CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Evidence Development & Coverage Advisory Committee

Meeting held virtually via Zoom

September 22, 2021

Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

Panelists

Chairperson

Peter Bach, MD, MAPP

Vice-Chair

Joseph Ross, MD, MHS

MEDCAC Members

Cecelia C. Brewington, MD

Michael P. Cinquegrani, MD

Ella Annabelle Effat Kazerooni, MD, MS

Stephen Lahey, MD

Brian J. Miller, MD, MBA, MPH

Alan Speir, MD

Allison Stephens

Sam Tyagi, MD

Gregory Thomas, MD, MPH, FACC, MASNC

Steven Waldren, MD, MS

I

Invited Guest Speakers

Sameer A. Ansari, MD, PhD

Walter Koroshetz, MD

Jeffrey L. Saver, MD

Adnan H. Siddiqui, MD, PhD, FACS, FAHA

CMS Liaison

Joseph Chin, MD

MEDCAC Coordinator

Tara Hall

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PANEL PROCEEDINGS

(The meeting was called to order at 8:00 a.m., Wednesday, September 22, 2021.)

MS. HALL: Good morning, everyone. Welcome committee chairperson, vice chairperson, members and guests to our virtual MEDCAC meeting. I am Tara Hall, the Medicare Evidence Development and Coverage Committee coordinator. The committee is here today to discuss health outcomes in cerebral vascular disease treatment studies. The MEDCAC panel will examine the growing challenges associated with the decreased level of evidence of certain new and innovative technologies. By voting on specific questions and by their discussion, MEDCAC panel members will advise CMS about the ideal health outcomes in research studies of cerebral vascular disease treatment technologies, appropriate measurement instruments and follow-up durations to help to provide clarity and transparency of National Coverage Analyses.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record.

The conflict of interest statute prohibits 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 conflict of interest during the 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 any Internet or e-commerce organization, that develops, manufactures, distributes and/or markets consulting, evidence reviews or analyses, or other services related to cerebrovascular disease treatment medical technology. This includes direct financial investment, consulting fees and significant institutional support.

If you require a financial disclosure statement, please email Ruth McKesson so she can send you the form for completion. Her email is ruth.mckesson, M-C-K-E-S-S-O-N, @cms.hhs.gov.

We ask that all presenters please

adhere to their time limits. We have numerous presenters and a tight agenda. Therefore, we cannot allow for extra time. During each presentation presenters will receive reminders informing them how much time they have remaining to stay within their allotted time. Presenters will receive a prompt two minutes prior to their speaking time to insure they are ready to present.

During the open public comment, attendees who wish to address the panel will have that opportunity on a first come basis. Please email Ruth McKesson if you want to address the panel by 9:30 a.m.

For the record, voting members present for today meeting's are Dr. Joseph Ross, Dr. Cecelia Brewington, Dr. Michael Cinquegrani, Dr. Stephen Lahey, Dr. Brian Miller, Dr. Alan Speir, Dr. Sam Tyagi, Dr. Gregory Thomas, and Allison Stephens. Nonvoting panel members are Dr. Peter Bach, Dr. Ella Kazerooni and Dr. Steven Waldren. 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.

We ask that all speakers state their name each time they speak, speak slow and concise so everyone can understand, speak directly into your computer mic and do not use your speaker phone to help achieve best audio quality. Ensure your devices are on mute if not speaking, and while speaking, please place phones on silent. Remove pets from your area and anything else that would minimize distractions and background noises.

This meeting is being held virtually in addition to the transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeness 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 the topic at hand take place in the open forum of the meeting. We are aware that many parties including the media are interested to speak with the panel about this proceeding. However, CMS and the committee will refrain from discussion of details of this meeting with the medial until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or at lunch.

And now I will turn the meeting over to Dr. Joseph chin, CAG deputy director.

DR. CHIN: Good morning, thank you, Tara. I wanted to echo Tara's welcome and to thank our chair, vice chair, panel members, speakers, stakeholders for attending and participating. We know that everyone is very busy as researchers, physicians, clinicians and experts in the field, and greatly appreciate your willingness and time and effort to assist CMS in review of the evidence related to the topic of the day, it is a great commitment and we really appreciate your input.

In general, a couple points to note. As a reminder, the MEDCAC helps CMS review and evaluate the clinical evidence related to benefits and harms and appropriateness of certain interventions with a specific focus on the Medicare population. The MEDCAC does not make coverage determinations, and while often we will have one calculated to an open consideration, we do not have one related to the interventions for this topic, but your input is really also very helpful for a number of other considerations that we have related to coverage and how we interpret the evidence.

Specifically for this topic, given that it's really a very highly specialized field, interventions are really highly specialized, the expertise that the MEDCAC brings is very helpful to CMS.

One other point to note is MEDCAC and CMS in general, we do not consider costs in our determinations, so related aspects are considered outside the scope of this meeting.

And I think as we go along through the day we'll hear a lot of discussions and it's a busy day, and so I think from that standpoint

we will be taking lots of notes to make sure that we document all the important input that we get during the day.

With that I will turn it over to Dr. Bach, our chair of the MEDCAC.

DR. BACH: Good morning. I would like to welcome everyone to the MEDCAC meeting on health outcomes in cerebrovascular disease treatment studies. I want to echo what Dr. Chin has said regarding thanking everyone for the time involved, not only today which we know is an important day where a lot of relevant topics will be flushed out for CMS, but also for your time in preparing for this today.

Without further ado, I think we should go on to the next step of the meeting which, Tara, is our disclosures; is that right, conflict disclosures?

MS. HALL: Correct.

DR. BACH: Okay, would you like me to start?

MS. HALL: Yes.

DR. BACH: Okay. So I'm going to call the names of the roster, but I'll begin with

myself. My name is Peter Bach, I'm a physician at Memorial Sloan Kettering Cancer Center, where I direct the health policy research group. I am also the chief medical officer of a private company named Delphi Diagnostics based in Baltimore, that develops blood-based tests for the detection of cancer.

Dr. Ross, could you do your disclosures please?

DR. ROSS: Thanks, Peter. Hi, my name is Joseph Ross, I'm a professor of medicine and public health at Yale University. I'm an associate editor of The Bridge medical journal. In terms of disclosures, I do receive research funding from Johnson & Johnson, but I actually have no idea if they make a cerebrovascular medical device, the work we do with them is really in clinical trial data sharing, but I thought I should disclose it.

DR. BACH: Thank you. Dr. Brewington?

DR. BREWINGTON: Good morning. I'm Cecelia Brewington, a physician in radiology at UT Southwestern in Dallas. I do have research funding by Cannon Medical Systems but it has nothing to do with neurovascular treatments. I

also sit on a Bracco advisory committee, which is an IV contrast company, but that also has nothing to do with neuro intervascular treatments.

DR. BACH: Thank you. And I, Doctor, first of all, please correct me if I get it wrong, but Dr. Cinquegrani?

DR. CINQUEGRANI: That's very good, thank you. Yes, I'm Michael Cinquegrani, I'm an interventional cardiologist and professor of medicine at the Medical College of Wisconsin, in Milwaukee. My industry relationship is clinical trials with Gore Medical for cryptogenic stroke, and for full disclosure, we're continuing an active trial in that area. I have no other disclosures.

DR. BACH: Thank you. And not to, I don't mean to single you out, but could I ask that participants in this meeting at all times or as close as you can approximate to all times, please have your cameras on, this is a public meeting. Everyone understands if you put your camera off to do something, but thank you very much.

Dr. Kazerooni?

DR. KAZEROONI: Hi, my name is Ella Kazerooni, I am a cardiothoracic radiologist at the University of Michigan, a professor of radiology and internal medicine. By means of disclosure, I recently am serving on the advisory board of Polareum, which is a company that looks at hyperpolarized gasses as a function of lung tissue, which is not relevant to the specific topic being discussed today. Thank you.

DR. BACH: Thank you. Dr. Lahey?

DR. LAHEY: Yes, my name is Dr. Stephen Lahey, I am now the emeritus professor at the University of Connecticut. I am a former chief of cardiac and thoracic surgery there. In terms of disclosures, I'm the chief medical officer for a company called Human Resolution Technologies and have a small amount of stock options amounting to about $14,500 in that company. The company is involved with remote patient monitoring and has nothing to do with the subject that we're talking about today.

DR. BACH: Thank you very much. Dr. Miller?

DR. MILLER: I am Dr. Brian Miller, I am an assistant professor of medicine and business at the Johns Hopkins University School of Medicine and the Carey Business School. In terms of disclosure I receive fees as an adjunct at UNC or the University of North Carolina, Health Resources and Services Administration, the Federal Trade Commission and the Heritage Foundation, and nothing related to cerebrovascular devices.

DR. BACH: Thank you very much. Dr. Speir?

DR. SPEIR: Good morning. I'm Alan Speir, I'm the medical director of cardiac surgery for the Inova Health System and I have no disclosures.

DR. BACH: Thank you very much.

(Background noise.)

Somebody has -- could you please mute your microphone if you're not speaking.

Allison Stephens?

DR. STEPHENS: Good morning. Yes, my name is Dr. Allison Stephens and I am the manager of a program, Healthy Outcomes Through Positive Experiences, at Tufts Medical Center,

really focused on reversible health, and none of that is relevant to today's topic, and I have no disclosures.

DR. BACH: Thank you, Dr. Stephens, my apologies for not using your title.

Dr. Tyagi?

DR. TYAGI: Hi, can you guys hear me?

DR. BACH: Yes.

DR. TYAGI: Hi, my name is Sam Tyagi. I'm assistant professor of surgery at University of Kentucky, I'm a vascular surgeon. In terms of conflicts, I serve on the aortic advisory board for Medtronic and Koch Medical, which aren't related to cerebrovascular.

DR. BACH: Thank you. Dr. Thomas?

DR. THOMAS: Greg Thomas, I'm a cardiologist, I'm clinical professor of medicine at University of California Irvine. I help direct cardiovascular programs at MemorialCare Health System in southern California. I have industry sponsored, NIH sponsored trials related to atherosclerosis and cardiac disease, none of which are directly relevant in terms of neurological interventions.

DR. BACH: Dr. Waldren?

DR. WALDREN: Good morning, Steve Waldren, a family physician and informatus. I'm the vice president and chief medical informatics officer for the American Academy of Family Physicians. I work on health IT national policy, and no financial disclosures.

DR. BACH: Thank you very much. I would like to move on to the first -- unless I've missed anyone. I believe, is there anyone I've missed? Oh, I'm sorry, we have a guest panelist, Dr. Brooks?

MS. HALL: Dr. Brooks is not on the panel.

DR. BACH: All right, thank you, Tara. I'd like to move on to the first presentation please, this is Dr. Andrew Ward from CMS, who's the director of the evidence development division.

DR. WARD: Good morning, and thank you for joining today's MEDCAC meeting. My name is Andrew Ward and I am the director of the evidence development division within the coverage and analysis group at CMS. We at CAG want to thank the MEDCAC panel and invited

guests for taking the time and dedication to participate in this important event. Next slide.

The Centers for Medicare and Medicaid Services is hosting and facilitating a Medicare Evidence Development Coverage Advisory Committee, MEDCAC, panel to examine what health outcomes in studies for cerebrovascular disease treatments with a focus on new technologies should be of interest to CMS, in order to provide clarity and transparency of investigating device exemption, IDE analyses, and national coverage analyses for the cerebrovascular disease treatment technologies. Next slide.

