when you're determining the adherence of a patient, the outcome of the trial, was the dosage adequate and so on, then it's certainly a more conservative statement to require two than just one.

The other conservative aspect of this in trying to be certain when you call somebody treatment-resistant is we're only talking about the treatments in the current episode, so that starts another large large question, because patients may have failed many treatments in the past. Are they relevant to the definition or are we only looking at the current episode? Of all the data that I presented today, and most of the data we have in the field, pertained to the characterization of treatment just in the current episode of depression, because it's so difficult to determine adequacy, dose and duration and so on, for episodes that have

occurred in the past.

DR. BACH: Thank you. Do you have a fairly -- we now have a backlog, so be concise.

DR. TRIVEDI: Sure. Two very concise

points. One is, I think this question of two treatment failures and sustaining, sustained effect or sustaining remission for a longer time is more complicated than just one factor, there are other factors.

And the second issue is when you raise the question of whether something else would be a better option, something else has to be shown to be better than this, and that's not been shown so far.

DR. BACH: I'm going to have to keep track. Dr. Pope.

DR. POPE: May I ask two if they're short, narrowed and focused?

DR. BACH: Yes, that would be terrific.

DR. POPE: Thaddeus Pope. Dr. Conway, I heard you emphasize several times the importance of centers of excellence, so I'm wondering if you could address directly one of the voting questions, which is whether or not a

TRD definition could be applied only in general psychiatric settings, or only instead in specialty psychiatric settings like Wash U.

DR. CONWAY: Chuck Conway from

Washington University. Yeah, I think for the purposes of, and this is a question that I think we struggle with, what would be, from a research perspective, I think, and I think that was sort of the focus of the meeting, an operational definition for further research, I think for novel treatments that are evolving, many of which are rather invasive like deep brain stimulation, vagus nerve stimulation, that kind of thing, I think because there is significant risk involved with these types of, or not significant, but there's more risk than taking a medication, that I think it's probably more reasonable and safe, and probably going to get better findings if you have centers that are specialized in recognizing and treating severe depression with resistance.

And perhaps further down the line when we get to what is a, what Medicare is going to fund or what Medicare is going to accept as reimbursement, I think that might be --

obviously we can't use centers of excellence for every treatment for treatment-resistant depression, but I think in terms of the research, that's the way I sort of, or we see

it.

DR. POPE: Real quick, Thaddeus Pope, and I guess this is for the, directed to the first two speakers. So the weight of the literature suggested the definition is the failure of two trials at adequate dose and adequate duration, and I guess maybe given the prior discussion, trials of two different classes. But the literature and even some of the presentations indicate that ECT is very successful, it's less successful after you've already failed, but it's still very successful. So my question is, could you address why not include in the definition not only the failure of the two trials, but the failure of ECT, you know, so it's not just treatment for TRD, but it's built into the definition?

DR. BACH: Either one of you two.

DR. RUDORFER: Matt Rudorfer from NIMH. Well, I think the short practical answer goes to the map of the U.S. that I showed this

morning, and that is that in many areas of the country ECT is simply not available, there are many practitioners who don't have access to it even if they wanted to refer somebody. And so

as a practical matter, there are many people for whom ECT would otherwise be clinically indicated who simply don't have access to it.

DR. TRIVEDI: I think my plea would be exactly that, that there's so many places in the country that ECT is not only not available, it is unwelcome, people make, there's a lot of social, political, media stigma about it, so that therefore, that becomes a threshold question, we will deny the very existence of millions of patients, and I think we have to be aware of that.

DR. BACH: Thank you. So we now have three categories, we have treatment resistance, we have treatment intolerance, and we have system intolerance as definitions.

So one clarification, the reason I stepped out just to make sure, and I take some blame for this, in question three, because there has been a lot of discussion around kind of the applicability of the clinical research

criteria into clinical care, an obvious issue with externalization or whatever you want to call it, question three is a question about clinical care. It can be interpreted as

(inaudible) this definition can be applied to the clinical care of Medicare beneficiaries. So as you're asking these questions, this is of course an umbrella issue around research, but that is a question that will be useful to CMS and will be answered too. I'm up to, a question of clarification, Dr. Gaynes?

DR. GAYNES: So when you talk about clinical care, does that mean clinical care in terms of the identification of treatment-resistant depression, or is that clinical care in terms of the management?

DR. BACH: I would say it's my read that it's a definition/identification issue, not a management issue.

DR. GAYNES: Because I think a lot of what we've been talking about in terms of the difficulties is in the management, but not on the question of whether it can be accurately defined.

DR. BACH: I take your point and will

continue to discuss it. I'm up to Dr. Lewis, and if I have you out of order, I apologize, and please put your tent card down as you're done.

DR. LEWIS: Roger Lewis, and I believe it was probably directed towards Dr. Sackeim. If I understood correctly, you had earlier with your colleagues previously developed a questionnaire that helped identify or create definitions for treatment-resistant depression, and I've heard concerns that may have reflected difficulty in a primary care setting identifying these patients in a way that is reliable, and I use the term reliable in the sense of different raters getting the same answer, not in terms of the literature.

So my question is whether there is direct head-to-head evidence for inter-rater reliability studies of the application of these criteria for determining treatment-resistant depression that compares primary care practitioners with psychiatrists or specialists.

DR. SACKEIM: As far as I know, the answer is no, that there hasn't been any

comparison of primary care versus specialty care. But in reference also to your question, a simplified form of the ATHF, one that is much more suitable for primary care, was created by

one of the companies, a TMS device company, and that has been successfully used with excellent validity data but no reliability data.

DR. GAYNES: You generally cannot have high validity without reliability, so if there was success in validity that would be implied. Can you define success?

DR. SACKEIM: Predicting outcome of the trial under double blind randomized conditions, that the assessment of treatment resistance in the Neuronetics trial was what got them their FDA approval because it was so fundamental in determining who got well with the treatment relative to sham versus where there was no effect, and so that helped validate their measure, which has now been used in other studies as well.

DR. GAYNES: Thank you.

DR. BACH: Okay. Dr. Gaynes?

DR. GAYNES: Yeah, can I make one point and then maybe one question? My point

being, you mentioned the difficulty in primary care doctors successfully identifying the presence in these studies, and I agree that that has historically been true, but my reading

of the literature, and I think this is consistent with what the U.S. Preventive Services Task Force now said, which is that people should be routinely screened for depression in primary care and other related settings, and with that screening piece in there, there's actually now the assumption that the standard of care is that folks can be identified and at least begun on treatment, so I think that the accuracy piece in primary care has been noted to improve.

The other point to make, again, just in discussion about what's been said here in terms of the concerns about barriers to adequate treatment, that most of the studies that look at barriers to adequacy of treatment are really sort of naturally representative of folks who are going in for initial treatment for depression, not only are still on it a couple months down the line, six months down the line, et cetera, but not specifically for

the TRD population, or those folks who failed two or more medication treatments or were said to have TRD, which is an algorithm of measuring care, when they're only faithful to the

treatment in about 80 percent of the cases, and that was in primary care settings as well as the psychiatric studies.

I guess what my question is, and I'm interested in hearing from any of the speakers, is in terms of that identification of TRD in primary care, not the management piece but the identification of TRD in primary care, from our speakers, how effective or how accurate do they believe the primary care doctors can be?

DR. BACH: Dr. Trivedi, Dr. Rudorfer, do you have an answer for that question, is there empiric information on that?

DR. TRIVEDI: So that is a point, Dr. Gaynes, we don't have data, so that is really a big mystery, we don't have the data to prove one way or the other. My suspicion is that it is going to be hard.

DR. BACH: Thank you very much. Professor Melkus.

DR. MELKUS: Gail Melkus. We heard

this morning about the great diversity in the populations affected by treatment-resistant depression, and that goes in terms of age and gender, race and ethnicity, and I wonder if

someone could speak to the reliability and validity of the Hamilton depression rating scale, particularly because it's one that's filled out by the health care provider, and for this population in particular versus somebody who had depression that was responsive.

And then I was also taken by the fact that the medical outcome studies, SF-36 was used in the population, and how much you would expect that to change, especially in the older population.

DR. SACKEIM: There are excellent data on reliability and validity of the Hamilton, the kappa is usually, for observer ratings that we see, .95 and above. It's something that trained raters are excellent at.

DR. MELKUS: Even in the population who are treatment-resistant?

DR. SACKEIM: Yes, even with ECT samples, which are highly loaded with treatment resistance, that's what we and many many

studies have found, and the correlation between the Hamilton and the PDI, for instance, in the treatment-resistant population is just what you see in the general depression population, that

the correlation improves with treatment, it's at the end of treatment .8 and above, so it has concurrent validity as well as reliability.

DR. MELKUS: What about as this country continues to get more racially and ethnically diverse and older?

DR. SACKEIM: Well, in these samples over two-thirds of the patients were elderly, they were above the age of 65. I can't address the racial diversity, whether these scales performed differently in them.

Our group just published in the last couple of years several papers on functioning using the MOSF-36 in ECT samples, and these treatment-resistant patients come in with scores that are unbelievably low, far lower than comparable depressed patients with comparable Hamilton scores. Treatment resistance in particular, as well as for ECT, is associated with deficits in functioning, that's one of the reasons people are referred

for that treatment. And after treatment, we could not distinguish the scores for this population from the normative data for the MOSF-36, so massive improvement.

DR. BACH: Thank you. How many categories does the Hamilton ratings scale have? I'm just surprised that you have a kappa exceeding .9 for anything.

DR. SACKEIM: It's not categorical, it's a continuous scale, the 24-item measure can go from zero to 57, 58, something.

DR. BACH: All right, thank you very much. Dr. Salive.

DR. SALIVE: Marcel Salive. I have a question for the first two speakers about, could you please comment on the proposal from Dr. Conway and his group on this two-stage treatment-resistant depression definition that he proposed? This is relevant to question number one. So, it appears to be based on the levels from the STAR*D trial, but it would be done I think for future studies from retrospective assessment, rather than enrolling people and taking them through the levels and failing. So can that be standardized, and

what's your opinion on it as a standard definition, what would you recommend?

DR. TRIVEDI: So, at least my understanding, I had not studied it before, my

understanding is it still defines treatment, adequacy of treatment steps the same way. That is, at the end of two treatment failures it becomes a quote-unquote stage one failure, and then later on a more extreme stage failure that introduces treatment options based on sort of current logic, to -- I should let them comment, but I don't think they have enough studies that would then tell us that at the end of two, three, four failures you should use this treatment and that treatment and not the others, right? Those kind of studies until they're done, I don't know how to recommend.

DR. SALIVE: Right. Do you think you could enroll people in such a study and then randomize them?

DR. TRIVEDI: After having had two treatment failures based on adequate dosing, I think that these measurement tools are not tested with any regularity. I think they give you a good idea of the duration and the dose of

the treatment exposure and then they can be identified. In a lot of quote-unquote treatment-resistant -- the field is actually accepting of treatment-resistant depression.

This is not a question in my field. In my field whenever a question is raised for treatment options, neurobiology studies, we actually use these instruments in order to identify and recruit patients to come and participate, and they have then been studied, so I think that is not, identifying that group in recent studies has been done clinically and scientists believe that it can be done, and if a doctor was interested with primary care, that would be another.

DR. BACH: Just to clarify, the question I've heard you ask, Marcel, is not, the answer didn't apply to the question I heard you ask, so let me try again, but then again, I might be wrong. I thought the question was whether the additional stratification gave us more insight into the clinical trial results, that this multistage category as opposed to simply binary distinction was going to make either trial feasible or unfeasible, and I

think you answered that question that it is feasible.

Or maybe it's my own question, so I'm going to take the prerogative I have to just

ask it. Would it help, would that further stratification of the patient population help us delineate the impact of the new treatment, the treatment under investigation, as opposed to having a simple binary approach?

DR. TRIVEDI: I think so, but it would be more important to have, to reach a national consensus on this in order to then entice more people to do the research studies to facilitate a new system. So it can be done, I'm just saying that will require more work.

DR. BACH: Thank you. I think Dr. Carpenter was next.

DR. CARPENTER: This goes back a little ways and I think it may be easier to ask the question, if you disagree with what I'm concluding from what I've heard. So, of course the different disorders are heterogeneous but the depression itself, I don't know if you can sort out the heterogeneity in the results, and I don't think you're asserting that the

treatment of depression is remarkably different depending on whether it's strong or there's more effect with respect to moving forward, it's more that there may be additional

treatments that should be given.

So in that regard the first question is, is there any reason to think that you cannot identify treatment-resistant depression in these different disorders? Then there may be another question about just sort of how to restrict to one or the other. And just to add to that, if we're considering clinical application, to me it's unthinkable that in clinical application that we would attempt to apply the stringent criteria that you need to be sure in the clinical trials. If somebody comes in that's, has had treatment failures in previous episodes, you're not going to tell him we're now going to spend the next three or four months proving that you qualify for treatment-resistant. So also, I'd like you to provide a comment on how you would think about the criteria differently in clinical application than you would for clinical trial purposes.