In the context of the MEDCAC, cerebrovascular disease refers to all disorders in which an area of the brain is temporarily or permanently affected by bleeding or restricted blood flow. The major types of cerebrovascular disease pathogenesis are occlusive injury intrinsic to blood vessels, occlusive injury extrinsic to blood vessels, cerebral hypoperfusion and cerebral hemorrhage. Stroke is the one of the most common outcomes of

cerebrovascular disease and will be one of the topics of conversation at the MEDCAC. The new technologies include a variety of treatment products for cerebrovascular disease, including drugs, biologics and medical devices. Although many people are interested in the Alzheimer's drug Aduhelm that received an FDA expedited approval, this MEDCAC is not about Aduhelm or the FDA's decision about Aduhelm. Next slide.

The Medicare Prescription Drug Improvement and Modernization Act of 2003, MMA, allowed Medicare payment of the routine costs of care furnished to Medicare beneficiaries in certain IDE studies. Covering the cost in these IDE studies removes a financial barrier that could otherwise discourage beneficiaries from participating, as well as providing a barrier to the development of new technologies.

Over the past several years IDE studies of cerebrovascular disease treatment technologies have become quite common. The volume of such studies is likely to remain quite large, and CMS reviewers often have challenges with the study protocols associated with such technologies, including the

identification of health outcomes required by the IDE valuation requirements. Sorting through and addressing these challenges during the review process often increases the process time, thereby causing delays in helping patients by use of the technology. CMS believes that it is an opportune time for a MEDCAC on the topic to give advice on outcome measurements in cerebrovascular disease research that will optimize the efficiency and timeliness of the IDE process. Next slide.

Given the increased emphasis on new and innovative medical products for treating diseases that have few proven therapies, studies of cerebrovascular disease treatment technologies submitted through the IDE pathway have focused less on date capturing long-term results and more on intermediate and surrogate outcomes. As a result, there are more frequent evidence gaps with respect to the clinically meaningful health outcomes for CMS beneficiaries and assessments of these kinds of medical technologies. The MEDCAC panel will examine the growing challenges associated with the increased reliance on, of intermediate and

surrogate outcomes used to support new and innovative cerebrovascular disease treatment technologies.

By voting on specific questions and through their discussions, MEDCAC panel members will advise CMS about the best practical health outcomes in research studies of cerebrovascular treatment technologies, appropriate measurement instruments, and follow-up durations, to help provide clarity and transparency of IDE analyses and national coverage analyses, NCA. MEDCAC panels do not make coverage determinations, but CMS benefits from their advice.

Although there is general agreement on the importance of using mortality as an outcome measure in cerebrovascular disease clinical research, there is little or no consensus on which or how to include other outcome measures. For example, should these studies include health outcomes such as stroke status and recurrence, hospitalization and healthcare resource utilization, clinician-reported patient functioning, and patient-reported outcome measures, PROMs? Next slide.

In the afternoon session the panel will vote and participate in additional discussion on the following questions which I will now read for the record. The voting questions, for each voting question please use the following scale identifying your level of confidence with a score of one being low or no confidence, and five representing high confidence, so you can see the Likert scale there. Next slide.

Question one, how confident are you that the following are standalone, meaningful primary health outcomes in research studies of cerebrovascular disease treatment technologies: A, major disabling stroke, defined as stroke in the treated vascular territory that results in a modified Rankin Scale of three or greater than three; B, decrease in the modified Rankin Scale of two or greater than two points compared to baseline; C, modified Rankin scoring of two or less than two, or equal to pre-stroke modified Rankin scoring if the pre-stroke modified Ranking scoring was greater than two; or D, other kinds of stroke, such as major ipsilateral stroke or morbid stroke.

Next slide.

Second question, how confident are you that the following are standalone, meaningful primary health outcomes in research studies of cerebrovascular vascular disease treatment technologies: A, hospitalization length of stay for index procedure; B, number of unscheduled readmissions that are related to cerebrovascular disease; C, discharge disposition to rehabilitation, home versus inpatient facility? Next slide.

Question three, how confident are you that each of the following functional assessments are standalone, meaningful primary health outcome measures in clinical research studies of cerebrovascular disease treatment technologies: A, the modified Rankin Scale; B, the National Institutes of Health Stroke Scale, NIHSS? Next slide.

And the final question that will be considered is number four, how confident are you that using EQ-5D to measure quality of life: A, is an adequate measure which reflects the patient experience in the context of cerebrovascular disease studies; B, should be

included as standalone, meaningful primary health outcome measure in research studies; C, should be included as a composite meaningful primary health outcome in research studies; and D, should be included as secondary health outcomes in research studies?

Thank you very much.

DR. BACH: Thank you very much, Dr. Ward.

I'd like to move to the first presenter please, who will be Dr. Walter Koroshetz, from the National Institutes of Health and the National Institute of Neurological Disorders and Stroke.

DR. KOROSHETZ: Good morning, folks, and I have no disclosures, of course I'm a federal employee, and I'm going to talk to you today, kind of a primer on stroke with relevance to the questions that you're going to be dealing with. And I apologize to Greg Thomas if he's heard a lot of my rantings in the past. It's been a while. Next slide.

Okay. So from the NIHSS standpoint, we think of our research in three different Venns. The greatest public health impact is

made by preventing strokes, and because it is so common as, you know, somewhere around 720 to one million a year, you know, preventing a certain percentage of these strokes has a huge public health impact and in actual fact, stroke rate declined by about 70 percent since the 1970s. That decline unfortunately has been slowed down most recently, which we think is related to the growing obesity in the United States, so we really have to kind of work harder to keep that decline going.

The greatest driver for stroke is high blood pressure, it's top one, two and three drivers of stroke, and our big message is that if we could get people to control their blood pressure, we could make a really big dent in this public health problem. So that's not what you're talking about today but I just wanted to emphasize, you know, from the public health impact, prevention is really what has the greatest benefits.

What we're talking about mostly today is acute treatment and this area, you know, really is not that old. I kind of got into it in the mid '80s, and the earliest studies came

out of Germany where people showed that if you could inject the thrombolytic agent into a clot, dissolve the clot, sometimes you got kind of amazing outcomes, you know, kind of quote-unquote miracle type of temporally related improvements in neurologic status, and that led to another, you know, 50 years of people trying how to figure out how to do that in acute ischemic stroke, and the rationale is that you can have an occlusion of a blood vessel, have fairly significant deficits and they will go away, those deficits will recover, you know, sometimes within a couple minutes, and that's called a transient ischemic attack. And so what people have tried to do is really convert ischemic strokes which are due to the blockage of a blood vessel into transient ischemic attacks by opening up the blood vessels. So that's kind of a simplistic view of acute stroke therapy for ischemic strokes.

Now there is also hemorrhagic stroke, they tend to take different forms, and we have not really been able to make a dent in kind of the acute clot removal area, although we have been trying, and I will talk to you a little

bit about that in the future. So the intracerebral hemorrhage where the blood is inside the brain, that's been really difficult to make a big difference to help those patients.

Subarachnoid hemorrhage we talk about where the bloods around the brain, we can make inroads by maybe supporting the patients through that period and they can sometimes have good recoveries.

And then blood inside the ventricle, similarly these patients have a high mortality rate but if one can support them through, they can make recoveries.

Recovery in this space, in ischemic stroke, is due to the fact that the brain rewires after the stroke, so what the patient is going to see long term is going to be a function of the damage and their ability to recover, so that's what complicates a little bit the issue of outcomes because there are features that affect recovery, particularly age, that are going to come into play in terms of how a patient benefit from the therapy. Next slide.

So this is what we were talking about in terms of vascular lesions that cause stroke, and so the thing to remember is that stroke is not a disease, stroke is a consequence of vascular disease, and depending on where the vascular disease is, it will affect the brain in different ways. Two major brain infarctions, major categories, one is embolism where you have, you know, something gets loose from the vascular system in the heart, the brain gets 20 percent of the blood flow, chances are it's going to go to the brain, one out of five. If the brain blood vessels have, you know, diameters of a millimeter, maybe two millimeters, so a small clot going to the kidney you will never know about it, but that same clot going to a cerebral artery, you could be potentially devastated, unable to talk, unable to understand, paralyzed on the right side, unable to take care of yourself. So embolism is the area where people have made the greatest impact in acute stroke by dissolving the emboli, allowing the blood to flow back before there is major tissue damage. That being said, in my experience there's always

some tissue damage and it's a matter of limiting the tissue damage.

Now in terms of the actual events that happen in the brain when a blood vessel is occluded, there's probably a number of factors, but the one that we know most about is what's called collateral flow. So in these pictures, both these patients have an occlusion in the middle cerebral artery. The one pictured here on your right, you can see the big black area and there's a little artery and it's blocked. On the other side you can see the same thing on, it's actually the left side of the brain there's a block, there's a gap, then all the blood vessels are filling distal to that gap, and that's because the blood flow is coming around a different pathway, in this case it's coming around the surface of the brain, up the middle part of the brain, around the brain, down the lateral surface and backfilling those blood vessels. So in this case where you have good collateral flow, that brain tissue may last longer before it dies, and on the opposite side where you see this big black area and there's really no blood flow, so that's going

to be important in terms of understanding outcomes in patients who undergo thrombectomy.

So the general simple idea is the patient with collateral flow, you can open the blood vessel, that brain tissue has been able to get by and you can save it. On the other hand the patient on the other side, that brain tissue has no blood flow, it's dying quickly and it's going to be very hard to save.

Now the one thing to also know is that you can't tell the difference between these two patients by examining them because the low flow seen in each of the cases is enough to shut down brain function, so the brain shuts down function and so the patient will have maximum deficits at flows that are above what it would cause to kill the cells, so that's how a patient can come in with massive deficits, have the blood vessels opened and the deficits go away, because if the tissue is not working, it's actually maybe a protective effect to stop the use of metabolic energy in a starved tissue bed. Okay.

Now there are also cases where there is actually a stenosis in the blood vessel that

causes low flow, oftentimes fluctuating symptoms, and these can lead to stroke. Oftentimes these strokes may occur over long periods of time, you may get, you know, an area of infarct on Monday, another area on Tuesday and they kind of add up, but -- and these are the kind of things that you see in intracranial stenosis and even the neck vessels narrowing, carotid disease, but even in carotid disease the general stroke cause is an embolus getting loose from the area above the stenosis and being flushed into the brain.

There are some cases where their collateral flow is so poor that the flow is actually low and you get low flow stroke as well due to carotid stenosis, but in general the problem is, even there, is embolism. Next slide.

Now in the case of hemorrhagic stroke, a little bit depends on what blood vessels break leading to the brain, so subarachnoid hemorrhage is caused by an aneurysm, it ruptures, it's basically like a, you know, if you have a bad tire and a bulging tire and the thing blows, that's what happens. In fact if

the hole in that aneurysm is not closed by a clot within a matter of seconds you will die, and that's because the pressure inside the head equals the blood pressure, because there's basically an opening between the arterial space and the subarachnoid space and that will lead to complete loss of blood flow to the brain since there's no pressure differential anymore, so about 40 to 50 percent of people die immediately with a subarachnoid hemorrhage.

Now interestingly, there are about 40 to 50 percent where a little clot forms over the hole, and those people can survive if the aneurysm can be repaired before it rebleeds and if the blood that irritates the space around the brain does not cause vasospasm to the point that you have multiple strokes. The blood is very irritative, in many people you get total spasm of all the blood vessels causing stroke, and the main goal in the post subarachnoid hemorrhage time is to limit vasospasm, treat vasospasm with either drugs or with endovascular techniques like stenting or angioplasty.

Many strokes are due to hypertension

and its effects on small blood vessels, these are small blood vessel strokes, sometimes they're called lacunar strokes, and these are generally in the deep territories of the brain, they're generally small, they frequently have better recoveries but what, the damage they cause is dependent on where they are located.

In terms of hemorrhages also -- I'm sorry -- and the hypertensive hemorrhages are due to these same kind of blood vessels rupturing inside the deep brain, and these can be very devastating because they're like a knife, a pressure knife that goes through the brain substance causing a tremendous amount of damage right and center of the brain.

And you also have malformations of various types, and you can get venous thrombosis in some instances which will cause backup of venous blood flow, and bleeding and edema.

Amyloid angiopathy is the same amyloid that you see in Alzheimer's disease, it coats the blood vessels and can lead to bleeding, oftentimes in the cortex, as opposed to these ruptures from a hypertensive artery in the deep

brain, these tend to be kind of more low pressure hemorrhages and have better, usually have better outcomes, but unfortunately once you have this you frequently have multiple, okay? And as I said, we've had very little success in being able to prevent the sudden brain damage from these severe arterial hemorrhages. Next slide.

So as I mentioned, the death of the brain function occurs as a function of how low the flow is, and so the blood flow may not be that low but again as I mentioned, the brain will not be working, you can't tell the difference by looking at the person, and how low the flow is versus how much time the brain sits at that low flow stage, and the goal of the reperfusion therapy, therefore, is to limit the time during which the flow is reduced.

As I mentioned, the flow decrement is a function of the degree of the vessel block and the level of collateral flow. Most emboli, you're basically looking at a hundred percent block. When first undergoing brain imaging, what you see is there is generally in people who have these major vessel occlusions or large

artery occlusions, what we call large vessel occlusions, there's generally a core of tissue that has very low flow that cannot be salvaged, surrounded by lesions with better flow that can be prevented from dying if the reperfusion occurs immediately, you know, within a second of having gotten the image. So the imaging has had a major role to play in choosing people who can benefit from endovascular therapy.

Now this is, I want to just go through this document a little bit. This is the relationship between the onset to puncture of the groin to do reperfusion, versus probability of good outcome on the Y axis, and the different colors relate to what's called the ASPECTS score, which is a score based on the BCP, usually CT, and that's a score that the lower the score the more a brain looks abnormal on the CT, as seen by low density on a CT scan. So an ASPECTS score of zero to four means there's a lot of brain tissue that looks like it's damaged on the CT scan. ASPECTS five to seven is kind of midway, eight to ten is better, and these are the probability of outcomes depending on the type of puncture. So

if you have an area of brain that looks really, you know, a lot of damage is going on quickly, you don't have much time, even with endovascular therapy you're not going to improve, you know, if it's out past, you know, 400 minutes or so. The less damage you see on the CT, the better the chance you're going to get good outcomes from endovascular therapy. So that's the main point.

The other point to make is that we need to understand why people with good ASPECTS all don't have good recoveries and that's kind of the future, is to understand how to improve recovery in each of these different classes. But I would point out that there is a problem where there are people who, you know, look like their brain is not so far down and they still don't make good recoveries. And the other thing is, there are also probably people are being treated that don't have a chance of improving with this therapy. So how to know where to draw the line for when not to treat is actually important, because the treatments are not without harm, doing an angiogram, putting catheters in the brain for instance, you know,

carry with them a chance of harm. So that's one of the things that we're most interested in pursuing. Next slide.

Now as, I mentioned this, that the outcome of the patient in these instances where you're trying to get the clot out, a lot you understand, very short timeframes, because the brain, you know, if it doesn't come back quickly it's probably not coming back. Quickly, you know, you can debate what that means, but clearly there's some people who, they go into the procedure, they're completely paralyzed, severe deficits, after the procedure they're walking and talking, and so you do see those kind of very rapid, you know, walk off the table events, and those people unless something else happens to them, are going to do extremely well. So there is value to the short-term assessment, but the deficits depend not just on how big the stroke is but where the stroke is located, so that's the problem with treating it like a, you know, cancer where the tumor burden is what gets you, here it's the burden but it's also location, and as I mentioned, what the patient ends up with

depends on how well they can recover.

So the convention has been in determining the clinical benefit to the patient to put it on the shoulder of a 90-day assessment, and the things that we know that affect how well someone's going to recover with the same degree of injury, you know, it's related to age, previous stroke, and possibly the presence of diffuse white matter disease related to hypertension. Next slide.

So the goal of acute ischemic therapy is then speed in opening the vessel, it is effectiveness in opening the vessel, getting complete opening, getting that flow back, and the risks are arterial injury at the puncture site or inside the brain and damaging the blood vessel causing spasm, perforating blood vessels causing subarachnoid hemorrhage, and the other one is the issue of sending embolic material from the embolus as you try and break it up and pull it out, if pieces can loose they're going to move distally and you can't get them, and so that would be, that would kind of put a damper on your chance of getting good outcomes because you're not getting all of the clot out, you're

sending some of it distally where it's going to cause infarcts. Next slide.

So what will happen to the person depends on, you know, what their imaging looks like when you start, whether the treatment caused secondary brain injury, and whether the acute treatment was related to comorbidities, aspiration pneumonia, you know, with somebody lying down on a table, they're unable to swallow because of the stroke, that opens the big problem with sepsis. But we do know, and here is a case where here you can see in the top panel on the left is where we see the damage is on MRI scan so a lot, most of the brain is not damaged, but if you look at the blood flow abnormality, the whole hemisphere below it is at a low flow state, so we would think that this patient would have a great chance of recovery if we can open up the blood vessel.

On the other side, on the right side at the top is the damaged area, it pretty much looks like the flow abnormality and that patient it unlikely to be helped, but these are the kind of things that before they go into

practice really have to be validated. Next slide.

So the futility, and this is another example of somebody who has no abnormality whatsoever but has a blood flow abnormality, so you should be able to completely cure that patient, but they are rare. Next slide.

So how and when will the person know if they benefit? I mentioned that the conventional was 90 days, and I show you this graph here which shows different severities of stroke and their rate of recovery. What you can see is that there's basically a plateauing out by about 13 weeks, which is around 90 days, so that's why we choose this 90-day period. There are definitely recovery improvement that goes on longer after that but the big huge improvement is really in that first 90 days, so that's why that is important. Okay, next slide.

DR. BACH: Dr. Koroshetz, you have three minutes left.

DR. KOROSHETZ: Okay. I was just going to talk about the scales now.

So the NIH Stroke Scale, that was kind

of a neurologic deficit scale and it was built prior to the tPA study for the purpose of measuring acute neurologic improvement with tPA, which is intravenous therapy, and it was made not to be used necessarily by neurologists but by any kind of medical professional who is basically counting the deficits.

The modified Rankin Scale is the one we use most commonly and it's basically seven crude bins to detect large functional levels and it's very good for, you know, these major stokes where someone if they're not helped will die or be permanently disabled, unable to care for themselves. It's not so good for, say lacunar strokes where the deficits are more, to know if someone is improving is more nuanced. So for looking at things like recovery of deficits, scales that are more attuned to measuring the actual, going deep into the actual deficits, you know, measuring speed of movements or agility or speech, speech production, or understanding, and kind of measuring whether things can improve there, those are probably what's needed, more fine grain measures of recovery.

And the Barthel Index is another functional scale. The issue with the modified Rankin is that it's so crude that you can actually get a pretty good assessment in the emergency room, but with the Barthel and the FIM, that's probably not going to be feasible. NIH Stroke Scale is feasible in emergency settings, that's what it was built for.

So those are the scales and those are the kind of reasons, you know, the biology behind, you know, trying, the biology that we're fighting against in getting good recovery for patients. So I'd be happy to help in any way with my thoughts, and thanks very much for your attention.

DR. BACH: Dr. Koroshetz, thank you very much both for the presentation and for ending on time. I forgot to remind everyone that my primary purpose as chair is to keep us on schedule, so I will periodically pop up.

Dr. Saver is going to present next. He's the vice chair for clinical research and a professor in the department of neurology at the David Geffen School of Medicine. And to remind everyone, panelists, please keep your cameras

on to the extent you can. Speakers, it's perfectly okay and actually modestly preferable if you want to keep your cameras off when you are not presenting.

DR. SAVER: Thank you very much, everyone, and thank you for the privilege of speaking to you today. I am a clinical trialist and, next slide, here are my disclosures. I have NIH funding and I do receive funding from multiple neurovascular companies for aiding in the rigorous design and conduct of clinical trials and also, UCLA has made a method of assessing the Rankin available freely on their Creative Commons license, and has a copyright on training vignettes in that system. Next slide.

So in the 25 minutes today, I will briefly run through the topics that the panel is considering focusing on first the distinctive aspects of outcome assessment in neurovascular disease, spending most of the time on acute stroke, especially the modified Rankin Scale, NIH Stroke Scale and EQ-5D, and then briefly alighting upon stroke recovery and prevention. Next slide.

So it is the case that there are aspects of neurologic disease in general, neurovascular disease specifically that are distinctive compared with the outcome assessment in other organ systems. Most importantly, that the disease compromises the organ that perceives and reports functioning accurately; patients can have language abnormality, memory abnormality, disordered management understandings, and that can affect their ability to report their status accurately. The hemispheres can have different emotional tones, the right hemisphere injury can result in denial of illness and again, patients may not give a full accounting of their status. As a result, proxy reporting between family and caregivers is often required, but does have limitations in that, especially if patients are in care facilities, any particular caregiver may not know their functioning perfectly well.

Another aspect, as Walter mentioned, degree of disability, is comparably even more important than mortality in outcomes in stroke, disability is a much more frequent outcome than

mortality, and the breakthrough therapies such as intravenous thrombolysis and endovascular thrombectomy alter disability substantially but mortality minimally.

Another aspect is that acute stroke outcomes are intrinsically non-dichotomous, they occur over a range of disabilities, and that means they can be analyzed in a variety of approaches, by ordinal scales which look at the shifts between, or levels by dichotomizing cumulative ordinal scales and looking at only one health state transition among the many that occur. And then also by continuous scales of a -- those have not been built up in a way that the community has accepted for disability ascertainment.

And then lastly, it's important to adjust for presenting stroke severity because the severity of deficits on presentation is a dominant determinative of outcome in stroke patients. Next slide.

With regard to the timing of outcome assessment after acute stroke, as Walter mentioned, considerations are that the timing of the stroke recovery is that most occurs

during the first three months, but some will continue up to a year. As you can see on this slide on the right, please click again, and you can see that the first three months the greatest proportion of recovery will have occurred. Once you keep following patients beyond three months, competing events, recurring stroke, myocardial infarctions and other events accrue with time and again, introducing noise into the understanding of the outcome of the treatment of the initial stroke. So you don't want to, it's felt you don't want to measure too early, say one month after stroke, because patients are still on the steep limb of recovery. Three months is the best compromise, most often used in randomized trials, and also when the federal government, Social Security determines that a patient has disability. And for more severe strokes, intracerebral hemorrhage, subarachnoid hemorrhage, the recovery may be more prolonged, and it can be appropriate to look at six months to 12 months as an outcome time point. Next slide.