DR. TRIVEDI: So, Dr. Carpenter, for

the first part, as we know, for bipolar

depression for example, the data are not there

to support the facility to go antidepressant

after antidepressant before you call them

treatment-resistant, because the data are actually questioning whether you should even be using an antidepressant medication to treat the depression, but most everyone recognizes you can go through the algorithm, so there is a much more different algorithm to use. So yes, you could define by polarization treatment-resistant depression by segregation of these subtypes.

Same thing with psychotic depression also probably; we don't have enough literature to show what to do with the sequential treatment of those with psychotic depression, but there also we're likely to use different parameters to define that difference.

To your last point about whether the exact research drive approach is going to be applicable in clinical practice, that's a very interesting important point. We don't do that in most of medicine. In depression, regular, in depression that is not defined as treatment-

resistant, randomized controlled trials that get FDA approval use the Hamilton depression rating scale as a measurement tool. In clinical practice very rarely is this used, so

that translation to clinical practice becomes a different parameter, and then people can talk about how to do it. Does that answer your question about that?

DR. CARPENTER: Yes, but just give me your estimate. In clinical practice I would assume clinicians would use past history of an adequate response, not to study twice in this episode. Is that type of change likely to make any remarkable change in the concept that's being captured, treatment-resistant depression?

DR. TRIVEDI: So I agree, yes, there will be slippage in terms of how stringently the criteria of dose and duration is applied, and so that would affect the group that would get defined as treatment-resistant.

DR. CARPENTER: So less stringent clinical care?

DR. TRIVEDI: Well, I wouldn't think so. I wouldn't think that less stringent is better clinical care.

DR. CARPENTER: What I imagine is people who have a life full of depression, clinical depression, we know a lot about them, and you're saying you don't really move them

into this category until they go through a very stringent criteria as far as having them exposed to these medications?

DR. TRIVEDI: No. I understand there is wanting to have a stringent criteria but it doesn't have to be prospective, it can be retrospective so that is allowed, normally you have to give them two more trials, but to be able to document how that adequacy was there, some degree of precision would be important.

DR. CARPENTER: Thank you.

DR. BACH: Thank you. I have Dr. Ollendorf, then Dr. Lystig, and after that I'm going to ask for last rounds for questions, so if you have more, that would be the time. Dr. Ollendorf.

DR. OLLENDORF: Dan Ollendorf. So, Dr. Conway, in your presentation I noted when you went through the responses to the voting questions it was a little rushed because it was towards the end, but you do mention that

there's consideration that an adequate trial of psychotherapy could be considered as equivalent to an antidepressant trial. I'm wondering if you or any of your colleagues have done work to

set parameters around that, is that based on a minimum number of sessions, is it based on core components or elements of the approach, certain types of psychotherapy might not be widely available in certain parts of the U.S.

And then as an adjunct to that question, it's sounding less and less operational as I think about it, but if this is something that could be considered as part of the TRD definition for patients on combination therapy, drugs and psychotherapy, would both aspects of treatment be subject to the TRD definition?

DR. CONWAY: I think the answer to the first question, I think operationalizing therapy can be challenging. I think the STAR*D trial, and Dr. Trivedi knows more about this than I do, the STAR*D trial did have an arm that operationalized psychotherapy, cognitive behavioral therapy, interpersonal therapy, so we would be in favor from a research,

Medicare-based research perspective, using therapies that are empirically proven therapies. Those two in particular are the most established, not that there aren't other

therapies that work well.

Then in terms of the availability, accessibility, I don't -- I think this is one of the reasons why we said it could be looked upon as a treatment trial but not a mandatory thing, because it's not available to everybody. The type of therapy that was done in the STAR*D trial, I believe this is correct, Dr. Trivedi can correct me, but it was weekly psychotherapy by someone who is specifically trained in a particular empirically based therapy for three months, it might be two months or three months, I'm not sure, but I think there are ways that are accepted in terms of doing standardized psychotherapy.

DR. OLLENDORF: Thank you.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Ted Lystig from Medtronics. I mostly actually have some previous questions but I want to solidify the thoughts. So I heard you, there was a question

along the lines of can ECT be considered a potential treatment to compare, and Dr. Pope, earlier you had asked about the role of ECT, and I heard the answer there saying it

shouldn't be a required step, but I believe it could be permissible. So I'm looking for confirmation from our first two speakers, is it the case that we can look at a may versus a must definition? So, a must definition would say you must try different antidepressant therapies, whether they need to be (inaudible) or not. It may just say there are multiple therapies (inaudible) including (inaudible), and isn't it the case that it would be a reasonable definition to say that failure of at least two of a class of treatments including antidepressants, ECT, psychotherapy, or does it rely on that possibility of saying whether or not it needs to be drug treatment or whether it can be drug treatment or some other.

SPEAKER: A single drug treatment.

DR. BACH: Okay, Dr. Rudorfer or Dr. Trivedi?

DR. TRIVEDI: I think the short answer is that would satisfy the general principles of

treatment resistance, and specifically if you want me to pin down and say yes or no, there is required data that we don't have, so you're asking the question that would require us to

have sets of studies where people have been randomized two or three steps to include ECT and exclude ECT. So it is conceivable that the same principle does apply in medication, which we have, I think a few data where you try psychotherapy efficacy data, where you try ECT efficacy data, and that would define having had adequate proof and trials, antidepressant-resistant trials, and those who then do not respond will be treated as treatment-resistant. Does that makes sense?

So it can include any permutation of antidepressant treatment and adds what's shown to be efficacious. That includes medications, that includes depression-focused psychotherapies, and includes ECT as approved by the FDA, but it's based upon failure that makes it resistant. Does that make sense? So that's sort of how I would think of it.

DR. LYSTIG: So, I'm hearing you say that it would be acceptable to consider the

inclusion of multiple therapy types in the definition of treatment resistance, and it appears we don't have great level data from these or these because these are fixed sequence

treatments and you don't necessarily have to do that sequence of treatments anyway.

DR. TRIVEDI: Right.

DR. BACH: I have Dr. Lewis and I have Dr. Yan, is that right? Go ahead. Dr. Lewis, that's who I called on.

DR. LEWIS: Roger Lewis. I'm going to try Dr. Lystig's strategy of telling you what I think I heard and then see if you agree. So, I hear very clearly that the treatment strategies for patients whose depression is complicated by psychosis, or it's bipolar, the issue is it is counted differently. What I didn't hear was whether an approach in which you count appropriate treatment trials for the disease the patient happens to have could be applied uniformly across those different etiologies or sorts of depression. So hypothetically, if one used the definition for unipolar depression which is based on two adequate trials of appropriate therapy, assuming you define

appropriate therapy correctly, would a similar type of definition apply to those with bipolar depression and those with depression with psychotic features, assuming again you have

separate definitions of what is appropriate for those set of classes of patients, would that make sense and capture the concept of treatment-resistant depression?

DR. CONWAY: I would say that with our standard level of knowledge, it can only be applied to unipolar depression, that we don't have, there is no bipolar equivalent of the STAR*D trial, there is no psychotic depression variable in the STAR*D trial, so my thinking would be at this point in time we would only be able to apply this to a unipolar nonpsychotic depression.

But if further data were collected, I think a similar model could be created down the line, but right now I don't think there's enough data.

DR. LEWIS: And I'm struck by the fact that right before you came up, some of your neighbors were nodding yes before you came up and said no, so I'm wondering if any of your

neighbors have an alternate point.

DR. BACH: Do we have any head nodders ready to come up?

DR. AARONSON: I would like us not to

get overly weighed down by what we have clear evidence for and what we don't have clear evidence for. In terms of general clinical practice, yes, when somebody that I've seen who has psychotic depression has failed two reasonable courses of treatment, you would consider that's a more difficult version of psychotic depression, that's a more difficult version of bipolar depression.

I understand Dr. Conway's concern that we really haven't operationalized that definition from a research standpoint, but from a clinical standpoint, from my everyday caring for folks with difficult to treat mood disorders, that's what winds up happening, and I do think that it would fall under the category of, let's call it treatment-resistant mood disorders. And what, the most important thing is to be able to differentiate so that you know from the get-go whether you're dealing with a psychotic depression, bipolar

depression, or unipolar depression, but I think that those can all be under the general topic of basically treatment-resistant mood disorders.

DR. BACH: Thank you, Dr. Aaronson. Dr. Yan.

DR. YAN: I have three questions. The first two questions are related to optimizing, and for this depression field and scores, it looks like most of these get their validity and reliability from cross-section studies. Have you seen these studies where there is a reliability or probability issue, for instance where a patient's score on a depression scale today is actually very different two weeks later, if other conditions are the same? That's my first question.

DR. BACH: Let me ask, you'll definitely get to ask all three questions, but let's get an answer to that question and then go on to the next one; is that okay?

DR. YAN: Yes, sure.

DR. BACH: Do you have somebody who you want to ask that specifically, or is there somebody who feels they have fluency with that

important technical issue? The question is within patient consistency or reliability of the scales.

DR. SACKEIM: Generally speaking,

particularly in the TRD population where you see much more chronicity, you don't see a lot of wild fluctuation in the scores, but if you see a progression in change over time, it's usually because of the beneficial effects of treatment so yes, there's high reliability to these scores. In fact, these scales are used intimately, for instance in the practice of ECT, it's these scale scores that determine how many treatments the patient receives, you're going by the change in these scores over time to direct the treatment.

DR. BACH: Thank you very much. Dr. Yan, your next question?

DR. YAN: My second question is, a lot of these studies talked about power, statistical power based on the primary outcomes, and it looks like most of the studies were also using multiple outcomes for a number of scales and also admission criteria. Have you seen this random discrepancy from the same

study and if there is, would this affect the statistical power? Because if the study is based on the primary outcomes you see from efficacy, but if the study is underpowered for

secondary outcomes, it might be a futile exercise. Have you seen these kind of discrepancies for primary outcomes and secondary outcomes?

DR. CONWAY: I think it's probably a reasonable criticism, more sort of a description of the evolution of psychiatric research, to say that up until about ten years ago, there wasn't a lot of evidence on measures of overall functioning.

One of the things that I probably didn't have time to get to in my seven-minute presentation was that I think, we think that one measure included in treatment or in studies operationally defining the question, you should have outcome measures that include overall functioning.

Now one of the things we do know about overall functioning is that that tends to trail the response from a depression standpoint, so the Hamilton score or the MADRS score will drop

but the SF-36 maybe a month or two later, it's where you're going to start to see massive improvement. So they're not equivalent in their timing course but generally speaking,

that's the trend you see when depression gets better and then the function either trails with it or slightly behind it.

DR. YAN: What about the remission, how do you measure remission?

DR. CONWAY: The remission is typically defined by, for each of the scales there's a set point. So for like the Hamilton 21 there's, a score of seven would be considered remission, or on MADRS a score of ten or below is considered remission. So, with minimal residual symptoms and we've affected a cure when we use the term remission.

DR. YAN: Thank you.

DR. BACH: Do you have a third question, or that was the third question?

DR. YAN: No, I have another. Can I --

DR. BACH: Yes, absolutely, but let me, can I comment on the second question? It strikes me, I also saw the multiple outcomes,

but it strikes me that they are to some extent nested or overlapping outcomes. We know there's remission, there's response and there's relapse, and those are all conditional on one

another, so I think although they're not perfectly mathematically intertwined, it strikes me as, personally, as not a huge problem of certain multiple (inaudible).

SPEAKER: And just to confirm, for example, starting with just looking at that primary outcome, it was going to be the same whether you looked at that primary outcome or also looked at those other secondary outcomes.

DR. BACH: Dr. Yan, you had a third question?

DR. YAN: I have a third question that, from the studies, really they're trial and observational studies in the literature, and almost all these studies are based on average and treatment effect, and it would be to me, my opinion is that it would be ideal if we were able to identify those patients who are more likely to be TRD before applying treatment. Do you see any barrier, because (inaudible) would be able to identify, pretty

much identify the risk of stratification before they develop the resistance, because once they are exposed to medication it will be harder to treat them than if we were able to develop a

method of prediction to identify those who are more likely to be TRD. Do you see any barrier or do you (inaudible)?

DR. TRIVEDI: I think the short answer is there's a lot of research in the country that is focusing on that question, not only treatment resistance because that is true for everything, including nonresistant depression, if we can identify risk stratification through biomarkers and behavioral markers or subtypes, obviously that might assist us in proceeding. All our attempts are aimed at trying to be able to predict that before you get to that point.

DR. YAN: Are you actually getting results in predicting, or how accurate have they been?

DR. TRIVEDI: They are not very conclusive.

DR. BACH: Thank you. Dr. Cuyjet, or no, please, Dr. Rudorfer?

DR. RUDORFER: I just want to add, it

was interesting to me when I looked at that British medical journal, Triumph, 1965, they made the comment that they had looked for, they were using three active treatments and placebo,

they were looking to see if there were any demographic or clinical predictors even in retrospect, to predict response to any of those treatments, and they found none, which I thought was interesting.

I was at a meeting a couple weeks ago discussing Alzheimer's disease, and I found myself suffering from biomarker envy, because when, to see PET scans of pathological amyloid deposits in people who are fairly preclinically ill was very striking, and again, it's certainly not ready for prime time or office use, but certainly just the issue of who should be in your trial because they have this condition and who should not be because they have something similar but not the same, and of course raising as you do, the idea of preventive intervention would seem quite amazing, and we are certainly not there yet in mental health, but we're striving towards that.

DR. BACH: Thank you. Dr. Cuyjet.

DR. CUYJET: Yeah, this question is for Dr. Fox-Rawlings and Dr. Conway. It's been alluded to before, and if you look at the STAR*D patient cohort it's clearly not

representative of the population that the literature is demonstrating, so I'm trying to frame this question number three, where TRD should be treated. I'd like some feedback or your opinion if it's a specialty psychiatric center with really good registry data, these trials take a long time and they're very expensive, what your opinions are on the use of registry data in a specialized clinic to look at differences in outcomes among the different populations that are receiving these interventions.

DR. CONWAY: Yeah, I think my inclination if I understand your question correctly is that the, one of the things that we've observed with other studies involving treatment-resistant depression is that because it does require a very careful analysis of who -- I mean, part of the reason why I brought up this whole model of two stages is because I wanted to point out, we wanted to point out as

a group that there's a spectrum of resistance. There are the people who are really really resistant, those are the kind of people I treat, that failed eight-plus medications, and

then there's the people with lesser resistance, and I think the different studies for the most severe ends of the spectrum that involve implanting devices in people and electrical stimulation, I think those types of things are probably better done at centers of excellence or centers that have expertise in dealing with the population.

I think for perhaps less invasive type treatments, you could see potentially using centers that weren't so specifically oriented towards resistant depression. Does that sort of answer some of your question?

DR. CUYJET: I was just trying to get an answer as to what your feelings are about having data that's not randomized, controlled, blinded, in populations at risk.

And the other piece of that, which I think you answered, was with the relapse/remission rate, which is after a 12-month period, not very convincing.

DR. CONWAY: Sure. My opinion would be that for most of the type of work that I think we like to see done in terms of pushing the barriers of knowledge in treatment-

resistant depression, that would be best done at centers of excellence or centers of expertise, that would be my opinion.

DR. CUYJET: Dr. Fox-Rawlings, you've been quiet.

DR. FOX-RAWLINGS: I don't really have much to add. I think if registry studies were done very well, and in a complicated issue like depression that may be very hard to do, they could still be useful in kind of understanding the natural changes that we see in treatment-resistant depression. But a lot of the really powerful research that are going to give us new treatments and supply new treatments are clearly, are probably going to have to be more prospective studies.

DR. BACH: Thank you. Dr. Burke, do you have a question? Otherwise, I'd like to -- okay. Thank you very much for all of the thoughtful answers. We're going to move to a discussion amongst one another. This is the

time where the panelists will probably bring more of their own knowledge to this discussion, along with questions.

I in general don't like to foreclose

the possibility of people providing more info, so although it won't be this same back and forth, please don't hesitate to stand up if you have something to contribute; the goal here is to get to the best answers. So, I'll start with Dr. Burke.

DR. BURKE: Interesting. Well, it's (inaudible) two-thirds or 68 percent of antidepressant prescriptions are written by primary care physicians, yet here we are, talking about specialty, secondary or tertiary care of these patients. So, I'm going to take another perspective.

I'm a primary care physician, I see depressed patients, I have my 15 minutes with them, okay? So, a couple things. Firstly, I want to comment on the pseudoresistance idea, because from a primary care perspective, you know, the idea that somebody is pseudoresistant because they're not adherent or they take a lower dose of the drug, it's really, you may be

22 talking about, you know, they don't have a
23 biological effect so there's really no
24 biological perspective.
25 But in my world, there are patients

who fail therapies because they're not adherent, but they are a failure just as much as anybody else is, okay? I have patients who I can't give full doses of these drugs to because they're elderly, they're 80-year-old ladies and they're just not going to tolerate it. So that's a true failure to me, that's a true resistance, even if it's not to you, to me that's a true resistance, it's not a pseudoresistance, okay? So I want to make that clear in the very beginning.

Secondly, I want to say that I'm looking for a measurement-based system that I can use as entry and exit scales, and allow for serial monitoring. I'm looking for a quick, simple, easy-to-understand definition, okay, and I'm looking for something that can work in my primary care practice. So in my definition, okay, talking about treatment-resistant depression, I'm going to see the results of your depression, you're going to see the

results of the treatment on the depression, okay? Now I'm going to treat it and hopefully much of the time I'm going to be successful, and it's my failure that you're going to see,

all right?

So what we're calling treatment-resistant depression is really what I call medication-resistant depression, right, because what's going to happen is that patient is going to come in, if we've got a screening tool that says the patient is depressed, I might give them a PHQ-9, a quiz, and the reason I give them is I can give them one of those instead of three. So let me be clear. You charge me a dollar per test, I'm not going to do it, okay, because I've been doing this over time, so any test that's going to cost a dollar per test with these guys, they can afford a dollar per test, they're specialists, they make big bucks, but primary care docs don't get the big bucks, so nobody is going to give me a dollar per test, so instead I'm going to use the PHQ-9 because it's free, okay?

So what's going to happen is they get the screen, the patient comes in, I sit them

down, we get a PHQ-9 and just go through that, and I'm not too sure what to do with this patient, right? So I'm going to put him on medication, I'm going to say okay, let me give

you this, have you come back and we'll follow up with another PHQ-9 and I'm going to see if I'm doing any good. If it doesn't do any good I'm going to try a different product and I'm going to say look, you know, this didn't work out for however many weeks, we're going to have to try something else, and then we have the problem.

The problem comes in when my patient, we've tried two drugs on him and it didn't work, the patient is still depressed, so what am I going to say? I'm going to say to these guys, I have a medication-resistant depression, because that's what it is, okay? I know it because the patient sees me year in and year out, okay, I'm going to do my bit, so then I'm going to refer my patient as a medication-resistant depression, that's what I'm going to do.

So I need a simple definition, so I circulated in advance exactly this, and I'm

going to read it to you now, but it's a medication-resistant depression, depression that does not respond to treatments of two appropriate antidepressant medications. And I

can handle that in 15 minutes, okay, I can deal with that, or maybe even 30 minutes if I'm feeling very lucky or the patient has some comorbidities or something.

Now I define depression based on a scale, so in my -- what, I use the QIDS only because STAR*D uses it, and you've got to have a threshold, so let's just say a QIDS score greater than five, okay. If you've got a guy on the threshold, consistent, he's on medication, treat him if the score's greater than five. Now maybe it's four today and six in six months, but I've got to have something.

And then what does not respond mean? Well, it means that the patient didn't have a remission, okay, with the appropriate dose and duration, and appropriate means appropriate for my patients, not appropriate for you guys who know the biological response rate, okay, because my patients aren't appropriate by numbers, they're appropriate my way, okay? And

then remission means on whatever scale I use, and if it's QIDS, it is now less than five.

So that's my definition. If depression doesn't respond to treatment with

two or more antidepressant drugs where I have a scale going in, measure on that scale, okay, and if it's below over the period of time that it takes then it's remitted, if that doesn't work I call it medication-resistant depression.

I don't know what treatments there are for depression because I'm not in the every treatment business, I'm not in the ECT business, I'm not in the nerve stimulation business, okay, and I'm not going to refer people. So if a patient comes in and says I'm depressed, am I going to give him ECT right off the bat, I'm sending you out for ECT today? No, I'm not doing it, I'm going to try an SNRI, okay? And if that doesn't work, I'm going to hand him another one, maybe an SSRI, okay? Then I'm going to refer him to somebody, because I'm not going to be referring him to ECT, I'm not going to be referring him to vagus nerve stimulation.

So my recommendation is that's

medication-resistant depression, because from a boots on the ground standpoint, okay, that's a definition that all your primary care docs will use, it makes sense to them. If it's

ambiguous, like what's treatment-resistant depression, is it for all treatments, is there a selection of treatments, is there a group of treatments, one, two, three, we don't know, okay? So (inaudible) and if they fail then that's medication-resistant depression and you guys get them and you can call them whatever you want.

DR. BACH: Thank you for that. And so just because -- all right. So, the purpose of the discussion --

DR. BURKE: That's just in general. I mean, I'm proposing, what is the standard definition of TRD? It shouldn't be TRD, it should be, medication-resistant depression should be the definition that we're talking about today, because I have no idea what treatment-resistant depression is. I mean, is it ECT and then meds, or meds with ECT, or what is it? It's too ambiguous for me, and in a medical context I think it would be too

ambiguous for Medicare.

DR. BACH: So first of all, we've gotten the worst possible criticism. We have to speak into our microphones and we are not

doing that, okay? So please speak into your microphones. All right, so let me --

DR. BURKE: Am I close?

DR. BACH: Perfect. Can you just say everything you already said again? No.

Let me try to put a point on it and please, other panelists may chip in. There are two alternatives to what you just said, right, which I interpret to be that the usefulness of some of the definitions that have been bandied about for TRD is limited in the primary care clinical settings, and so there are two alternatives.

One is sort of work upstream, if you will, to try and create a practical clinical definition that's applicable, and apply it in the clinical research context, and the other is to sort of believe that there's a clinical kind of research quality definition which as you've described it in primary care, is difficult to translate. But either of those, in terms of

thinking about the questions and how we're going to characterize our views on them, those are both possibilities, and so I think as we're talking about the research question of TRD, we

should take that into account, that you can end up in either of those two spheres.

DR. BURKE: And I'm saying this is a two-step process. I'm saying the first step is to recognize the primacy of primary care, the first step initially has to be, because that's what's feeding you guys, and so the first step is literally, you're a conditional population, all right, okay? So in other words, these folks are all conditional, they're conditional on me having failed through medication.

DR. BACH: First of all I want to go to Dr. Lewis, but to clarify, to differ with you, this structure of the MedCAC and structure of the question emanates from the research definitions of enrollment, and then if you will, filtering out into the primary care. So I want to go to Dr. Lewis.

DR. BURKE: Okay, but let me just finish. So the second point is the research definition, so once you clear the hurdle that

primary care has failed and the two medications have failed, then you move into the research domain and properly so, with the presenters we've had today. And so that then would be

their definition of these people that are coming to them, okay, from the primary care community.

DR. BACH: Okay, thank you very much. Dr. Lewis.

DR. LEWIS: Roger Lewis. So, I have not heard anything that suggests to me that this is a useful dichotomy, breaking the research definition from the clinical definition, with apologies to Dr. Burke.

DR. BURKE: That wasn't me.

DR. LEWIS: In terms of a way forward in general, the degree with which the research definition matches a practical feasible clinical definition in both primary and referral-based practices will help us generate evidence that can then be accurately applied in those settings because we'll actually be able to identify the population to which those research findings apply.

I think it's highly likely that no

matter what we come up with, we will learn over time as we understand mechanism better that any definition that this group produces will in fact be identified in a highly heterogeneous

population, we just don't know how to characterize that heterogeneous community at this point.

So again, borrowing shamelessly from Dr. Lystig, what I would like to suggest is that there's a way forward that includes elements of the care that's available in different settings, to come up with a single applicable definition. So given what happens in a practice setting when these medications are the primary or only mode of therapy, then there will be a way to satisfy the definition of treatment-resistant depression that's dependent only on medications.

If in fact for whatever reason one was in a setting in which other modalities that have been found to have similar treatment efficacy were used routinely, then that would also provide an answer as to what location might meet that definition. My justification for that strategy was the amazing consistency

with which failure in one drug, or one drug class or one mode of therapy was correlated with but not perfectly predictive of failure in another arbitrarily chosen treatment. That's a

remarkable thing that probably underscores the unmeasurable heterogeneity of the population, so I would like to suggest that that's a way forward, details to be determined.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: I'll take my stab at this. So, treatment-resistant depression would be a measure of severity, not a category. I think it has to be recognized in clinical factors and I think we have reason to think it could not be, and it's going to get recognized in the setting that you described where there's less expertise and less time for detailed assessment.

So if we're talking at the level of clinical application, I think we're trying to derive what's applicable from the research that's been done and then when we talk about clinical trials, then that's a different matter. So I think we need to know actually what is the evidence that all forms of

treatment are equivalent.

(P.A. announcement on speakers.)

DR. BACH: Okay, that is for this room, and I asked them to make that

announcement so that everyone agrees we have to be out of here by one p.m. tomorrow.

(Laughter.)

DR. CARPENTER: Well, I'll not start from the beginning again. So, for the clinical care, it seems to me that clinicians will make a judgment about this and they're not going to make a judgment based on implementation of a form that's used in research that's more detailed, but it is important to know whether this is a medication or of any treatment, so whether the different forms of psychotherapy and CBT are equally predictive of nonresponse to a medication, or is simple medication enough. I'm going to presume for the moment that where the strength of the evidence is is that if you fail on two trials of medication, the next medication is not going to work out very well for you, and we don't know whether we can substitute other forms of treatment in that.