As I mentioned, it's very important to

address the presenting deficits using almost always the NIH Stroke Scale because severity is such a predominant outcome predictor. Age is also important but comorbidities are much less important. Here on the right you can see the relationship between scores on the NIH Stroke Scale that run from zero to 42 for mortality, and there's a strong linear relationship, and models in Medicare beneficiaries have shown that mortality projection increases in accuracy substantially if the NIH Stroke Scale is included. For this reason, after recommendations from American Heart, American Stroke Association and other stakeholders, CMS piloted the addition of the NIH Stroke Scale to ICD-10 codes so it would be available in administrative data sets, and it has shown initial good performance and it's anticipated that in 2022 CMS will incorporate it into the hospital performance reporting. Next slide.

Now let's turn to the acute, to the modified Rankin Scale, which is the leading outcome measure in acute stroke, and it measures global disability. The World Health Organization's current definition of global

disability focuses on the interaction between a person with disability in the environment, and recognizes the disability arises from three components: Impairments, problems in body function or structure; activity limitations encountered in executing a task; and participation restrictions in a person's involvement in life situations. And the Rankin scale taps all three of these. NIH Stroke Scale, for example, only taps impairments, it does not look at activity limitations an participation restrictions. Next slide.

There is the modified Rankin Scale, it is a clinician-reported measure in it's original form, it's the most common primary outcome measure in stroke trials and clinical practice, and it assigns patients to one of seven possible levels of disability that range from zero, no symptoms at all on one end, to six, dead, on the other, and providing intermediate levels of disability in between. And what you see on the right is the original wording of the Rankin Scale in its entirety by John Rankin in 1957. This was all there was and the clinician used this to make a very

intuitive kind of holistic judgment about which level to assign a patient to. Next slide.

You can see from this that the range of disability covered by the modified Rankin Scale is very broad, and almost every step on the modified Rankin Scale as a result is clinically significant and covers a very important change in a patient's functioning and health state. Next slide.

A consensus group this year suggested that these health state descriptors should be used for the Rankin Scale, because saying mild, moderate, moderately severe, scaler terms become hard to follow, and have recommended for the Rankin levels: Normal; Rankin 1, they're symptomatic but not disabled; Rankin 2, disabled but independent, they can't work but they can live alone; Rankin 3, dependent but ambulatory, they can't live alone but can walk; Rankin 4, nonambulatory or body care self capable; Rankin 5, needing 24-hour constant care; and Rankin 6, dead. Next slide.

The Rankin Scale is widely accepted by the community, it is the most commonly used in clinical trials, it's been endorsed by

consensus groups both in the U.S. and Europe, it is used by regulatory agencies including FDA and the NIH in the Common Data Element platform, by hospital accrediting bodies for performance measures to assess hospitals in the U.S., by specialty societies and by the U.S. Clinical Practice Registry that covers 70 percent of patients. Next slide.

I will mention that the Get With Guidelines stroke registry does cover 70 percent of U.S. patient six million patient records per year and the primary outcome measure here in clinical practice in addition to clinical trials is, a primary outcome measure is the modified Rankin Scale which is obtained at discharge in all hospitals and obtained at 90-day followup in patients who have undergone revascularization procedures. It's hard to track patients down in regular practice 90 days later, so for noninterventional patients the discharge Rankin is used as a more accessible endpoint. Next slide.

As I mentioned, the initial Rankin Scale was a very holistic scale, that's on the

top row here using intuitive clinical judgment, and that has poor inter-rater consistency. Next slide.

Therefore, a variety of techniques and instruments have been developed to assign Rankin scores in a more reliable manner. They each have advantages and disadvantages, and their features on a variety of parameters are shown in this slide.

Let me focus, next slide, on one particular aspect and that's the assessor type that several of these instruments like the simplified modified Rankin Scale questioner converts the Rankin to a patient-reported outcome and again, that can be a bit challenging when patients may not be reliable informants about their disease state. Others retain the clinician rater approach to assigning the Rankin. Next slide.

Because the Rankin is an ordinal scale there are a variety of ways to analyze it over seven levels. Next slide.

If we look at all seven levels and the shift in outcomes across all seven levels, this is how most clinical trials are reported, so

you can see the impact of the treatment across all health states in an ordinal analysis. Next slide.

But also for simplicity, sometimes a fixed dichotomous analysis is done, next slide, most often looking just at the health state transition across the three to two order from dependency to disability, and there you have more precision, but you also are missing important effects of treatment with it. Next slide.

Also commonly looked at is the Rankin zero to one versus two to six transition. Next slide.

And here you're looking for the ability to go back to work with the equivalent person not being able to go back to work. Next slide.

A more recently developed approach is to weight the ordinal levels using utility weightings. Next slide.

And for that, two sets of informants were considered, patients reporting their quality of life, and physicians and nurses who assess multiple patients doing person tradeoff

analyses to come up with utility and disability weights for each Rankin level. Next slide.

Here you can see the patient-reported assessments of the quality of life with each level, and physician assessments and nurse, next slide, which turned out to be very similar when averaged together, next slide, were used to give a utility rating to each level of the mRS. Next slide.

And you can see here that only two of the levels, between six, dead, and five, continuously disabled, unable to -- bedridden, are valued about the same. Some patients think being permanently bedridden or in a vegetative state is a worse outcome than death, some think it's better, but all the other step changes in the Rankin from five to four to three to two to one to zero cover broad changes in health and are clinically important, although not equal in the amount of utility they deliver. Next slide.

This can be used to develop cost effectiveness analyses but I know we're not supposed to cover that so I'm going to skip through the next slide and next slide, and go

to the next slide.

Some practical aspects of mRS use. In acute stroke studies you really can't reliably use an mRS change score because you can't, you can make some gross estimates but you can't reliably assign a patient a Rankin score just within the first minutes after their presentation. They haven't yet attempted functional activities and their functional capability can't reliably be assessed by raters. You can assess their neurologic deficits from the NIH Stroke Scale score, and so the Rankin score is not usually measured at baseline but outcomes of three months are adjusted for a baseline severity on the NIH Stroke Scale for what it looks like in the baseline state.

You do want to incorporate the patient's pre-stroke Rankin, what was their level of disability before this stroke happened. Most trials exclude patients with pre-stroke disability, but in clinical practice patients may have had prior strokes or dementia or arthritis, congestive heart failure and have severe disability before the stroke came, and

here you can't just see if they are already disabled and had a Rankin of three or four before the stroke, stroke treatment is not going to get them to a Rankin of one or two, and there it's useful to have a return to the level of the pre-stroke mRS as an additional aspect if you're doing a dichotomous analysis. Ordinal analysis handles this appropriately without any adjustment.

Once you begin moving into the subacute stage, from day four forward, then Rankin scores can be reliably assessed by raters and you can look at Rankin change scores. For each individual patient every single one-point step on the Rankin is highly significant except as we saw, for the five to six change. For group differences, you know, if one patient among eight has an important change, that is going to be clinically significant. And so if you're looking at means with greater group differences of .12 or higher, that exceeds the MCID. Next slide.

The approaches to analyzing in the clinical trials are shown here from a recent poor person's meta-analysis that we ran showing

that most common recently has been analyzing the Rankin Scale over the entire ordinal range as the primary mode of analysis in 20 clinical trials. Next is fixed dichotomy, also used roughly equally but with different cutoffs, most commonly being Rankin zero to two versus three to six as the most commonly used cutoff, with zero to three versus four to six for much more severe stroke states, and some now using the more recently developed utility weighted Rankin. Next slide.

With regard to the minimally clinically important differences on this scale to help in both anchor-based and practice-based studies, and they suggest that for fixed dichotomous analyses rate difference between the groups of 1.3 percent or greater exceed the MCID. For ordinal analysis, means have been mentioned of .12 or greater MCID, and for utility weighted analyses, utility values greater than .02 to .03 exceed the MCID. Next slide.

Let's turn to the NIH Stroke Scale next, next slide, and this is the most common measure of neurologic deficit in acute stroke.

It measures 13 items in seven domains, looking at patients with motor deficits, visual deficits, sensation, language articulation, score from zero to 42, zero to four is mild, five to 15 moderate, 16 to 42 severe. Next slide.

It is a skewed distribution in patients. The median NIH Stroke Scale in clinical practice is four, most patients have mild strokes when they present, although patients who are treated with devices for thrombectomy much more severe, have a 16 to 17 score, and with TPA a nine to 12 score. Next slide.

It is widely accepted as the best measure of presenting severity. Next slide.

For measuring long-term outcome it's generally avoided for several reasons. First, it has this odd distributional property that at three months is highly bimodal, with dead patients rating at the severe end of the scale and patients who recover clustering at the other end of the scale. Also, point changes on the NIH Stroke Scale are not comparable, a two-point change in weakness is much more

important than a two-point change in sensation, and it only assesses impairments not functioning in the real world. Next slide.

However, it can be helpful to measure early treatment response. If you look at the change in the baseline NIH Stroke Scale from baseline to 24 hours or 72 hours, that is a strong predictor of outcomes at three months if you want an earlier readout from your, some clinical measure. Next slide.

DR. BACH: You have about five minutes left.

DR. SAVER: Thank you, next slide.

The MCID is not well developed but in general for severe deficits, changes by four or more are the ones that are clinically recognizable and clinically important, moderate deficits two or more and mild deficits one or more. Next slide.

With regard to health-related quality of life, next slide, there are a variety of instruments both generic, health-related quality of life, and stroke specific. Most often used has been the EQ-5D, the European generic quality of life instrument, next slide,

which grades patients on five domains, self-care, pain and discomfort, usual activities, et cetera, on a patient-reported measure. Next slide.

And with regard to administrative measures for acute patients, a discharge destination is a useful one. Besides home and any inpatient facility, it's helpful to distinguish between home and discharge to an inpatient rehab versus a skilled nursing facility. Inpatient rehab patients will go there for one to two weeks and then go home, they have a very different trajectory than skilled nursing facility patients who often never get home, and also patients discharged to hospice. So it's more of a four-level variable and these can approximate the Rankin Scale. Next slide.

Also useful is home time, the number of days a patient spends at home in the first 90 days after onset. The good patients get home very quickly, the poor patients may not get home at all, and that correlates very well with the Rankin, and CMS and all payers have access to this data. Next slide.

Length of stay is confounded by short stays for patients who do very poorly and die, and correlates poorly with three-month functional outcomes, next slide, and potentially in the future the discharge Rankin if it could be made into an administrative measure, could also be used. Next slide.

I'll briefly mention for stroke recovery, next slide, that as opposed to global measures, domain-specific measures are more important. You're trying to improve motor function in a patient with a motor deficit, language function in a patient with a language deficit. During the subacute period in the first three days to six months in the control group you have a moving baseline with a proportional recovery rule. Beyond six months you have a stable baseline in the control group and changed scores are appropriate to analyze here. Next slide.

Here's examples for different domains of clinician-rated patient-reported outcomes and functional testing for recovery. Next slide.

And it didn't line up correctly, but

this shows which of these have been endorsed by consensus groups, next slide, both motor recovery and language recovery when I fix the spacing for you. Next slide.

Just to show you what these look like is the commission-rated Fugl-Meyer for motor deficits which looks at 33 movements and gives a total of 66 points, next slide, and here's the functional measure for motor deficits, the action research arm test where a patient manipulates wooden blocks and marbles and ball bearings. Next slide.

And here's the patient-reported measure for motor hand deficits where a patient reports how well and easily they're able to use that limb in regular daily life. Next slide.