In the clinical practice if you're making the right referrals, there'll be more than one form of therapy simultaneously anyhow, so it does seem to me that we have to say will

this translate into clinical care apart from how you use it in the research, and in that regard I would think that its essence is going to be the assessment of depression and the effect depression is having, and you mentioned several scales, but there are clinicians who use different things to get to that.

DR. BACH: Thank you, Dr. Carpenter. And so just to keep, I'm going to keep bringing everyone back to the questions and to look at them so we conceptualize the conversations. If you look at, and again, I'm not trying to suggest a particular way of voting in any sense, but question one addresses whether or not it is the sense of the MedCAC that there is a standard definition, and I'll characterize that as whether you like it or not, if you will, but there is a standard.

In question two, if there's particular votes on question one that are leaning toward higher confidence, then there's a discussion or

opportunity to sort of weigh in on possible dimensions, singular or multiple dimensions of that definition. So just to be thinking about your future voting, those are questions that I

think are very much circulating around right now.

I'm going to go to Dr. Lystig unless there's questions regarding what I just said. Please.

DR. MELKUS: So for question one and two as you read it, it's in the context of clinical research studies.

DR. BACH: Yes, right, one and two are about clinical research studies, question three is about clinical applicability outside the research context, and all is relevant to Medicare beneficiaries. Please, Dr. Trivedi?

DR. TRIVEDI: A very quick point. I think Dr. Carpenter's point is how most primary care practices today operationalize this without having the definitions. They provided a point at some point where they say I've done what I can with two or three treatments, and say now you go see the psychiatrist, so they're kind of embracing the idea of failures anyway.

DR. BACH: Understood. Dr. Lystig.

DR. LYSTIG: Thank you. Ted Lystig from Medtronics. It is Lystig, not Lytig, please, but that's okay.

So, I did like your points earlier about saying that we should be considering the types of treatments surveyed. So STAR*D for example, very explicitly included psychotherapy as one of the steps that were given in treatment, and I think it seems straightforward to accept that different persons are going to have different tolerances in terms of what we're going to look for as they progress down treatment spectrums and what sorts of tests they want to take before escalating from that. People have different decisions in terms of personally what they will think and what they might use.

I think it's also useful to think about this idea that while we can talk about a dichotomization and whether or not it is treatment-resistant depression, there is certainly additional information that is valuable about the extent of that resistance, and we have more information available if you

have failed precisely two trials within the same class, versus someone that's failed three different classes plus ECT plus psychotherapy.

So while we can talk about a binary

switch in terms of starting out with TRD, perhaps it would be useful to keep us in the concept of is it helpful to collate and report additional information about the severity of the resistance that we're talking about, and that could have use in deciding either treatments or the sense that we want to foster further evidence on that side of the scale.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Yes. I think a couple of, the earlier discussions actually addressed a couple of the points that I was going to make. I think the additional point, however, is just a reminder that most of what was discussed this morning came from relatively large scale trials conducted both in psychiatric as well as primary care settings using tools that are usually used. There's self report; self-report tools work just as well as the heavily trained M.D. administered, so these have been translated into primary

care, they have been used to show how well they can monitor response to treatment. And they can't, the ones that are used even today, they don't cost anything, there's the PHQ or the

QIDS or whatever. So they have been translated, they have been, they do work in primary care.

I think one of the things that we need to figure out some way, I'm trying to figure out how the patient-centered gets into it, because that might actually allow some of that counseling or psychotherapy treatment to potentially be done before the primary care doc is deciding whether to prescribe that first antidepressant.

So I guess the main point is that I think what we have been discussing as kind of a definition of TRD as well as its ability to be translated into primary care has actually been done in most of these studies, and in fact there is a lot of what folks are doing as they're following either the U.S. Preventive Services Task Force guidelines or American College of Physicians guidelines.

DR. BACH: Thank you. Dr. Zarate, you

had your card up?

DR. ZARATE: No, I was just, the previous speakers have already addressed what I had as concerns, but I just didn't want to

limit it to kind of two antidepressant trials because, you know, if you happen to have a good psychologist who's working in the same group practice as you might be seeing them concurrently, so it depends. So I would say that preventatively, or permitted to be validated, either medication or psychotherapy would count as an inadequate trial.

In some sense I would have concerns on two psychotherapies back to back or repetitive, for example, so, you know, it all depends. You know, some patients may not have been exposed to medication and then you can expose them to something more severe, so it all depends on the patient's medication history, have they been able to be exposed (inaudible) severe treatment with more acceptable profiles. We're assuming that some of these treatments in TRD are better targeted, and many of them are not.

DR. BACH: Thank you. Dr. Cuyjet or, sorry, Dr. Salive.

DR. SALIVE: Marcel Salive. I wanted to just give my take on the questions and I think, you know, the context today is coverage with evidence development questions, and so

question one is really inclusion criteria for such a trial, can they be developed. So to me that's more straightforward than the way it's worded here, because I think the word that I stumble on is standard, because I didn't hear any ringing endorsement from any specialty societies today or leading specialty groups or research organizations, I heard mainly from individuals giving this, and so I think in a study it can be defined in an operational way for CED type research projects.

And then after you go through that, then two is the components of the definition, and I think we've heard a lot of good discussion of that.

Three is where you would enroll people from and I don't think you have to, you know, worry greatly about that. I think it would be helpful to people developing such a trial to enroll people from primary care clinics, I think just so it does become more generalizable

rather than, you know, but of course I recognize how the research enterprise exists today, so it's just more of a pragmatic issue. And I think that third question is not super

important to this deliberation, but that's just me.

I think four is on the outcome measurements for such a study and, you know, I would agree with my colleague next door that specifying primary outcomes is key in having analysis of TRD, and then the design is mostly fine.

So it, to me it all hangs together very nicely, and I think we've had a good discussion.

DR. BACH: Thank you. Dr. Melkus.

DR. MELKUS: Thank you very much for looking at it that way conceptually, because that cleared things up for me with number three, because as stated, it would really depend on where you get the patients from and when you think about primary care settings, primary care providers, I would think of how we're going to evaluate these people just in terms of health literacy, language, and it's

rural areas too. I mean, I'm from the Tri-State area and it's really problematic; I mean, the majority of patients we see, English is not their first language, so I think that's

something we need to consider.

And I also echo the sentiment that we do have clinical licensed psychologists who could do the CBT and do other psychotherapy, and so maybe we could factor that in.

And the other point I want to make is, unless I -- I think there's an assumption here being made that psychiatrists are plentiful and they're not, so I want to know how we refer people so readily from primary care settings to psychiatrists. You're laughing, because you can't find them.

DR. BACH: Please.

DR. TRIVEDI: Just one thought and I hope it doesn't make your task more complicated, but I think both psychotherapy and STAR*D have been mentioned many times, so I should clarify. In STAR*D actually, we were very clear the psychotherapy option was available in the second step, which meant that before you go to the third step, and there was

an additional medication step which was used for those who did not do well on psychotherapy before they go to a formal third step. So therefore, we did not automatically substitute

a second step psychotherapy to define treatment, just to give you a clarification.

DR. BACH: Dr. Burke.

DR. BURKE: All very good points, thank you very much. So what I'm hearing, so, I also have not heard of a standard definition, and also I think the reason is because treatment-resistant depression, the treatments are so heterogeneous and they're given in so many different orders in so many different ways at so many different times, I think it's going to be very difficult to come up with an actual concrete definition for treatment-resistant depression.

So, my thought is that it's a failure basically in the sense of, it's a failure of primary care physicians to achieve a remission, that is what you might call treatment-resistant depression. In other words, if a primary care physician fails with, say, cognitive and/or medication resistance, do they have cognitive

or medication-resistant depression? If they fail with two, okay, either two medications or cognitive and a medication, then that by definition is a treatment-resistant depression,

and that then sets you on to the second step, okay, for research, so this is your patient population, this is your research population, those people who failed that first step.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: So, that's the big question, but first I want to respond to the conversation that has just been had. I'm still thinking about question three in terms of its application to clinical practice, not in terms of studying enrollment, or at least not in terms of that alone, but I think --

DR. BACH: I believe that's how you should think about it.

DR. OLLENDORF: Okay. That answers my question there.

I have a specific question that maybe some of the guest panelists or other clinical experts can address, and that's on question two, whether we should be thinking about suicidal ideation and suicide attempts as a

single construct, because I know we saw data showing that patients with TRD have a higher rate of suicide attempts, but, and I'm a non-clinician so tell me if I'm wrong, but

suicidal ideation can be triggered at times by disease and at times by therapeutic choices that are made. So, should we be thinking about just this one item in terms of a defining characteristic or an outcome, or more than one?

DR. GAYNES: This is a very important question. Just recall, if you look in the large (inaudible) depression (inaudible) HIV studies, somewhere between 40 and 50 percent who have endorsed suicide ideation to some degree, say question nine with HCQ-9 for example, and maybe 75 percent of that is probably passive SI, but I think you're making a good point, that globally considering the suicidal ideation together with suicide attempts is not a good marriage, because that's not going to truly be able to distinguish TRD from what's commonly presented with most depressed illness.

DR. MELKUS: And also, suicide attempts, ever, how long ago, how recent?

DR. GAYNES: Yeah, but those can be difficult histories to collect, for sure.

DR. BACH: So, I don't see anyone else waiting, so I'd like to ask you each to take a

moment to look at the questions in anticipation of us discussing them or maybe asking further questions, clarifying between one another, so that we can then, once we're through that, we can move on to voting.

DR. GAYNES: I do have one question about number two, the second characteristic, or I'm sorry, number, duration, and/or classes of antidepressants attempted. I was trying to decide whether, is that meant to reflect something I think we've been discussing a lot here, which is the number of failed antidepressant attempts at some point, is that captured adequately or not, because it seemed -- I wasn't clear on that.

DR. BACH: I'm actually not -- my instinct is the answer is yes but I'm not sure, I want to be sure I understand what your question is.

DR. GAYNES: So I guess what I'm thinking is when I'm thinking about treatment-

resistant depression's operational definition, I'm thinking of two failed prior trials of some kind of adequate duration and dose. But I can't tell if that is what the number,

duration, dosage, and/or classes of antidepressants attempted means, because it's not clear to me that we've identified that they've failed to remit, or whether they've failed to be of adequate dose or duration.

DR. BACH: All right, let me take a stab at it. I think I understand your question now. I'm going to take a stab at it and I'm just going to propose something and see if you agree or disagree. The way I read that is as a somewhat general statement about the use of multiple agents in the cadre on the way to defining TRD, but not as a granular definition of each dimension that we have to independently answer for now. I think, at least what I've heard most of the morning is that there's a great deal of nuance in that first bullet, but at some level I think it's just sort of acknowledging that bullet matters and it sort of determines our important defining characteristic, and so we feel that it is or is

not an important characteristic, but go ahead.

DR. MILLER: This is Dr. Miller and

yes, that would be a correct interpretation,

that this is how we would begin to define

adequacy of a trial of medication, yes.

DR. BACH: Dr. Pope.

DR. POPE: So question one is, how confident are you that there is a standard definition, so if somebody already decided what's standard, I'm wondering, is there a distinction between, is there a standard that already exists, or whether one could be constructed or synthesized from the available studies, and just to clarify, what is the exact question that we're answering?

DR. BACH: All right. So, I think the question as written, the definition of the word is in that context is not in dispute, so it is is, currently, and as I characterize it, whether you like it, whether you like the definition or not, given the body of research we've heard discussed, whether or not you feel, you know, that it mostly converged on a standardized definition or not.

Now for the purposes of discussion, I

think it is also becoming clear that further refining interactions and development of such a definition would be useful, in fact that's always true, but I think you do have to sort of

say which way is the wind blowing.

And again, I'm not trying to bias your responses in any way. In order to get to question two, just recall that you need to sort of be committed that there is a definition at some level or we skip it, which is fine too.

So I have Dr. Lewis.

DR. LEWIS: So for clarification in the subparts of question five, the first three options clarify whether the study designs would include blinding, d, e and f do not. Should we assume that those study designs would be blinded or unblinded?

DR. BACH: We should just make a decision about what is meant here. I believe that those are all unblinded. I'm not sure I know the difference between c and d.

(Inaudible colloquy.)

SPEAKER: Any study design could be blinded or unblinded and they have different vulnerabilities based on that, so I think the

chair might just make a decision.

DR. BACH: Oh, great.

SPEAKER: I would suggest the chair find them unblinded.

DR. BACH: So we're talking about c, d, e and f as unblinded to, and just in fairness, it's unblinded to the patient with that ratio, correct, in d, e and f?

DR. MILLER: Yes. This is Dr. Miller again. They are unblinded.

DR. BACH: Okay, to the beneficiary?

DR. MILLER: Well, they would be unblinded either to the beneficiary or to the investigator.

DR. BACH: Another clarification? Go ahead, please.

Dr. LYSTIG: Regarding number two, ECT, electroconvulsive therapy, so, did we agree it was a must or may?

DR. BACH: I'm sorry, where are you?

DR. LYSTIG: It would be number two, the use of nonpharmacological treatments such as electroconvulsive therapy, or it could be transcranial magnetic stimulation, for example.

DR. BACH: All right. These are

yes-no questions, this is where we get to use the cards, and the language here is, answer whether the following are important defining characteristics, so in that context if you feel

that nonpharmacologic treatments, if you will, failure of one of the nonpharmacological treatments is an important element to the definition of TRD, you vote yes.

DR. LYSTIG: So it's a must, or may?

DR. BACH: It's a must. The way it's phrased, vote on each bullet separately, and in that bullet they're saying is it, must is an extremely strong word but that's what is intended, is it a requirement or important characteristic of TRD that the definition of TRD, that somebody has failed a nonpharmacologic treatment.

SPEAKER: So you are basically excluding all psychotherapy in that patient.

DR. BACH: Pardon me?

SPEAKER: You've got to clarify whether you mean to say important or required, not and.

SPEAKER: If you require failure for electroconvulsive therapy, right, what happens

to psychotherapy and what happens to medication?

DR. BACH: Do you feel -- right. The question to you would be, do you feel it is an

important element of the definition of TRD that someone has failed a nonpharmacologic treatment? Put a different way, you either think that TRD can be comfortably defined without somebody failing, for example just medication, or you feel it is important that they also fail a nonpharmacologic intervention like ECT, and yes or no. That is the question as I understand it.

DR. LYSTIG: So that's not exactly a dichotomy, you sort of split the space up into three spaces and call two of them there. So I think another way to phrase this is to say if you think it's important, then some consideration should be given to that, consideration could be, depending upon your point of view, that that must be involved in the definition or that may be a definition, both of those choices could fall under I think it's important. The important doesn't necessarily require that it is a necessary

step.

DR. BACH: I understand what you are saying. My read of this question is it heavily leans towards must, it might not really be must

a hundred percent, but it is -- a different way of saying it is if you saw a trial with the enrollment criteria of people called TRD and they had not failed, or it was not a requirement or was not highly prevalent that they had failed a nonpharmacologic intervention, you would be like, I don't think that's a TRD. That's my read of the bullet. I have no view of whether it is or is not important.

DR. CARPENTER: So if they've never had that treatment, how do you make your judgment as to whether you consider it important?

DR. BACH: This is a definitional question, whether or not patients end up in the TRD bucket without having a trial of a nonpharmacologic treatment, do you care, is another way of saying that. And you can say no, I'm comfortable, if they failed a couple of drugs I'm comfortable they have TRD, or you can

say absolutely not, they have to fail a nonpharmacologic intervention for me to consider them TRD.

And I'm, to Dr. Lystig's point, it is

unfair to be sort of binary, but I'm trying to locate the intent of the question.

DR. CRUZ-FLORES: And this may be a better answer, if we can say our vote and then say yes under the circumstances, can we qualify it?

DR. BACH: Yes, if that's a process question. What we are going to do is we will vote, you'll hold up the cards or vote on the screen, depending if it's numerical or not. Then I will poll each of you, at which point you state your vote, your name, and then you can proceed to clarify. I would rather you don't entirely disavow your vote, although maybe on the second voting you can, but that's the idea.

SPEAKER: I just have a question for consistency in question two, suicidal ideation and suicide attempts are combined in a single category and in question four they are separated, so I would appreciate an expert

opinion as to whether we should leave them separate, the question has already been raised, or combine them.

DR. BACH: I agree. Can we get some

view on -- I'm happy to break those into two separate questions, ideation and attempts.

DR. CONWAY: I would agree with you. I think it would be okay to break them into separate questions. I think suicidal ideation is more common in treatment-resistant depression for sure, but the majority of people with treatment-resistant depression do not have suicidal ideation, so it is not an intrinsic characteristic of treatment-resistant depression.

DR. SALIVE: So, my question is on the same number, the one bullet above that, so I think everything else is a little bit dichotomous but the score changes on a scale? So if you're saying it's a defining characteristic of resistant treatment that the score change, so, you know, there's such a thing as the meaningful clinically important difference and, you know, because it seems like if they got better it's not resistant, if they

didn't get better but it changed, is that what this is asking?

DR. BACH: Thank you for picking that up.

DR. GAYNES: Can I offer a perspective?

DR. BACH: Yes, please, I appreciate that.

DR. GAYNES: The way I understood that is that when I was thinking of score changes, I was thinking of score changes, for example, whether it met a remission threshold or not. After you explained to me what a was in terms of number, duration, dosage, and classes of antidepressants could indicate, you know, number of failed depression trials, given that interpretation it seemed to me that scores tended to be conflicting with when you have a score change, whether it's a clinically meaningful difference or it meets the definition of remission by meeting some certain threshold.

DR. BACH: I'm comfortable with that as well. A different way of saying that is that you can view these bullets as domains more

so than the terms are directional, I appreciate that, and again, this is on me, because I had a chance with these questions earlier. It could have been phrased more tightly, but the general

question, I think is, they would like you to answer is, do you think scores measured over time are going to be an important component of the TRD definition, is that fair? Okay.

Other questions? Dr. Pope, you had another? Actually, I think Dr. Lystig is next, and then Dr. Pope.

DR. LYSTIG: Yeah. So, I just wanted to come back briefly to number five which we talked about very very little here, and we're talking in there about how confident we are that the following strategies represent meaningful and realistic study designs in research investigations. We have this list and I think sure, there can certainly be a hierarchy that when all things are equally possible, one might have a presence for going through this, but it seems to be set up a little bit in terms of, again, this binary thing about can such a study provide meaningful and realistic evidence or not, and in that

context I'd just like to point out, and I come from more of a device setting, that's what my attention is, and for example in our FDA regulations there is language that states that

the evidence for the FDA approval shall be just primarily well controlled investigations, but there's also language called other mechanisms that can be acceptable.

And even in the language around evidence development there's this discussion about how you could use registries, how you could arm registries or keep registries out, so I just want a key person to be careful about thinking the difference between what your ideal study would be and whether or not some of these alternative designs could provide meaningful and realistic information is something to consider, and we're not necessarily saying it's so important, but there was discussion earlier about evolving registries. Could there be a mechanism by which data from registries could inform our knowledge about the treatment? So I urge you to keep that in mind, don't simply use it in terms of what is the best option, but rather whether these could be viable options.

DR. BACH: I appreciate the comments and I believe that you're also saying you'll be true to how the question's phrased, it's realistic, it's meaningful, are the two

critical terms in there, so absolutely, if there's a pure form of research that can't always be achieved. I have Dr. Pope and then Dr. Burke.

DR. POPE: On the earlier discussion about question two, and this is maybe to capture the most robust information as possible, and this would not require a change at all to the wording of the question, but every other question had a one-to-five weight scale, and whether or not that would be applied to subparts of two as well. In other words, the question would be, is it important, binary, yes-no, but the question would be answered how important it is. I think that that would address Dr. Lystig's, you know, concern, is it may, is it must. I mean, I'm just suggesting that as a way to get more value of collection captured.

DR. BACH: I appreciate that, and while you've given how we structured it is that

when you give your response, I would invite you, that's a great opportunity to add more characterization of it, I said yes and I really mean it, I said yes but I'm not real sure, or

you can apply the same one-to-five scale, whatever you prefer, and you are not required to do that.

But, Dr. Burke, and then Dr. Carpenter.

DR. BURKE: For answering these questions, does the chair have a standard definition of TRD?

DR. BACH: No.

DR. BURKE: So the is, it means what, because you said is means is.

DR. BACH: We're looking at question one and it says to each of you, not to me, how confident are you, Dr. Burke, that there is a standard definition of TRD that can be applied to Medicare beneficiaries?

DR. BURKE: So taking this in the totality, wouldn't a standard definition be two consecutive effective antidepressant failures? Would that be pretty much what we've heard today, that it would be two consecutive, and it

has to be effective, antidepressant failures? In other words, two things that are effective in treating depression, they're consecutive, and both fail.

DR. BACH: Let me propose that the way we have phrased it does not, weirdly maybe, or actually hopefully, everyone can say yes to question one and everyone can still disagree on what that definition is. That would be a highly unlikely event, but the first question is simply, is there a starting point in the current state of the evidence, all right, with current research, is is the verb. So I would invite again, when you cast your vote, I think that's a perfect time to then articulate that, you know -- and you know, if you vote, let's say, and I'm not giving you, not leading you to a particular vote, but you say yes, absolutely, give it a five, then when I poll you I'll ask you to then say, and again, you don't have to, but if you'd like to you can then say, and my definition is X.

And it's not what you wish it to be, that's a topic of question two to some extent, it is what do you believe the current state of

affairs is in the research community with the definition of TRD. Fair? Dr. Carpenter.

DR. CARPENTER: Just get me on the scope on two things. On number four, why is it

decrease in suicide ideation rather than decrease or increase, wouldn't it be an outcome if they were getting better or getting worse?

DR. BACH: I don't have any problem with the directionality of those, those are both undesirable, right?

DR. CARPENTER: But improvement in function is desirable, if you find it desirable. It just doesn't parallel.

DR. BACH: All right.

SPEAKER: And that would also reasonably reflect, you know, some concerns, you know, might there be some increase in suicide ideation for particular age ranges.

DR. BACH: I apologize, okay? It's simply, I will ask you to interpret all five, a through e, as an alteration of clinical, that has a meaningful clinical difference, without directionality. The implication is, of course, that there's a desired directionality. Fair?

DR. CARPENTER: Yeah. So the other

one I'm trying to get unstuck on, so we're scoring over time on number two, is that what you said?

DR. BACH: I'm sorry, what was your

question?

DR. CARPENTER: I'm back to number two.

DR. BACH: I'm on two, yes?

DR. CARPENTER: And I believe you said that these were things to be scored, so I'm stuck. Is this relating to what needs to be in the identification of the category of TRD, or is it meant to be tracking progress of a patient?

DR. BACH: No, the former. You could think of them as entry criteria for a clinical research study.

DR. CARPENTER: So the scoring over time didn't apply to this, that you said earlier?

DR. BACH: Again, this is my interpretation. It would be the scores over time that define, like these other, all of these definitions are intrinsically sort of to the left of entry, right, they are longitudinal

in nature.

DR. CARPENTER: So it's not a change?

DR. BACH: Well, it could be a change,

if there's something about these four that they

are, if you will, to the left at the time of entry, so it's, you know, failures of multiple therapies, consistency of scores, so be it, but these are all things that you would choose to have within your definition of TRD, that when somebody has X, Y and Z, at that point you can then say they have TRD.

SPEAKER: The minimum definition of TRD, because, you know, what is the gateway to get into a study?

DR. BACH: It is what you think are important.

SPEAKER: Because all of these are very important in TRD and some data could have all of them but they would be at the higher end of the spectrum, so to get into a TRD trial, at the minimum you would need two antidepressant failures or a failure of a combination.

DR. BACH: Absolutely. No one is saying any of these features, domains or experiences of patients are unimportant, this

is a clinical research question about what the entry criteria would be, if you will.

Dr. Gaynes, and then Dr. Pope.

DR. GAYNES: A question on number

five, just wondering where exactly this will fit in. So for number five when we're wondering about meaningful study designs, so where would large scale pragmatic clinical trials fall under, would that fall under either a or b depending on whether they're single or double blinded, or is that something else? I'm thinking about large scale databases and clinical research networks covering some hundreds of thousands of folks, and that you're doing trials on a large scale.

DR. BACH: All right, so if I can rephrase, you're asking about large scale observational research with no experimental design?

DR. GAYNES: No, there is an experiment. You've randomized folks in some settings to one treatment, some to another treatment, but you're monitoring them through electronic health records so you're able to follow thousands and thousands of them.

DR. BACH: Okay, fair enough. Is it blinded?

DR. GAYNES: It could be single or double blinded. So I guess my question is,

would that fit under either a or b, depending on whether they were single or double blinded, when it's just a large scale trial design?

DR. BACH: Yeah, fair enough. I would ask you to narrate your answer with respect to that, because I think as you just said, and my understanding as well is that that, the scaling issue, the pragmatism, the allocation methods, although they differ, probably all fall under traditional research study designs.

DR. GAYNES: Okay.

DR. BACH: Dr. Lystig.

DR. LYSTIG: So, I would say when you're talking about the large scale pragmatic trials, you're not talking so much about either the assignment treatment nor of your knowledge of the treatment design, you're talking more about the recruitment of the patients and the monitoring of them over time. As such, those two elements actually don't speak to design as we're talking here.

So just to underscore, talk specifically about the elements here, that type of trial setup doesn't fit within this.

DR. BACH: Thank you. Dr. Yan. Is

that everybody? Okay, great. We are going to vote. I recommend we take a five-minute, not five-minute-and-one-second break.

(Recess.)

DR. BACH: Panel members, you have a pink sheet in your packet which is your hand scoring sheet, and we're all going to electronically score -- oh, sorry? Some have yellow, pink or yellow. Under question two, this relates to the very last bullet. We're splitting suicidal ideation and suicide attempts, so I'm going to ask you to cross out the word other, which we are not going to vote on, cross out suicide attempts in the line above, and then write suicide attempts where the word other was.