With regard to prevention outcome measures, next then slide, I do want to say that it's important to --

DR. BACH: Dr. Saver, please wrap up.

DR. SAVER: Okay. I think prevention is not the core focus here so I'll come back to that if there's an issue, but I will mention it's important to distinguish between stroke severity that the NIH Stroke Scale measures and

stroke detection. Patients can have a stroke and then improve between visits, so it's important to ask in the questionnaire about stroke symptoms between visits to identify whether a stroke has occurred. Next slide.

And measuring recurrent admissions can be helpful administrative --

DR. BACH: Dr. Saver, we need to wrap up please.

DR. SAVER: Thank you. I think this was my last slide, so I thank you, no worries.

DR. BACH: Thank you very much, and my apologies for being the time cop here. We'll move on to Dr. Sameer Ansari, who's a professor of radiology, neurology and neurological surgery, and director of neuroendovascular research and quality at Northwestern University Feinberg School of Medicine.

DR. ANSARI: Next slide please. Disclosures, several NIH-funded studies unrelated to this topic. I do have some industry support from the neurovascular space, nothing related to the area of thrombectomy which is what I will be concentrating on, but mostly related to clinical trials, data set

monitoring boards. Next slide.

My affiliations do include that I'm, as the director of the SNIS safety organization and on the governance council of the CRN-DAISI data registry, which is the second topic that I will be discussing after the value of the clinical registries. Next slide.

And I thought I would start with just describing how we arrived at value-based statements and really the goal of registries and how they may be beneficial to payers. Next slide.

As you are all aware, CMS is comprised of four major payer components, hospital costs, physician fees, private co-ops and prescription drug costs. These are funded by two main trusts, including tax revenues, premiums and interest on these trusts. It's interesting that hospital payments are solvent through 2030 but the supplementary medical insurance trust which funds physician fees and prescription costs, typically have been funded annually to match them. Next slide.

To note the fee for service model that started several decades ago, which was usually

controlled through physician billing, started to come under fixed schedules by Medicare and to reduce costs. This was followed by the DRG fixed fees and then finally under the Bush administration, the Omnibus Budget Reconciliation Act, which was sort of historic in developing the resource-based relative value scale, which would monitor physician volume and through the Medicare physician fee schedule reimburse the provider costs. Unfortunately, these policies inadvertently incentivized volume. Next slide.

And so in 1997 the Clinton administration's Balanced Budget Act tried to link the GDP to a sustainable growth rate formula to limit the annual increases in these physician fees. This was fine until the start of the millennium when the GDP economic crisis was affected, and what was required for the next decade was that Congress would have to supplement the budget to prevent very drastic reductions, unsustainable reductions of 20 percent follow until the Affordable Care Act could be passed. Next slide.

You know, but how does that really

high cost that we were experiencing in the United States measure up with quality, and you can see that this is the Organization Economic Cooperative Operation, and development data on top economies. Looking across at 2012 and then 2020, you can see how there's been no significant change, the U.S. still spends about two-and-a-half times all other developed countries whether it be private or public costs, and how does this relate to quality. Next slide.

The Commonwealth Fund, which is a private U.S. organization to study and promote healthcare quality and equity looked at the top economies, western economies, and identified that the U.S. despite the high cost was still at 11 of 11 in their overall rankings, kind of midway in quality of care but certainly last in access and efficiency. Next slide.

And hence, we've arrived at the Affordable Care Act in 2010 which really was a monumental change since Medicare establishment and the Social Securities Act, increasing revenue taxes as well as Medicare cuts of approximately $500 billion over the next ten

years would allow to provide universal health coverage, as well as an eventual transition to value these costs and really preserve and enhance the quality of care through various models. The ACA also established two independent boards, the Patient-Centered Outcomes Research Institute and the Independent Payment Advisory Board to study quality of care as well as costs, as well as the CMS Innovation Center that was to develop and test these payment models to optimize value. Next slide.

This was followed by MACRA, the Medicare and CHIP Reauthorization Act in 2015, 2016, and that really ended that physician growth formula and really allowed for near zero growth for locking in Medicare reimbursements to very small annual increases that would sundown in 2020, and then eventually small increases that would be dependent on the value payment track. It was a new framework that would reward providers for value over volume, and would combine the existing quality reporting programs into what became known as the Quality Payment Program. The two main methodologies for this was the merit-based

incentive payment system, which was a fee for service type model with the inherent quality and volume metrics but also more advanced alternative human models that would be initiated, and certainly a more valuable shared risk platform that they were hoping to move institutions towards. Next slide.

Now the MACRA MIPS program was reconsolidated with what was previously known as the volume-based payment modifier and Medicare EHR incentive programs, blending into four categories that would have to be reported. One was quality, with various measures they could report on. In our space, the interventional diagnostic radiology space we would try to measure, report on clotting stenosis measurements and rate of asymptomatic endo carotid artery stenting, major complications, et cetera, and there were several registries that were established to be able to report some of these quality metrics such as the NRDR from the ACR as well as VQI from the Society of Vascular Surgeons. Next slide.

The other three categories were

resources where there was no real reporting required, just through medical claims; meaningful use which was called advanced care information, certified EHR technology and information exchange, also reported through what would become known as the qualified clinical data registries; and then the fourth category to report on was critical practice improvement activities, and this could also be performed through qualified clinical data registries. Next slide.

In fact the MACRA statute under MIPS encouraged the qualified clinical data registries, that was the goal. Next slide.

We had certainly contemplated developing these types of registry structures for our constituency for physicians and interventionalists to mimic the ACR and STS platforms but just failed to do that because many of our physicians were institutionalized and reporting through their larger hospital systems in group reporting structures. But you can see that these QCDRs, these qualified clinical data registries were really a very efficient way to report all performance

categories that required reporting. Next slide.

But other than that, we really felt the need to develop these registries because they really promoted clinical excellence in many ways, from multiple stakeholders obviously, the patients, the quality assurance rate, procedural safety and efficacy, complications, outcomes of these procedures that we were performing and delivering feedback of prospective and serial data. It monitored also for us providers to promote best practices, evidence-based practice improvement. There was a lot of interest from industry as well as the FDA to look at the devices that were being used in our spaces, to expand indications and academia for research purposes, and obviously they could be used by payers and CMS potentially for, because of the granular data that could just assess quality outcomes and resource utilization. Next slide.

And so the SNIS patient safety organization, the Society of Interventional Surgeons was really formed with the endovascular quality initiative initially, a

quality data registry for interventional procedures. Next slide.

And this was certified by the Agency for Healthcare Research and Quality as a patient safety organization. Next slide.

Patient safety organizations really are bound by the Patient Safety Act and Patient Safety Rule that provided a framework for us to voluntarily report to the PSOs privileged and confidential information on patient safety events and procedures, next slide, and created the safe and confidential space protected from medical legal liability reporting in an environment through registries for efficient reporting of allied large data sets, and really compare costs from the collective data to assess how one institution was doing, but we also have requirements in patient safety organizations to feed back the data and educate, audit the data for quality improvement, as well as keeping this confidential and certain restrictions on marketing and research. The primary goal, of course, of these patient safety organizations is to improve patient safety and the quality of

care and hence protecting patients, also providers. Next slide.

We did the early analysis of our ischemic stroke registry. What we saw was the first 1,400 cases that were reported, approximately 25 centers, we looked at some of the important metrics that we consider in ischemic stroke combatting procedures. There was quite a variation in arrival time of these patients to the time that they had the puncture. The amount of revascularization reperfusion that they were able to obtain was also highly variable across the centers, and that really resulted in the outcomes, whether it be early neurological improvement at discharge on NIH Stroke Scales, or final clinical outcomes on a 90-day modified Rankin score that Dr. Saver went through, the importance of that, we saw quite a distribution across the centers including mortality rates that were from five to 40 percent mortality in some of these centers in variation. Next slide.

Our first official PSO quality project and report that we fed back to our sites was in

April 2020 and we decided to concentrate on the workflow of the ischemic stroke thrombectomy procedures looking at the analysis of arrival to puncture times at these centers. At first you could see a gaussian distribution within the centers and approximately 50 percent of these centers were meeting or close to meeting the AHA guidelines for 90-minute arrival to puncture times, but very few meeting the SNIS guideline of 60. Next slide.

And so this NVQI-QOD registry really expanded over the last several years. We merged with the neurological society, the AANS and NPA registries to really have a both open and endovascular interventional procedure registry. We expanded to projecting about 40 sites and will be in about 20 percent of the stroke centers in the United States at the end of the year, and just this last year combined with the Society of Vascular and Interventional Neurology for really being an official registry of all three main neurointerventional vascular surgical societies in the United States, and we certainly feel that the accumulating volume of data will now enable us to continue our quality

mission.

Also, there's been significant movement with academia interested in research, and multiple abstracts of it have been submitted and presented in various physician-led meetings. And the NVQI-QOD registry is a component of the FDA devices for the acute stroke intervention project, as well as developing industry interest to assess our devices that we use in the thrombectomy space as well as, could this be used by CMS or payers as acute QDRs to consolidate and improve that work, or other alternative models or data that support an NCD remains to be seen. Next slide.

So our governance council is composed of the three main neurovascular interventional procedural societies, and this registry governing council of course has components for quality work, research that we hope to be engaged with CMS and payers for utilizing this data for value assessments and clinical outcome assessments. Next slide.

Although I'll be concentrating here on the acute ischemic stroke thrombectomy registry, I want to note that the registry does

have other modules for hemorrhagic stroke assessment, cerebral aneurysm ruptures, cerebral AVM/AVF repair, and we are contemplating increasing that to subdural hemorrhage, intraparenchymal hemorrhage procedural registries as we're seeing increases in both intravascular embolization now as an adjunct or preemptive treatment for subdural hemorrhages as well as new technologies in endoscopic and minimally invasive surgeries. We also share carotid artery endarterectomy and other interventions with the Society of Vascular Surgeons. Next slide.

You can see how powerful these registries are becoming, the NVQI registry over the last five years, but the VQI registry has over 30,000 carotid artery stent procedures and 120,000 carotid endarterectomies, but we are also approaching critical mass of 6,000-plus procedures and 5,000 aneurism procedures. Next slide.

So with respect to the acute ischemic stroke thrombectomy registry, next slide, there are several measures that I would highlight that could be used for and valued by CMS and

the other payers. Dr. Saver certainly went over several of these, but I kind of divided them into stroke intervention processes, time and techniques metrics, obviously time from the patient's arrival to some type of intervention, whether it be thrombolysis or puncture for stroke thrombectomy, and then how long it takes for that patient to be reperfused and blood can be reestablished to the brain to salvage that tissue. Secondly, what type of (unintelligible) successful, was it more than 50 percent, is it complete, or near complete, and how many passes did it take for this person, so you give a time, complexity and a single pass intervention associated with improved outcomes.

As far as clinical outcomes, long-term outcomes, what we really strive for at the three-month mark, functional independence, so the patient has a modified Rankin score of zero to two, and mortality.

Secondary outcomes were earlier neurological improvement, what is their NIH Stroke score at 24 hours, what is it at discharge, do they have significant

improvement, did the NIH Stroke Scale get reduced by eight or more points, was it near normal, zero to one at 24 to 72 hours post thrombectomy.

With respect to complications, we are interested in symptomatic intracranial hemorrhages where the NIH Stroke Scale worsens by four or more points, whether this be with an early reperfusion or delayed infarct transformation hemorrhage; vascular injury such as perforations, cervical dissections, intracranial dissections; residual or new territory emboli, neurogenic emboli; and access site complications.