So, we're going to commence with the voting. Does everyone have their things, their electronic things? All right. Beginning with question number one, and again, if there are questions of clarification or concern, this is

a process intended to achieve useful

information, please stop me or ask questions.

And just to make sure, Dr. Gaynes,

Dr. Carpenter, you don't have questions right

now but your cards are still up, your tent cards are still up? Okay, great.

Question one -- so you're supposed to use your gizmo here, and I understand the people at the end of the table don't have one, in which case we'll ask you to vote verbally, and also of course record it on your sheet.

How confident are you that there is a standard definition of TRD that can be applied to Medicare beneficiaries in clinical research studies of therapies for this disease?

(The panel voted and votes were recorded by staff.)

MS. ELLIS: We're just waiting on one person to register their vote. If you can, can you please just push your last vote again? Thank you.

DR. BACH: All right. The score on that is 3.8. I'm now going to poll the panel for your individual responses and if you recall based on our discussion, you have the option to

add anything you want, but what some of the people were asking for was, you can for example state what you believe the standard definition is, but I ask you to be concise, and I'm going

to start with Dr. Cuyjet.

DR. CUYJET: I voted four.

DR. BACH: Dr. Burke.

DR. BURKE: I voted five, because I believe that the standard definition is failure to achieve at least two consecutive effective antidepression remissions, so failure to achieve remission using at least two consecutive effective antidepression therapies, that's it.

DR. BACH: Thank you.

Dr. Cruz-Flores.

DR. CRUZ-FLORES: I voted two, because I think we need to include the alternative of other therapies like ECT or psychotherapy.

DR. BACH: Okay, thank you very much.

Dr. Lewis.

DR. LEWIS: I voted four, and I agree with the prior speakers' comments.

DR. BACH: Dr. Melkus.

DR. MELKUS: I voted four as well.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: I voted three for the same reasons that have been listed earlier.

DR. BACH: Dr. Pope?

DR. POPE: I voted four.

DR. BACH: Dr. Salive.

DR. SALIVE: I voted three.

Dr. BACH: Dr. Yan.

DR. YAN: I voted five.

DR. BACH: Okay. And then you four didn't vote electronically, right, so this will be a complete outlier. Dr. Lystig.

DR. LYSTIG: So, I voted three. I think the definition exists, it's more in terms of could it be applied well, and I think there are challenges with the current existing definitions we have been talking about.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: I believe that --

DR. BACH: And speak into the microphone. I was asked to have you not address me but to address the audience, that's easier to remember to speak into the microphone.

DR. CARPENTER: So, I voted five. I

think the construct is simple and straightforward, I think it's incredibly important that it be used in clinical practice. I think the research shows that they're

reliable and valid ways to do it, they have enough ingredients that could be translated into clinical practice.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Yes, I voted five based on both clinical trial experience as well as reviews of how accurate these tools can be with beneficiaries.

DR. BACH: Dr. Zarate.

DR. ZARATE: I voted four. I think there's room for improvement, including a little bit more clarification of some of the definitions, such as the significance of psychotherapy.

DR. BACH: Thank you. We're going to move on to question two, and I'm going to ask the four of you at the end, do you have cards? Okay, great. I don't think we've ever done this before, have we? This is going to be fun, this may be something you want to Instagram or something. Please also mark your vote on your

sheet, and I ask you to do it now so we don't end up with a reconciliation problem down the road, for question one.

Number two, I'll read each -- I'm

sorry.

(Inaudible colloquy.)

DR. BACH: I'm going to begin reading the question. If intermediate confidence is noted above, please vote yes or no as to whether the following are important defining characteristics of TRD that are to be considered in clinical research? Bullet one, yes or no, the number, duration, dosage, and/or classes of antidepressants attempted. Please raise your cards. And please indicate your vote on the sheet.

(The panel voted and votes were recorded by staff.)

DR. BACH: Okay. Next bullet, the use of augmentation --

SPEAKER: Did you want our comments?

DR. BACH: Okay. So what I'm going to do if this is okay with you is, I want to do them all and then ask for comments. Otherwise, I think we'll be hopelessly caught up. Again,

if you feel like that's not a good process --

okay, could you vote again on bullet one, and

Dr. Cuyjet?

DR. CUYJET: Yes.

DR. BACH: Dr. Burke.

DR. BURKE: No.

DR. CRUZ-FLORES: Yes.

DR. LEWIS: Roger Lewis, yes.

DR. BACH: Dr. Melkus?

DR. MELKUS: Yes.

DR. BACH: Dr. Ollendorf?

DR. OLLENDORF: Yes.

DR. BACH: Dr. Pope?

DR. POPE: Yes.

DR. BACH: Dr. Salive?

DR. SALIVE: Yes.

DR. BACH: Dr. Yan?

DR. YAN: Yes.

DR. BACH: Dr. Lystig?

DR. LYSTIG: Yes.

DR. BACH: Dr. Carpenter?

DR. CARPENTER: Yes.

DR. BACH: Dr. Gaynes?

DR. GAYNES: Yes.

DR. ZARATE: Yes.

DR. BACH: Great. Next bullet, the use of augmentation/combination pharmacologic therapies, please vote.

(The panel voted and votes were

recorded by staff.)

DR. BACH: And while you're holding your cards, we'll just go down. Dr. Cuyjet.

DR. CUYJET: Yes.

DR. BACH: Dr. Cruz-Flores?

DR. CRUZ-FLORES: Yes.

DR. BACH: Dr. Lewis.

DR. LEWIS: No, because I was interpreting that as --

DR. BACH: Oh, I'm sorry. Dr. Burke.

DR. BURKE: No.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Yes.

DR. BACH: Dr. Lewis.

DR. LEWIS: No, because I was interpreting this as being a mandatory element.

DR. BACH: Okay. Dr. Melkus.

DR. MELKUS: Yes.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: No.

DR. BACH: Dr. Pope.

DR. POPE: Yes.

DR. BACH: Dr. Salive.

DR. SALIVE: Yes.

DR. BACH: Dr. Yan.

DR. YAN: Yes.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Yes.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: No, mandatory element issue.

DR. BACH: I didn't hear what you said.

DR. CARPENTER: No, and for the same reason, the mandatory element.

DR. BACH: Okay. Dr. Gaynes.

DR. GAYNES: Yes, and I also considered a switch to be possible.

DR. BACH: Dr. Zarate.

DR. ZARATE: Yes.

DR. BACH: On to the third bullet, type of depressive episode, for instance unipolar, bipolar, psychotic, atypical, or other.

(The panel voted and votes were recorded by staff.)

DR. BACH: Dr. Cuyjet.

DR. CUYJET: Yes.

DR. BACH: Dr. Burke.

DR. BURKE: Yes.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Yes.

DR. BACH: Dr. Lewis.

DR. LEWIS: Yes, with the intent that it simply means that this must be incorporated into the definition.

DR. BACH: Dr. Melkus.

DR. MELKUS: Yes.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Yes, with what Dr. Lewis said.

DR. BACH: Dr. Pope.

DR. POPE: Yes.

DR. BACH: Dr. Salive.

DR. SALIVE: No. I don't think it's always necessary or useful.

DR. BACH: Dr. Yan.

DR. YAN: Yes.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Yes.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Yes.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Yes.

DR. BACH: Dr. Zarate.

DR. ZARATE: Yes.

DR. BACH: Okay. Let me pause for a second. The editorial comments are extremely valuable, they are not required, but I am trying to move us through but in no way am I asking you to hurry on your editorial comments. Dr. Lewis had a comment that I considered relevant; take your time to explain what you think so that we can get it on the record and do not be rushed by my simply just calling on the next person, okay?

Okay, next bullet. The use of nonpharmacological treatments such as ECT.

(The panel voted and votes were recorded by staff.)

DR. BACH: Dr. Cuyjet.

DR. CUYJET: No. I don't feel that meets the requirement to define clinical research into TRD.

DR. BACH: Dr. Burke.

DR. BURKE: No.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Yes, to the extent that it can be added as an alternative, it may add to the definition.

DR. BACH: Dr. Lewis.

DR. LEWIS: No, because I don't believe it should be a required element.

DR. BACH: Dr. Melkus.

DR. MELKUS: I say no for the same reason as Dr. Lewis.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: I say yes because it can be a variant of the definition in certain settings.

DR. BACH: Dr. Pope.

DR. POPE: No, potentially relevant but not essentially required.

DR. BACH: Dr. Salive.

DR. SALIVE: No.

DR. BACH: Dr. Yan.

DR. YAN: No.

DR. BACH: Dr. Lystig.

DR. LYSTIG: No, not as a requirement, but again, it should be considered as an option.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: No.

DR. BACH: Dr. Gaynes.

DR. GAYNES: No, it should not be a

requirement, but whether a trial was predicated on having failed an ECT treatment, they would likely consider them to be treatment-resistant.

DR. BACH: Dr. Zarate.

DR. ZARATE: No, for the same reason as my colleagues.

DR. BACH: Okay. I'm going to pause again. I'm actually hearing something fairly consistent, which is it is one of several alternative paths to the definition. Another way of saying it is you would not consider it an exclusionary criteria if you don't fail the ECT, is that fair? Okay.

The use of psychotherapy.

(The panel voted and votes were recorded by staff.)

DR. BACH: Dr. Cuyjet.

DR. CUYJET: Yes.

DR. BACH: Dr. Burke.

DR. BURKE: No.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Yes.

DR. BACH: Dr. Lewis.

DR. LEWIS: No, because I would not want it to be a required element.

DR. BACH: Dr. Melkus.

DR. MELKUS: Yes, because I think it should be a required element.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Yes, for the same reasons I gave for ECT.

DR. BACH: Dr. Pope.

DR. POPE: No.

DR. BACH: Dr. Salive.

DR. SALIVE: No, not reported.

DR. BACH: Dr. Yan.

DR. YAN: Yes.

DR. BACH: Dr. Lystig.

DR. LYSTIG: No, agree with Dr. Lewis.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: No, but also because of the many settings you want to recruit from where psychotherapies have not been given, I would not want to exclude people.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Yes, it's an important

element, but not having --

MS. ELLIS: I'm sorry, we can't hear you. Can you guys please speak into the mic?

DR. GAYNES: Yes, because it's a

consideration in treatment-resistant depression but it's not something that should someone not have it, that they would not be defined as having TRD.

DR. BACH: Dr. Zarate.

DR. ZARATE: Yes, I believe a good therapist can give a good trial and that should be considered as adequate for considering TRD.

DR. BACH: Score changes on standardized and validated depression rating instruments, for example the Hamilton Depression Rating Scale.

MS. ELLIS: I apologize, excuse me. Could all the panel members, could you please speak directly into the mic, because people on the web are unable to hear you, as well as our transcriptionist. Thank you.

(The panel voted and votes were recorded by staff.)

DR. BACH: Dr. Cuyjet.

DR. CUYJET: Yes.

DR. BACH: Dr. Burke.

DR. BURKE: Yeah, this is one of the critical elements.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Yes.

DR. BACH: Dr. Lewis.

DR. LEWIS: Yes.

DR. BACH: Dr. Melkus.

DR. MELKUS: Yes.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Yes.

DR. BACH: Dr. Pope.

DR. POPE: Yes.

DR. BACH: Dr. Salive.

DR. SALIVE: Yes, I think it's a severity measure.

DR. BACH: Dr. Yan.

DR. YAN: Yes.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Yes.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: I'm voting yes because I'm ignoring the change, I don't know what it means by change, but if it means indicating severity, then it's a yes.

DR. BACH: Right, and we discussed this, and change consists of just the notion of having one of the scales as a defining characteristic was what we zeroed in on. So,

Dr. Gaynes.

DR. GAYNES: Yes, and I specifically want to identify the importance of remission as one of those measures.

DR. BACH: Dr. Zarate.

DR. ZARATE: Yes.

DR. BACH: Remember, we broke the next one so it's suicidal ideation as the next one.

(The panel voted and votes were recorded by staff.)

DR. BACH: Dr. Cuyjet.

DR. CUYJET: No.

DR. BACH: Dr. Burke.

DR. BURKE: No.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: No.

DR. BACH: Dr. Lewis.

DR. LEWIS: No.

DR. BACH: Dr. Melkus.

DR. MELKUS: No.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: No.

DR. BACH: Dr. Pope.

DR. POPE: No.

DR. BACH: Dr. Salive.

DR. SALIVE: No.

DR. BACH: Dr. Yan.

DR. YAN: No.

DR. BACH: Dr. Lystig.

DR. LYSTIG: No.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: No.

DR. BACH: Dr. Gaynes.

DR. GAYNES: No.

DR. BACH: Dr. Zarate.

DR. ZARATE: No.

DR. BACH: The next bullet, and on your score sheet it no longer reads other, I hope it should now read suicide attempts and so can you vote on that, suicide attempts, please.

(The panel voted and votes were recorded by staff.)

DR. BACH: Dr. Cuyjet.

DR. CUYJET: No.

DR. BACH: Dr. Burke.

DR. BURKE: No.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: No.

DR. BACH: Dr. Lewis.

DR. LEWIS: No.

DR. BACH: Dr. Melkus.

DR. MELKUS: No.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: No.

DR. BACH: Dr. Pope.

DR. POPE: No.

DR. BACH: Dr. Salive.

DR. SALIVE: No.

DR. BACH: Dr. Yan.

DR. YAN: No.

DR. BACH: Dr. Lystig.

DR. LYSTIG: No.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: No.

DR. BACH: Dr. Gaynes.

DR. GAYNES: No.

DR. BACH: Dr. Zarate.

DR. ZARATE: No.

DR. BACH: The next question is number three, go back to your other pads for voting. How confident are you that this definition,

meaning -- hold on a second. I'm going to propose this, I want to discuss this, we're going to take a small pause here because of the pronoun this, how confident are you that this

definition can be applied to Medicare beneficiaries? I want to clarify that this question refers to the application in clinical practice, but I'm hung up, and maybe it's just the hour, I'm hung up on whether or not this definition refers to the standard definition of TRD in question one or the definition as constructed through the integration of the responses to question two, which would be some definition that had important defining characteristics. Maybe Dr. Lystig is about to resolve this for us.

DR. LYSTIG: Well, no. I think the question there starts, you're basing it on what happened in question number one, so you should bring it back to one and not think about question two.

DR. BACH: Good. Is there any disagreement on that? Okay. So in question three, you're answering a question regarding the application of the standard definition of

TRD as in question one. How confident are you that this definition, that is the standard definition of TRD, can be applied to Medicare beneficiaries, with your buttons, for point a,

in primary care settings.

(The panel voted and votes were recorded by staff.)

DR. BACH: All right, 2.6. I'm going to poll you for your votes and again, if you have comments, that's great. Dr. Cuyjet.

DR. CUYJET: I voted a four.

DR. BACH: Dr. Burke.

DR. BURKE: Two. I didn't think this would give sufficient guidance to primary care physicians.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Two.

DR. BACH: Dr. Lewis.

DR. LEWIS: I voted four, and I believe that there is a definition that could be applied in this setting.

DR. BACH: Dr. Melkus.

DR. MELKUS: Three. I'm not sure that it can be given the constraints of time and resources.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: I voted one, because of the reported high rates of pseudoresistance in this population and because the instruments

that would be used to measure response or remission are not necessarily applicable to primary care practice.

DR. BACH: Dr. Pope.

DR. POPE: Three.

DR. BACH: Dr. Salive.

DR. SALIVE: Three.

DR. BACH: Dr. Yan.

DR. YAN: Two.

DR. BACH: Dr. Lystig. Sorry?

DR. YAN: I did have a comment. For rural areas and primary setting it might be, because there are not many general psychiatrists and clinics, so it might be difficult for rural patients to access this.

DR. BACH: I take the term primary care to refer to nonpsychiatric physicians, family practitioners, internal medicine doctors, and not general psychiatrists, which I think as addressed by bullet b, or point b; does that help you?

DR. YAN: Well, if it was just a rural area I would vote a one, but I voted two because in a rural area they go to a primary care doctor, and a primary care doctor is able

to provide initial assessments of something.

DR. BACH: I understand the distinction, okay. Dr. Lystig.

DR. LYSTIG: Two. I think there would be challenges applying it in a primary care setting.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: I did a four, not because there are not challenges, but because I think the construct would be understood, I think it has to be applied, and I think perfect would be the enemy of the good, so I'm not too concerned if sometimes somebody is only slightly resistant, and I think they're qualified to proceed to treatment modalities.

DR. BACH: And what I heard you say is it can be applied, not is currently applied. Dr. Gaynes?

DR. GAYNES: I gave it a four, with two points. One, I think the increasing use of the electronic health record would help that

dosing question get answered, and then the second point is just to clarify that the tools to identify whether someone had TRD in terms of depression measures, they have been validated

and used well in primary care settings.

DR. BACH: Dr. Zarate.

DR. ZARATE: Three, but there would need to be education efforts.

DR. BACH: Thank you. Can I ask you to vote on the next bullet, same question, in general psychiatric settings.

(The panel voted and votes were recorded by staff.)

DR. BACH: All right, the score on that is 3.8, I'm now going to poll the panel. Dr. Cuyjet.

DR. CUYJET: Again, I voted four, and it's common when we're trying to direct care to primary care and having simple standards so that they know when patients meet the criteria and the need for further evaluation and treatment is appropriate regardless of time constraints and other considerations.

DR. BACH: Dr. Burke.

DR. BURKE: I gave it a three because

I still think that the definition is too ambiguous and vague to be readily applied.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Four.

DR. BACH: Dr. Lewis.

DR. LEWIS: Five.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Three.

DR. BACH: Dr. Pope.

DR. POPE: Four.

DR. BACH: Dr. Salive.

DR. SALIVE: Three.

DR. BACH: Dr. Yan.

DR. YAN: Four.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Four.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Five.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five.

DR. BACH: Dr. Zarate.

DR. ZARATE: Four.

DR. BACH: The last bullet, three, in

specialty psychiatric settings, please press your buttons.

(The panel voted and votes were recorded by staff.)

DR. BACH: You can't vote twice, so you can try again. There you go. Dr. Cuyjet.

DR. CUYJET: Four.

DR. BACH: Dr. Burke.

DR. BURKE: Four.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Five.

DR. BACH: Dr. Lewis.

DR. LEWIS: Five.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Five.

DR. BACH: Dr. Pope.

DR. POPE: Five.

DR. BACH: Dr. Salive.

DR. SALIVE: Five.

DR. BACH: Dr. Yan.

DR. YAN: Five.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Five.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Five.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five.

DR. BACH: Dr. Zarate.

DR. ZARATE: Four.

DR. BACH: Thank you. We're on to question four. How confident are you that each of the below is a reliable, valid and meaningful health outcome for Medicare beneficiaries in a trial of an intervention for treatment-resistant depression? We're going to vote on them separately. 4.a, improvement or decline in depression as measured by depression scales, and please vote with your pads.

(The panel voted and votes were recorded by staff.)

DR. BACH: 4.4. Dr. Cuyjet.

DR. CUYJET: I voted four.

DR. BACH: Dr. Burke.

DR. BURKE: Five.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Three.

DR. BACH: Dr. Lewis.

DR. LEWIS: Five.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Five, assuming that

this includes outcomes meaning remission and/or response thresholds.

DR. BACH: Dr. Pope.

DR. POPE: Three.

DR. BACH: Dr. Salive.

DR. SALIVE: Five.

DR. BACH: Dr. Yan.

DR. YAN: Five.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Five.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Five.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five.

DR. BACH: Dr. Zarate.

DR. ZARATE: Five.

DR. BACH: Next bullet, improvement or decline in function. Please vote.

(The panel voted and votes were recorded by staff.)

DR. BACH: 4.6. Dr. Cuyjet.

DR. CUYJET: Four again.

DR. BACH: Dr. Burke.

DR. BURKE: Five.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Five.

DR. BACH: Dr. Lewis.

DR. LEWIS: Four.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Five.

DR. BACH: Dr. Pope.

DR. POPE: Five.

DR. BACH: Dr. Salive.

DR. SALIVE: Five.

DR. BACH: Dr. Yan.

DR. YAN: Three.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Four.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Four.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Four. It's challenging to measure.

DR. BACH: Dr. Zarate.

DR. ZARATE: Four.

DR. BACH: Next bullet, improvement or decline in quality of life, please vote with your pads, and I'll just ask you preemptively

to vote multiple times, we have a couple Chicago natives up here. It worked, 4.6, awesome. Dr. Cuyjet.

DR. CUYJET: Four.

DR. BACH: Dr. Burke.

DR. BURKE: Five.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Five.

DR. BACH: Dr. Lewis.

DR. LEWIS: Four.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five.

DR. OLLENDORF: Five.

DR. BACH: Dr. Pope.

DR. POPE: Four.

DR. BACH: Dr. Salive.

DR. SALIVE: Five.

DR. BACH: Dr. Yan.

DR. YAN: Four.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Four.

DR. CARPENTER: Four.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Four.

DR. BACH: Dr. Zarate.

DR. ZARATE: Four.

DR. BACH: Decrease, and as I noted before, this should actually be phrased in a bidirectional way but it is currently phrased as decrease in suicidal ideation. Please vote multiple times.

(The panel voted and votes were recorded by staff.)

MS. ELLIS: We're just waiting on one person to register their vote; if you can, can you just please click your last vote again. Thank you.

DR. BACH: All right, the score on that is 3.8. I'm now going to poll the panel for your individual responses and if you recall, based on our discussion, you have the option of stating if you believe this fits within the standard definition, and I ask you to be concise. Dr. Cuyjet.

DR. CUYJET: I voted three on this one.

DR. BACH: Dr. Burke.

DR. BURKE: Four.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Three.

DR. BACH: Dr. Lewis.

DR. LEWIS: Two. I was stuck on the meaningful term.

DR. BACH: Dr. Melkus.

DR. MELKUS: I voted five, in that if there's a decrease in suicide ideation, that's a good thing, and if the people in the study had that and reported it in the history, that's how I interpreted it.

DR. BACH: Oh, hold on. I apologize, thanks. Dr. Ollendorf.

DR. OLLENDORF: I voted two, because given that there are high rates of suicide ideation outside of the TRD realm, I wasn't sure how meaningful this would be.

DR. BACH: Dr. Pope.

DR. POPE: One.

DR. BACH: Dr. Salive.

DR. SALIVE: Three.

DR. BACH: Dr. Yan.

DR. YAN: Two, because this may not be

available for everyone.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Four. If you can show it, it's very valuable, but I would put a

caveat that I wouldn't make a requirement that you would have to demonstrate this change.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: I did a three, partly because it's not applicable to many patients, but also because sometimes suicidal ideation increases with clinical improvement, so it's not an unequivocal bad sign in terms of their response.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five, with an up or down on its importance to clinical meaningful outcome.

DR. BACH: Dr. Zarate.

DR. ZARATE: Four.

DR. BACH: Thank you. Decrease in suicidal attempts, and please again, vote multiple times.

(The panel voted and votes were recorded by staff.)

DR. BACH: 3.6. Dr. Cuyjet.

DR. CUYJET: I voted four.

DR. BACH: Dr. Burke.

DR. BURKE: Five.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Three.

DR. BACH: Dr. Lewis.

DR. LEWIS: One, still concerns about the meaningfulness of it.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five, for the same reasons on ideation.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Four, if you can measure it.

DR. BACH: Dr. Pope.

DR. POPE: Three.

DR. BACH: Dr. Salive.

DR. SALIVE: Three.

DR. BACH: Dr. Yan.

DR. YAN: Two.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Four, for the same reasons as ideation.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Two, because it's such

a rare phenomenon in the context of clinical trial, I don't think it's very meaningful.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five, for the same

reasons as ideation.

DR. BACH: Dr. Zarate.

DR. ZARATE: Four.

DR. BACH: Thank you. Oh, it's fill in the blank time. Other, if you want to vote, you can. No, we're going to go on to the next question unless, is there an endpoint, reliable, valid and meaningful endpoint that we should have had on this list that's come up in the course of this discussion, in which case I think we could fill in an other, but I don't want to vote on other without a clear definition of what is meant, so I'm happy to pause here. Dr. Gaynes, you look like you have something to say.

DR. GAYNES: Yeah, one possibility might be some measure of sustained remission. We talked about the temporality and I know it generated some discussion here, so that's one possibility.

DR. BACH: You don't think that's

subsumed in a?

DR. GAYNES: It might be, but no one mentioned it specifically as a comment.

DR. BACH: Okay.

DR. GAYNES: I don't think we need to vote on it. I guess we've now discussed it.

DR. BACH: I'm happy to fill it in as the answer and then vote on it, if that's the one that's on the table. Dr. Salive.

DR. SALIVE: Safety is one.

DR. BACH: Safety, okay.

DR. MELKUS: I was thinking about adherence, you know, somebody who takes their medication a hundred percent versus 90 percent or versus 80 percent, is the dose effect the same when people have good outcomes?

DR. BACH: Okay. Yes, speak into your microphone, but Dr. Burke said that -- we're talking about the outcome. The question is, how confident are you that each of the below is a reliable, valid and meaningful health outcome, and so I think what's on the table now is duration of remission, safety of the medication, and adherence?

DR. MELKUS: No, because that's not a

health outcome, that's just a measurement perhaps, but not an outcome.

DR. BACH: Okay, safety not an outcome. Dr. Ollendorf, you look like you want

to say something.

DR. OLLENDORF: I was going to ask if we could, the sustained remission one, if we could add relapse as the counterpart to it, because we talked about that as well today.

DR. BACH: Okay. Dr. Lewis.

DR. LEWIS: To pull this together, maybe time to relapse, like in a survival study, so that it includes a subgroup of patients not yet observed to be relapsed, that captures the time to event and captures the proportion of relapse during the observation period. So with the chair's permission, f would be time to relapse.

DR. CUYJET: And if I could put on my cardiology hat, we talk about the readmission rate and this is clearly analogous. You want patients to stay in remission, so time to relapse would be an important measure to capture.