And furthermore, the other value of these registries because there's so much granular data there, I think it's also important to have some risk or population adjusters within our measures, what is the time from the patient symptom onset to their arrival to the hospital, patient age, comorbidities, the severity of stroke presentation on NIH Stroke Scale, large vessel occlusion sites. And then the imaging selection, CT ASPECTS that you've heard about earlier, core infarction

volumes, if the imaging was done with diffusion or MR diffusion. Next slide.

And what is the power of this data? We did a project at Northwestern here using the NVQI registry, we wanted to reassess the real world evidence and practice improvement of stroke thrombectomy in the U.S. over the last five years. Next slide.

Multiple randomized control trials really have solidified the benefit of endovascular stroke thrombectomy and there's really been a revolution in stroke care of interest, large vessel occlusions within six hours, in 2015 five trials were published fairly rapidly, really one after another, and that data comprised in the HERMES meta-analysis really established that you would need only two to three patients to treat with endovascular thrombectomy to reduce disability by greater than one point on a modified Rankin score. In fact we see that at least 30 to 40 percent of patients undergoing thrombectomy are independent mRS zero to two, at three months.

Furthermore, in 2018 another transition occurred where the DAWN and DEFUSE-3

trials, randomized trials extended the benefit out to 24 hours in certain select populations with advanced imaging selection. So it's quite a powerful technique with a significant interventional time window that was established. Next slide.

And we wanted to look at how is this functioning in the real world, and could we use this registry with success and compare it to the randomized control, you know, optimize data and then assess how the practice improved over time, specifically after the DAWN/DEFUSE randomized control trials expanded this window up to 24 hours, and we stopped at the COVID, pre-COVID March 2020 time point. Next slide.

When we looked at approximately five years data, at that time there was 23 centers that were feeding into the registry for that amount of time. They identified about 3,000 patients using various statistical analyses. Next slide.

And you can see that the majority of 3,000-plus strokes anterior circulation occlusions, the majority MCA occlusions. Patients were severe, presenting with a median

NIH Stroke Scale scores of 16, but only 50 percent of the patients received IV tPA thrombolysis, immediately suggesting that we were offering treatment to populations outside the clinical trials, the initial clinical trials of treating patient within six hours, and that's not surprising after 2018. Next slide.

It is nice to see that the majority of patients were having some type of CT as well as CT angiography imaging to confirm these large vessel occlusions before going to the laboratory, and almost 50 percent of the patients, greater than 50 percent of the patients had some advanced imaging with MR or CT perfusion imaging to assess the core and function volumes, obviously selecting patients more carefully, or too selectively perhaps.

You can see that the ASPECTS scores were also slightly different in the clinical trials, there was 20 percent of patients who had significant ASPECTS less than seven.

If we look at the time metrics, you see that the onset to arrival times were about two hours, and that actually increased from

after 2018, again indicating the expanding interventional time window, but the actual processes and stroke workflow at these hospitals was improving, the 82 minutes versus 113 minutes in 2018, as well as you can see the times going down. Next slide.

The technical outcomes and complications reported were very excellent, 87 percent of patients were able to be reperfused successfully, technical failures about six percent, intraprocedural complications about five percent, and under reporting of the hemorrhage and hemorrhagic transformation we do not have at this time. Next slide.

The symptomatic hemorrhage rate was not in our registry and this was added in a registry update after 2020, you should have that moving forward. In-hospital mortality was about 11 percent, 90-day mortality 21 percent as a total, that increased actually from 2018. Followup was available in about 65 percent of patients, but only about 40 percent of modified Rankin scores were reported, favorable clinical outcomes of 39 percent, slightly reduced but not significantly from 2028. Next slide.

If we looked, compared the real-world data here to the HERMES meta-analysis of the five randomized trials, we see patients that were treated significantly older, presenting with very similar stroke severities, certainly had lower high ASPECTS scores, 80 percent versus almost 100 percent in the HERMES data suggesting larger core infarction volumes of 50 percent, nearly 40 percent receiving IV thrombolysis, also reduced from the randomized control trials within that six-hour window. And successful recanalization certainly significantly increased compared to what was being done in 2015 and previously. The 90-day mRS score was slightly reduced and the 90-day mortality was slightly higher, as you would expect from a bigger population being treated with higher morbidity. Next slide.

So despite these patients being a little older, having less IV TPA utilization, larger core and function volumes, and not selecting them as much as most of the HERMES meta-analysis trials, and the treatment window being larger, we saw that the reperfusion actually was a little better, and this was

probably because of devices, operator experience. Mortality was slightly higher but if you compare it to MR CLEAN, which was the largest trial in the meta-analysis, from the meta-analysis it was fairly equivocal, and the clinical outcomes were slightly less, 39 versus 46 percent, but still greater than MR CLEAN, which was 32 percent good outcome in the intravascular arm of the trial that did not use any selection criteria with advanced imaging. And it certainly indicated that the treatment and benefit of the larger population was likely the result of this, what we called the denominator effect, a larger population, a greater number of patients, the life saving procedure would show some decrease but not significant.

DR. BACH: Dr. Ansari, I'm sorry, please wrap up.

DR. ANSARI: Sure. Next slide.

And when we looked at our practice improvements over the first two years and then the last two years, next slide, next slide, you can see that we certainly after the DAWN/DEFUSE trials were including larger populations with

IV thrombectomy as you would expect, the treatment window was expanded, the comorbidity and age increased, the thrombotic process and workflow and efficacy continued to improve, increasing the puncture and procedure times and increasing reperfusion rates with no significant change in favorable clinical outcomes and despite this, a modest increase in mortality. Next slide.

There are limitations, of course, in registry data. The several missing data elements as I commented on, self-reporting bias and non-adjudicated data, but there is an inherent power of larger sample sizes, and we believe the future will leverage EMRs and PACS imaging data with AI adjudication to improve the quality of this data, and CMS projects with incentivized payments will be able to capture both quality and value-based reimbursement models which will augment this registry work. Next slide.

And the last slide is --

DR. BACH: Please wrap up.

DR. ANSARI: Yes. In conclusion, I think you can see that evidence-based

thrombectomy practices are being mimicked in the real world, that populations are being expanded with still a significant benefit, and that further quality and reporting guidelines will improve followup and will augment the value of these quality reporting registries. Thank you.

DR. BACH: Thank you very much. I would like to move on to Dr. Adnan Siddiqui, who is the chair of the joint cerebrovascular section of the AANS and CNS, secretary of the Society of Neurointerventional Surgery.

DR. SIDDIQUI: Thank you very much, Peter. So, I think it's great that I'm following these incredible talks, Jeff Savers, we'll -- well, starting off with Dr. Koroshetz, a great description overall of this space, followed by Jeff's description of outcomes and Sameer's description of measures that are utilized in these trials.

So what I'm going to try to do -- next slide please -- is cover this material in a slight different perspective, trying to counter the narrative that we don't have enough evidence to support these treatment options.

Here are my disclosures. I have multiple NIH grants, I have financial interests, serve as a consultant and run multiple trials directly related to the materials that we are discussing today, so I'm about as conflicted as a human being can get in this space because everything I do every single day revolves around the neurointerventional space and the trials and the products and the procedures that we deal with. And as noted in my introduction, I did serve, now I'm the former chair, my term just ended this fall, as former secretary of the SNIS and chair of the CR section. Next slide please.

So I appreciate the goals of MEDCAC and I have a long list of slides but I'm not going to read through everything, but maybe if this is part of the public record you can always go back to something, I'll just highlight a few of these as we go through the talk.

And so I want to really focus on step one or point one, which is implications of approving devices without well established evidence, so that is the narrative that I will

try to counter. I think it's a sliding scale, I don't think it's a dichotomous scale, it's continuous. And I think depending on disease entity we have different levels of evidence that are there, but it's not a lack of well established evidence, so let's start point two, this next slide please.

So we'll start off by talking about intracranial aneurysms. What we know about intracranial aneurysms and their natural history is based on decades of experience of treating patients conservatively who had intracranial aneurysms. We did that in the '50s and '60s into the '70s and what we realized was that this condition had about a 50 percent overall mortality, 50 percent, and most survivors had severe disability, only 20 percent without, so it is a major catastrophic disease when the aneurysm ruptures. Next slide.

There are a variety of different types, next slide, yes. So this gives you the overall population and if you look at the overall population, this is worldwide, it's not that big, it's a pretty small number, so

ruptured aneurysms are probably 15 to 20,000 per year in the United States. Next slide please.

And so a variety of treatment options that are available for these, next slide, is that these include open procedures or clipping, or bypasses, and there are a variety of developing endovascular procedures, which is partly what we're talking about today in terms of a real revolution in terms of less and less invasive and more effective treatments that seem to be coming forth. Next slide please. Next slide.

So if you look at the devices that have been approved, the first intravascular device that was approved was back in 1989, clips were approved in the '60s and then progressively we have had this increasing number of devices available, you can see the yellow there. Coils were the first and there were a variety of different stents to constrain the coils in the aneurysm. Then there was this remarkable technology called flow diversion, a different kind of stent, and the most recent innovations are these endosaccular iterations

where you put a singular device into the aneurysm to treat it. Next slide please.

What we know about risk is very difficult to ascertain based on the fact that we have no real good natural history studies based on the fact that we know what the natural history was when the aneurysm ruptured, but what little data we have, one of the most important determinants is the size of the aneurysm, the larger the size the higher the risk, and I'll come back to this in a little bit. Next slide please.

So this was the first major trial that was done. It included a very small portion, one in five aneurysms that had ruptured, and divided them between primary coiling which was the only thing available back then, and clipping, so these were the aneurysms people thought we could treat both ways. It's important to note when you look at the people who were disabled from this procedure after treatment, there was a six percent absolute difference in favor of endovascular treatment. Next slide.

However, this came with a higher risk

of possible need for retreatment with endovascular, so the cure rates were lower but outcomes were better. So this is what we learned from retreatment rates in the ISAT trial. Next slide please.

We also realized that if you followed them long term and you didn't treat them, there was a risk of rerupture, so this is important, it's important to realize that you finish the job rather than leaving the aneurysm untreated completely. Next slide.

However, it was also important to note that this occurred in both categories, it occurred in endovascular more than clipping, but there was no perfect technique for treating people. Next slide.

So the important thing was that when you looked at outcome proportion of patients at five years, five years, long term, it's still quite similar, quite similar. So the differences that you had at one year tend to obviate by the time you got to five years. Next slide.

And so these are some examples that the initial morbidity difference kind of

succeeds, but long term has declined, at about five years. Next slide.

So the rationale that came out of this was if you're treating younger patients, clipping might be a better option rather than older people, but this is not, this is a neurosurgeon from Australia's perspective but it's not dogma, and that part is not clear, but both are effective methodologies, and in most institutions this is a multidisciplinary approach to try to figure out what's the best way to treat. That said, there has been a significant decline in the aneurysms that are clipped and there's a significant increase in the aneurysms that are treated endovascularly. Next slide.

ISUISA was the first attempt to try to categorize the natural history of aneurysms, and it included two parts. The first part included a retrospective analysis which was ISUISA I, and then the second part was a prospective analysis which was ISUISA II, and they presented with different sets of results. So when you look at overall, the initial results with no prior hemorrhage, the rate of

rupture for unruptured aneurysms was exceedingly low, 0.05 percent annually unruptured. However, those that had ruptured previously, it was almost a tenfold increase in risk of about a half percent per year rupture risk. Next slide.