DR. BACH: For the experts in the

room, is there a methodologic issue with that?

DR. AARONSON: Scott Aaronson. It's actually very easy because you've already done your outcomes measures, so all you need is that

outcome measure over time, all you're looking at is to make sure that nobody has shown relapse over the course of time that your study has left. So it's actually very related to your primary outcome measure, this is just duration of a positive outcome.

DR. BACH: Okay. Let's vote. The bullet is time to relapse, and please vote multiple times.

(The panel voted and votes were recorded by staff.)

DR. BACH: 4.2. Okay, Dr. Cuyjet.

DR. CUYJET: I think I'm stuck on four.

DR. BACH: Dr. Burke.

DR. BURKE: Three.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Four.

DR. BACH: Dr. Lewis.

DR. LEWIS: Four.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Five.

DR. BACH: Dr. Pope.

DR. POPE: Three.

DR. BACH: Dr. Salive.

DR. SALIVE: Five.

DR. BACH: Dr. Yan.

DR. YAN: Five.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Five.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Five.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five.

DR. BACH: Dr. Zarate.

DR. ZARATE: Five.

DR. BACH: Okay, hold on. The next thing we need to do is discuss the a priori parameters to define successful or failed treatment for those that got a score of 2.5 or more, which are the majority. We're going to go, I only notated the last couple so we're going to go from the bottom up. Time to relapse got a 4.2 so the question is, what are

the a priori parameters that define -- I'm sorry, let me pause.

On your pink sheet you have the questions from MedCAC. I don't believe you

have the discussion bullet that followed this question. So, what the discussion bullet asks us to do with relation to question four, is for each of the characteristics that receives a favorable score of 2.5 or higher, we can discuss the a priori parameters that define successful treatment, or the opposite of which would be failed treatment.

So this does not need to be lengthy, of course it can be if needed, but to some extent we're just seeking information on directionality and maybe some inclination on magnitude. So for example on time to relapse, I'm allowed to weigh in here, the a priori parameter that defines successful or failed treatment would be a lengthening of the time to relapse, I would argue, and then there would be other measures such as remission rates or response rates that would also be important to mention. So that is the flavor of what we should discuss for each of these.

Starting there, time to relapse, if there are dimensions that are important to capture. Dr. Gaynes, or no, sorry, you faked me out. Dr. Lewis.

DR. LEWIS: So, this was mentioned in the time to event study, the natural measure of the treatment effect would be a hazard ratio, however it's proposed, but a hazard ratio of one point -- actually, let's do it the other direction, of two-thirds, which would be a lengthening of time of one-and-a-half or greater would be a clinically meaningful difference.

DR. BACH: Okay. Other comments on time to relapse?

SPEAKER: I echo Dr. Lewis's comments, and also add that using a Cox personal hazards model or other multivariable design that could be delivered to the control group or between group differences as well.

DR. BACH: Thank you. Dr. Burke.

DR. BURKE: I think these are literature dependent, and I think one has to go to the literature for the answer.

DR. BACH: Okay. Dr. Yan.

DR. YAN: I agree, the only way you can say that is the study needs to have longer duration in order to have more statistical power. It would then generate even if the

events rate is lower, and then you will have to have a very large study in order to find any statistical significance.

DR. BACH: First of all, the number of people who get in remission in the first place affects the measure.

DR. YAN: But that affects effect size.

DR. BACH: What about decrease in suicide attempts, there was mixed --

MS. ELLIS: They were all over.

DR. BACH: They were all over, okay. Decrease in suicidal attempts, the parameters that define successful or failed treatment?

DR. CARPENTER: Scott Carpenter. So, that's problematic because most people in trials, when would they have had an attempt? So for most of them it might be zero, and if it's not zero, there's going to be a question of what time frame are you looking at, the last ten years, five years, and then virtually

nobody is going to attempt it in the course of the trial, so I don't see how you turn that into a meaningful criteria.

DR. BACH: That's useful. What about

decrease in suicidal ideation?

DR. CARPENTER: Same problem, they are very infrequent, and just a reminder that sometimes you get suicidal ideation associated with recruitment into the study.

DR. BACH: Changes in quality of life.

DR. SALIVE: I believe there is a clinically meaningful difference in quality of life scores, I think there was a lot of questions in there related to mood, and those are where the action would be.

DR. BACH: And improvement or decline in function, I think the same there, right? And what about a, improvement or decline in depression as measured by depression scales, is there a clinically meaningful --

DR. BURKE: It's defined in the scales, they actually have the criteria.

DR. SALIVE: And a reminder that changes in score above certain thresholds represent remission and/or response on the

scales as well, so those would be separate measures that are driven by the same thing.

DR. BURKE: And then they're actually in the measures themselves.

SPEAKER: And you could look at remission as well as sustained remission.

DR. BACH: Is sustained remission the same as time to relapse?

We're going to move on to question five barring further comments, and I appreciate everyone's stamina on this. How confident are you that the strategies below when applied to Medicare beneficiaries represent meaningful and realistic study designs in research investigations performed to evaluate interventions for TRD? Again, voting using your key pads, the first option is randomized sham-controlled double blinded study.

(The panel voted and votes were recorded by staff.)

DR. BACH: Can you vote again? 4.8. Dr. Cuyjet.

DR. CUYJET: Four.

DR. BACH: Dr. Burke.

DR. BURKE: Five.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Four.

DR. BACH: Dr. Lewis.

DR. LEWIS: Five.

DR. BACH: Dr. Melkus.

DR. MELKUS: Five.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Five.

DR. BACH: Dr. Pope.

DR. POPE: Five.

DR. BACH: Dr. Salive.

DR. SALIVE: Five.

DR. BACH: Dr. Yan.

DR. YAN: Five.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Four.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Four.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five.

DR. BACH: Dr. Zarate.

DR. ZARATE: Five.

DR. BACH: B, randomized sham-controlled single blinded study, which I take to be that the subject is blinded but the

investigator is not. Please vote.

(The panel voted and votes were recorded by staff.)

DR. BACH: 3.7. Did Dr. Melkus's

button get pressed?

MS. ELLIS: Yes.

DR. BACH: Okay, Dr. Melkus, thank you. Dr. Cuyjet.

DR. CUYJET: I voted three because of potential bias.

DR. BACH: Dr. Burke.

DR. BURKE: Two.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Four.

DR. BACH: Dr. Lewis.

DR. LEWIS: Two.

DR. BACH: Dr. -- what's Dr. Melkus's vote?

MS. JENSEN: Four.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: Four.

DR. BACH: Dr. Pope.

DR. POPE: Four.

DR. BACH: Dr. Salive.

DR. SALIVE: Five.

DR. BACH: Dr. Yan's vote?

MS. ELLIS: Five.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Four.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Three.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Five, in appreciation that somebody thinks more of what happens in real world settings.

DR. BACH: Dr. Zarate.

DR. ZARATE: Four.

DR. BACH: Great. Randomized controlled unblinded study.

(The panel voted and votes were recorded by staff.)

DR. BACH: 2.4. Dr. Cuyjet.

DR. CUYJET: I voted one.

DR. BACH: Dr. Burke.

DR. BURKE: Two.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Three.

DR. BACH: Dr. Lewis.

DR. LEWIS: Two.

DR. BACH: Dr. Melkus?

MS. JENSEN: Four.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: One.

DR. BACH: Dr. Pope.

DR. POPE: Three.

DR. BACH: Dr. Salive.

DR. SALIVE: Three.

DR. BACH: Dr. Yan?

MS. ELLIS: Three.

DR. BACH: Dr. Lystig.

DR. LYSTIG: I put a five for this and actually because I'm looking at the fact this is the first one that is not controlled against the sham, it actually has the possibility for an actual comparator, which I think is very relevant here, and also the fact that we're looking for both meaningful and realistic for it to be properly executed.

DR. BACH: Thank you for that. Dr. Carpenter.

DR. CARPENTER: Two.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Three. The important key here, actually both patient and clinician could be unblinded, but as long as the research

outcome assessment is blinded it would give you a pretty decent measure.

DR. BACH: Dr. Zarate.

DR. ZARATE: Two.

DR. BACH: Thank you. Randomized crossover design.

(The panel voted and votes were recorded by staff.)

DR. BACH: All of the remaining ones are unblinded. Please vote again. 2.3. Dr. Cuyjet.

DR. CUYJET: Three.

Dr. BACH: Dr. Burke.

DR. BURKE: Yeah, I voted two, and the only reason I gave them that was because of the randomization. The unblinding severely decreases it.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Three.

DR. BACH: Dr. Lewis.

DR. LEWIS: Two.

DR. BACH: Dr. Melkus.

MS. JENSEN: Three.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: One. I think I'm

challenged by all of the unblinded designs because the measures of interest are self-reported or clinician-measured.

DR. BACH: Dr. Pope.

DR. POPE: Two.

DR. BACH: Dr. Salive.

DR. SALIVE: Two.

DR. BACH: Dr. Yan.

MS. ELLIS: Three.

DR. BACH: Dr. Lystig.

DR. LYSTIG: I voted four here because I'm thinking both of the fact that a crossover allows you to deal with inpatient comparisons which is very important within a heterogeneous population, and for the concept that was raised earlier, that just because the patient and the physician are unblinded does not mean that the assessor cannot be blinded to it, so you can still get responsible information from it.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Two. Two comments. One is, I think in this population it's going to be extremely difficult to have a person have the same starting point after the crossover is made in the beginning, so it's a real

compromised design.

And just to comment on all my ratings, which are a point lower than I would give otherwise because of the problem of

generalizing from the clinical trial in the real world population for substance abuse and lots of other things confounding.

DR. BACH: Thank you. Dr. Gaynes.

DR. GAYNES: Two.

DR. BACH: Dr. Zarate.

DR. ZARATE: Two.

DR. BACH: Nonrandomized crossover study.

(The panel voted and votes were recorded by staff.)

DR. BACH: 1.7. Okay, Dr. Cuyjet.

DR. CUYJET: Two.

DR. BACH: Dr. Burke.

DR. BURKE: One.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Two.

DR. BACH: Dr. Lewis.

DR. LEWIS: One.

DR. BACH: Dr. Melkus.

MS. JENSEN: Three.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: One, for the same reasons as before.

DR. BACH: Dr. Pope.

DR. POPE: Two.

DR. BACH: Dr. Salive.

DR. SALIVE: One.

DR. BACH: Dr. Yan.

MS. ELLIS: Two.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Two, and I'll point out the symmetry and whether this is in addition to existing evidence. There might be a different answer if this was going to be our sole source of evidence for the treatment.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: One.

DR. BACH: Dr. Gaynes.

DR. GAYNES: Two.

DR. BACH: Dr. Zarate.

DR. ZARATE: Two.

DR. BACH: Pre/post study design.

(The panel voted and votes were recorded by staff.)

DR. BACH: 1.4. Dr. Cuyjet.

DR. CUYJET: Yeah, two. If you have unblinded studies, you have no way to control for placebo effect.

DR. BACH: Dr. Burke.

DR. BURKE: One.

DR. BACH: Dr. Cruz-Flores.

DR. CRUZ-FLORES: Two.

DR. BACH: Dr. Lewis.

DR. LEWIS: One.

DR. BACH: Dr. Melkus.

MS. JENSEN: Three.

DR. BACH: Dr. Ollendorf.

DR. OLLENDORF: One.

DR. BACH: Dr. Pope.

DR. POPE: One.

DR. BACH: Dr. Salive.

DR. SALIVE: One.

DR. BACH: Dr. Yan.

MS. ELLIS: One.

DR. BACH: Dr. Lystig.

DR. LYSTIG: Two.

DR. BACH: Dr. Carpenter.

DR. CARPENTER: Two.

DR. BACH: Dr. Gaynes.

DR. GAYNES: One.

DR. BACH: Dr. Zarate.

DR. ZARATE: Two.

DR. BACH: Okay. I'm going to take the prerogative of the chair to delete other,

because two of our panel members are no longer here so we can't elicit their votes or views on it.

And I believe that is it, except for I'm supposed to say something, and Tamara, you're supposed to say something too. I go first? Okay.

First of all, thank you to the speakers and the other attendees for this. We all know it's a long day, but we will be out in time for tomorrow's session at one o'clock, and appreciate that it is the very vagaries of everything we've discussed today that are the purpose of having these panels. We don't have MedCACs when everything is nicely served up around the evidence or things are clear in either direction.

So, I also want to thank my panelists for putting up with me as the chair and for this discussion, and for the steady focus on trying to clarify things, so thank you all very

much.

MS. JENSEN: I just want to reiterate what Dr. Bach has just said. Thank you, panelists, it was a long day but it was a very

good day for us. This is an extremely important topic for the Medicare population and this is a topic that we have been struggling with, so all of you have really helped us decide what our next step forward might be, so again, thank you for your comments, thank you speakers, invited and the public speakers as well, we really do appreciate that.

And panel, thank you for your comments and your votes. We are going to be looking at them closely, and again, we'll be deciding what to do next with what we did today, so thanks again.

(The meeting adjourned at 3:37 p.m.)