And so when you looked at the treatment options, again, this was in favor of morbidity and mortality, which was slightly in favor of endovascular treatment and clipping, but it was not significant, and what was realized was M&M exceeded the 7.5-year risk in aneurysms which were smaller than ten millimeters, this was ISUISA I. Next slide. Next slide please.

So then, this was a prospective observational cohort study and again, this included about 1700 natural history and then a larger proportion of patients that were clipped. Again, these are older cases, the only endovascular option back then available was coiling, so it was a smaller group of patients. Next slide.

And what we realized in this case was the natural history was more ominous than had

been predicted by the retrospective analysis, so that even in aneurysms that were smaller than ten millimeters there was a risk of rupture, and this was higher for both peer speculation and PCoA. Next slide.

So there is some heterogeneity in the results in terms of location, in terms of size. Now this was a randomized trial done at the Barrow, a very highly experienced center that took all their patients and randomized all of them depending on the day of the week into endovascular versus clipping, and the important thing to note is their results were not that dissimilar from the ISAT trial, with about an absolute difference of seven to eight percent in favor of endovascular treatment, even in the most experienced hands. So this is not lack of data, this is clear data to support that there is a better outcome early on. Now, next slide.

These guys have followed their results for three years and five years and that delta just disappeared just like it did with ISAT at about five years, where the results are quite similar. So endovascular treatment, people recover faster because it's less invasive, but

long term both treatment modalities are effective. Next slide please.

Keep going forward, I don't think we need to cover this. Next slide.

And so this is the one last thing I want to cover here, is that there is a risk of rerupture with lack of complete occlusion. This has always been in favor of clippings but with newer methodologies this is a progressively declining component even with endovascular treatments, so it's important to be able to cure. Next slide.

So this is a meta-analysis that we did and I think it's important to note this Gaussian distribution, that while the majority of ruptured aneurysms hover around six to seven millimeters as is noted in this schematic on the right side, there is a significant proportion of aneurysms that rupture lower than that, at four or five millimeters. So when you see an unruptured aneurysm which is four or five millimeters and you know the natural history following a rupture, how do you decide treatment? This is the essential conundrum that we have and there's only one way to really

deal with this and that is through registry data collection. I think randomized trials would be very very difficult, especially when you have to ascribe a patient to a natural history, I think the natural history is best measured through registry effort rather than through randomization, which is one of the reasons these randomized trials have not been successful in terms of measuring natural history of patients, at least since the '70s when there were no treatment options. So it's important to note that aneurysms rupture at significantly smaller sizes than ten millimeters. Next slide.

And so what do we do? Well, we have some rupture risk assessment score, the UIATS, the PHASES. Then we have complication rate established based on initially the HDE and most recently PMA trials, which measure outcomes. We have angiographic rate; I made the point that this is important and we need to really establish, that the treatment will actually cure the aneurysm. And then we have the re-hemorrhage rate, I think it's exceedingly low in this era. And then we have the

retreatment rate, which is an important determinant of what, if you're doing something, if it needs retreatment what is it. And again, I think registries are very important because they use longitudinal long-term data, currently it's the lowest with flow diversion and highest with coils alone. Next slide.

For ruptured aneurysms, it is essentially the same factors except for the fact that we want to make sure we measure the re-hemorrhage rates and based on all estimations that remains quite low. Next slide.

So moving on a little bit to AVM, these were covered by Walter as well. These are hemorrhagic lesions, here on angiogram you can see these are short circuits seeking arteries and veins that we believe are congenital, rarely can be acquired, and have a natural history again established for the 1950s, the '60s and '70s, when all we did was provide these patients a bed and see what happened and never offered any treatment, and the rate that we established based on that data was two to four percent annual risk of rupture,

and there were some risk features which were higher, some were lower. We knew there was a bump in the rate of rerupture after a rupture that subsided over three to four years, that happened to be the rate of two to four percent. We also realized each time there was a hemorrhage, there was a ten percent mortality and about a 30 percent major morbidity associated with each incident of hemorrhage. Next slide.

And so ARUBA was a trial that was NIH sponsored to measure the natural history versus interventions. A few problems. This trial was stopped over three years. This is a lifelong natural history so we did not really establish long-term efficacy and what we realized was, in a procedure that was done in sort of a multidisciplinary way with majority being treated in Australia endovascularly, when the majority practice treated probably with radiosurgery or microsurgery, which were a smaller cohort, the interventional arm ended up with a higher risk profile for the period that was measured, so next slide. So this -- next slide.

So what this, this is primarily to see the composite from death for any symptomatic stroke. Next slide.

And this was really the reason that what they were hoping is 400 patients and to measure a difference between 12 and 22 percent over five years. The trial, next slide, was stopped at three years with only a hundred patients that really were available to be treated in the trial so you can imagine, 1500 patients were not enrolled in this trial. Next slide.

These were unruptured AVMs and this is the key figure. At about 33 months the primary outcome was ten percent in the interventional arm and 30 percent -- I'm sorry, ten percent in the noninterventional arm and 30 percent in the interventional arm. Next slide.

The way we look at it is clearly the risk of the treatment that was offered in this particular trial for unruptured AVMs was, had significant morbidity but more importantly, was established even in those 33 months that there was an annual rupture risk of about 2.2 percent and -- next slide.

And I think that's really what we came to. Now if you compared this small data set to this much larger data set, this is the NASSAU registry for radiosurgery for AVMs, a singular modality treatment, next slide, you see that in almost 1300 patients were treated with gamma knife radiosurgery, and over a 25-year period, and followed for morbidity and mortality. Next slide.

You see that these curves clearly diverge but for you to note the divergence you need to follow these patients over a longer period of time. So similar to aneurysms and a similar theme that's developing is that we need longer followup and we need registries to measure these instruments rather than singular freestanding trials, so we need to have a registry to be able to measure these outcomes, and that's what I really want my plea to be today, is that it would be great to have coverage for evidence development in a lot of these conditions, because what we need is not one-year data or three-month data, we need five-year data, we need ten-year data. Next slide please.

And so when you look at ruptured AVMs and fistulae, we know there's a complication rate, we believe it varies from procedure to procedure, and the best way to measure it is to carefully articulate it and develop registry efforts like the one we have for AVMs and that was presented earlier. We also want to know endovascular cure rate because the AVM like aneurysm can rerupture if they are not cured. We need to know what the re-hemorrhage rate is, we need to know what the retreatment rates are, and these are rates which are not available freely.

Now let me just caution you that we are talking about less than 5,000 cases per year in the United States, so this is not a large population of patients, this is a small population, and it's very heterogeneous and it's treated in many different numbers of ways, so we need registry efforts to be able to correlate this data long term. Next slide please.

And similarly for unruptured, there's no in difference. Next slide.

And then moving on to acute ischemic

stroke, again, I would not go through the etiologies, these were covered well by Walter, but let's move forward. Next slide.

The goal of treatment is to try to restrict this to the smallest score as possible. Sometimes there is no score and sometimes there is very little to salvage, but there is no imaging modality that we know of that can definitively identify what score is most salvageable for any patient. There appears to be a time dependent effect that, the earlier you treat the more likely you are to salvage, the later you treat the more reliant you are on imaging to identify if we can help these patients. Next slide please.

So again, we have about just shy of a million patients who have strokes, we believe a vast majority of these are of the ischemic variety, and a substantial proportion of these are because of vessels which might be amenable to endovascular therapy. Next slide.

And so when you look at the HERMES, I'm going to just briefly cover this, is the meta-analysis of all the major trials. The most important thing to note is the number

needed to treat for these trials, when you talk about not having enough evidence, the number needed to treat in these randomized trials was 2.6, so for every 2.6 patients you helped one person. The last time we had something this effective was when we discovered penicillin, so this is the most effective surgical therapy that we have ever come across at least in the neuro space, probably in any space for that matter. Next slide please.

So when you look at the meta-analyses by age, by CT, by location, by severity, everything is massively in favor of intervention. Next slide.

And so these initial trials provided evidence for intervention but they had no evidence of what to do when patients come in after six hours, we weren't quite sure about what to do with imaging to see reperfusion, which is an important thing to use. We weren't quite sure if there was value in posterior circulation or distal location, and we weren't quite sure if the only thing we should use is standard achievers versus these other tubes where we suck the clot out. Next slide.

Subsequent to that we have done a lot of work, again, clinical trials. Next slide. This shows the COMPASS trial which showed level one evidence that there was really no difference between outcomes, next slide, between aspiration or thrombectomy, and so whether it was looking at how many vessels we opened up, next slide, or what our rate of good outcomes were. Next slide please.

DR. BACH: You have about two minutes left.

DR. SIDDIQUI: Okay, great. Next slide. So whether there were radiographic outcomes, these were all quite similar. Next slide. Next slide. And they were equally safe. Next slide.

Then we found out that with imaging we could treat patients up to 16 hours, and by the way, the number needed to treat was still between two and three. Next slide. Next slide. And then we went all the way to 24 hours with imaging criteria and the number needed to treat remained between two and three. Next slide. Next slide.

We realized that we needed to get

these patients faster, so there's a lot of technology being developed in terms of figuring out who's got the stroke, where to take these patients, how to get them opened as quickly as possible, and that remains an area of really great importance. Next slide.

So I think there's an evolution of all these treatment strategies from originally IA thrombolysis as Walter said, to aspiration and stent retrievers. Next slide. And there are a variety of different devices that have been approved, most of them with randomized evidence against medical therapy, and now randomized evidence against other approved therapies. Next slide.

And that includes aspiration as well. Next slide. And a variety of different catheters that we can get distal. Next slide. I'm almost done.

So what is still not in the guidelines is what we do about pediatric populations, lower NIH Stroke Scores, poor looking CAT scans, beyond 24 hours, posterior circulation, distal location, these are all areas that are currently being studied with clinical trials

and think I again, these clinical trials whether they're NIH sponsored like the STEPSTONE project that I'm part of which is looking at more distal locations in other populations compared to ongoing trials like ENDOLO and TESLA which are look at other populations, I think we'll have the data. But again, a registry effort sponsored or supported by CMS can really help provide this incredibly helpful and lifesaving therapy for our patients. Next slide.

So I think when you look at the outcomes of these patients, the most important thing to keep in mind is how well the vessel opens up and how well these people do. I think Jeff talked very well about the outcome measures but I want to leave you, I think I'll stop with this, if you go to the next slide I think this might be the last one. Yes. No, let's go back to the previous slide please.

So I think it's important to realize that yes, we started off with very poor evidence 20 years ago and that's why the FDA treated this NRY code which was for revascularization, but in 2021 the devices that

we use we use because we help patients based on reduction of disability, and I don't think we need to repeat natural history studies of the '60s and '70s when we do our therapy. I think these are very helpful therapies but we need better accounting of the procedures and their outcomes and that's best done through a mix of clinical trials such as those being sponsored by NIDS, as well as these registry efforts which are being led by the interventional societies, primarily NVQI-QOD to really measure these longitudinal outcomes, and I recommend five or ten years really to be able to come back to you and demonstrate that these are life changing therapies that do have value, and I'll stop there. Thank you.

DR. BACH: Thank you very much, Dr. Siddiqui, for a very interesting preparation and for staying on time.

We are going to take a break now. We are a little bit behind schedule, entirely my fault. We're going to break until 10:30 eastern time. Please be back on time so we can start with the set of scheduled public comments.

(Recess.)

We are going to start again in a couple minutes. Thank you, welcome back. The next section of the morning is reserved for scheduled public comments. We have nine speakers, each will speak to us for six minutes. I'll ask everyone when you are speaking please turn on your camera and please stay on time, I will warn you when you have one minute left, but given the number of speakers, I'm sure you can understand the importance of trying to stay on schedule.

Our first speaker is Michael Chen, Dr. Michael Chen from the Society of Neurointerventional Surgery. Thank you, Dr. Chen.

MS. HALL: Peter, let me interject, the first speaker is going to be Dr. Katzan.

DR. BACH: I'm sorry, the first speaker then is Dr. Irene Katzan, from the Neurological Institute at Cleveland Clinic.

DR. KATZAN: Great, thank you. Can you hear me okay?

DR. BACH: Yes, we can, thank you.

DR. KATZAN: Great, thank you. So my

name is Irene Katzan, I'm a neurologist from Cleveland, Ohio, and I'm speaking on behalf of the American Stroke Association today. I will be providing the consensus of the expert reviewers from the ASA to the questions that are posed today. Next slide. Next slide please.

Thank you. I have no disclosures. Next slide.

So the first question that was asked referred to specific outcome definitions utilizing the modified Rankin Scale or the mRS. The expert reviewers from the ASA had already an intermediate level of confidence in these definitions. They felt that the proposed outcome that economized the mRS at three was appropriate only if it was used in a trial that had a population limited to severe strokes.

The reviewers also felt that using a decrease in mRS of two or more points from baseline may be reasonable as a primary outcome if the term baseline refers to a premorbid or pre-stroke mRS.

The reviewers felt that there may be a rationale for comparing a post-stroke mRS to a

premorbid mRS if there were future trials that included patients with preexisting disability, but it's important to note that the measurement of a premorbid mRS is only marginal in a rater reliability.

We did not feel it was appropriate to assess change from the initial mRS taken at the time of the stroke, that was the definition for baseline, as it's not possible to evaluate disability in an acute setting, but the NIH has traditionally been used to address the severity of stroke and it was felt to be an acceptable method of measurement rather than an mRS taken initially.

We felt that the data supports 90 days as an appropriate follow-up period. Next slide.

Question two inquired about using administrative data as primary outcome measures and the ASA reviewers have low confidence in using those as outcome measures at all. We felt that there are many confounding factors at both the patient and hospital level such as family support, insurance data, regional resources, that preclude their use as a primary

outcome measure. The discharge disposition is considered the most useful measure from the list but we still felt that discharge disposition is best considered as a surrogate measure of the functional status at three months in studies where the direct assessment of functional status is not possible. One year is felt to be an appropriate follow-up period for these measures of healthcare utilization. Next slide.

The ASA does have high confidence in the use of the mRS and the NIH. They are very familiar to vascular neurologists being used by most in clinical practice and they are commonly used, of course, in acute stroke trials. Regarding the mRS, like all scales it has limitations. For instance, it's heavily weighted towards mobility and it does not include all the domains that are relevant or important to stroke survivors. And because of these limitations, we feel that it's important to include other relevant secondary outcome measures in these clinical trial or possibly even use a composite measure that includes a patient-reported health status measure.

The expert reviewers noted that using shift analysis or utility-weighted analysis of the mRS as mentioned by Dr. Saver this morning provides more information than a dichotomized mRS outcome and there was a strong preference for this type of analysis over the outcome definitions that were listed in question one.

Regarding the NIH, it is primarily used as a study inclusion criteria or to detect early change from the initial stroke severity, and we felt that instead of using it as a primary outcome it's really best used to define neurological complications or perhaps to be included in a composite measure.

The Fugl-Meyer scales are useful as part of the outcomes specifically for intervention trials targeting motor function for patients with chronic stroke. Next slide.

It's important to note that the AHA and the ASA have long advocated for the inclusion of patient-reported health status in clinical research, and there was a scientific statement on this that goes back to 2013 in fact. And this is because the goals of many therapeutic interventions is to alleviate

symptoms and improve health status and optimize quality of life, and these are best discussed by patient report. That said, there are many limitations to the use of the patient-reported outcome measure as a primary outcome in a clinical trial. For example, there's a lack of validated assessment tools to determine the premorbid patient-reported health, methods to handle proxy assessments have yet to be completely sorted out, and there are many factors apart from medical interventions that may impact patient-reported health status scores.

So because of these limitations we felt that patient-reported measures of health status or quality of life should be included as a secondary outcome or perhaps in a composite measure when more data are available. The chosen patient-reported outcome should reflect whether the intervention is intended to provide a narrow benefit, say a specific motor function, or a holistic benefit, in which case a score with more heterogenous components is preferred.

DR. BACH: Dr. Katzan, please wrap up.

DR. KATZAN: Okay, one final slide. These are just the variety of viewpoints on PROMs that we will leave for another time, but if you have any questions, I will be happy to answer. Thanks.

DR. BACH: Thank you very much. I would like to next go to Dr. Lourdes Carhuapoma and please, my apologies if I didn't pronounce your name directly, from the division of neurosciences and critical are at the Johns Hopkins Hospital School of Nursing, and the University of Virginia.

MS. CARHUAPOMA: Thank you. This presentation we were planning on jointly presenting with Noeleen Ostapkovich and Dr. Daniel Hanley.

DR. HANLEY: We want to confirm that you understand that, Peter, and that we will go through three presenter times; is that correct?

DR. BACH: That's absolutely fine. You collectively have 18 minutes.

MS. CARHUAPOMA: Thank you.

DR. HANLEY: I would like to begin by introducing myself as a trialist who, for the NIH has investigated ICH for the last 20 years.

DR. BACH: Dr. Hanley, it's up to you but if you want to turn on your camera, that would be great.

DR. HANLEY: No problem, thank you for reminding me. Lourdes Carhuapoma is a nurse clinician who will give her own bona fides, but she has been studying the area of quality of life in ICH, and Noeleen Ostapkovich is a trial project manager with 25 years experience in running multiple large Phase II and Phase III clinical trials. Lourdes, would you like to introduce the area of quality of life?

MS. CARHUAPOMA: Sure. Next slide. We have no disclosures other than research support for the MISTIE III trial. Next slide.

Intracerebral hemorrhage is a severe subtype of stoke accounting for approximately ten to 15 percent of all strokes and 30 percent of all stroke-related deaths. No Class I interventions are currently available for intracerebral hemorrhage. It is estimated that 50 percent of patients with intracerebral hemorrhage will die within 30 days, and only 20 percent are expected to have a full functional recovery at six months. Patients with an

intracerebral hemorrhage are typically younger in age and have a higher burden of disability than an ischemic stroke, where Class I interventions are available to achieve a greater level of functional recovery. For these reasons the recovery trajectory from intracerebral hemorrhage differs from that of ischemic stroke. Recovery in ICH is prolonged and unpredictable, resulting in challenges in estimating long-term functional recovery and health-related quality of life. Next slide please.

Using data from the minimally invasive surgery with thrombolysis and intracerebral hemorrhage evacuation trial, MISTIE III, we performed a matched cohort analysis using an established severity index to compare ICH survivors with patients who had withdrawal of life sustaining treatment. We used multivariable logistic regression adjusting for six pre-specified variables, five of which include disease severity, age, Glasgow Coma Scale, deep ICH location, stability ICH and intravenous hemorrhage volume. Comorbidities were included to the published severity index

as a factors described influence, do not resuscitate status in patients with intracerebral hemorrhage. This resulted in a modified severity index score which we will refer to as MSI from here on out.

After matching survivors with equal MSI coefficients, withdrawal by treatment of patients at baseline, modified Rankin Scale and EuroQol visual analog scale scores were evaluated at three time points, day 30, 180 and 365.

And I'll now turn it over to my colleague Noeleen Ostapkovich, who will discuss the functional outcome analysis.

MS. OSTAPKOVICH: Good morning, and thank you for the opportunity to present our findings to this panel. As a senior project manager I have been involved in the coordination and management of several large multicenter and international clinical trials in ICH, SAH and IVH for 35 years. Additionally, I have ten years of experience working on a multicenter trial studying arterial venous malformations. I have also led family and survivor support groups, which has

led me to an interest in long-term outcomes of survivors from hemorrhagic types of stroke. Most of the clinical trials that I have managed followed the ischemic stroke model of assessing outcome at 90 days following hemorrhagic event. We have in MISTIE a rare opportunity to look at longer-term outcomes to see if this is a better model for hemorrhagic stroke. Next slide please.

Okay. As shown in the MISTIE III CONSORT diagram, there were 379 survivors on day 365. We wanted to focus on those patients who based on their clinical factors were likely to have poor prognosis for functional recovery. Poor prognosis as related to functional recovery for our purposes was considered to be a modified Rankin of four to five. To determine disease severity, we used the methodology that Lourdes has described. For calculating the MSI scores for all ICH survivors and those patients who had had withdrawal of life sustaining treatment, which we refer to as WoLST. Using the MSI scores for WoLST and survivors, a matched cohort of 263 survivors with poor prognosis were identified.

However, due to variants a second match between WoLST and poor survivors was performed using the individual severity coefficient from the multivariable regression model, and this resulted in a cohort of 104 survivors. Next slide please.

This table shows the characteristics of the final match of the 104 survivors compared to WoLST. The only variable when matched on the coefficients from the multivariable regression model that did not match was comorbidities. The matched cohort of 104 survivors was then followed for functional recovery and disposition at 30, 180 and 365 days following their hemorrhagic event. Functional recovery was evaluated using the modified Rankin Scale. We did use the dichotomized outcome of zero to three to be considered a good outcome. Next slide please.

This slide shows the mRS distribution of the cohort at each follow-up visit. At day 30 all patients are at a Rankin four or five with only 40 percent in the acute care facility, 44 percent had progressed to rehab or home, and 17 percent were in a long-term care

facility. The biggest improvement in mRS is from 320 to day 180 as seen in the reduction of patients who are mRS five. By day 180, 56 percent of patients had transitioned to home. There is continued improvement at all mRS levels by day 365. Next slide please.

If we take a closer look at day 365, 72 percent or 69 of the patients who had been deemed at 30 days to have a poor prognosis were living at home. Of the patients living at home by day 365, 56 percent had achieved an mRS of zero to three, which we consider to be a good outcome. An mRS of zero to three means that these people are independent of ADLs, can walk and are able to be left home for at least eight hours a day. They require minimal assistance in the long term. Our data shows that many ICU patients with clinical factors that suggest poor outcomes when given time of up to a year can achieve a favorable outcome and return to home.

My colleague Lourdes will now present our patient-oriented health quality of life data.

MS. CARHUAPOMA: Thank you, Noeleen,

next slide please.

As an acute care nurse practitioner in neurocritical care at Johns Hopkins, I've cared for patients with stroke and their families for nearly 15 years. As a doctoral candidate at the University of Virginia my clinical experiences with this patient population have inspired my research interest which focuses on improving the quality of informed shared decision making within the context of intracerebral hemorrhage. We care about health-related quality of life outcomes because it matters to our patients and families. When we talk about the families of critically ill and intracerebral hemorrhage patients they want to understand what type of quality of life their loved one can expect to achieve, and based on this information they make consequential goal-secured care decisions to continue, limit or withdraw life sustaining treatment. While these decisions are highly individualized, we simply do not have sufficient quality of life data to provide to patients and their families facing these difficult decisions.

As opposed to an externally determined score such as the modified Rankin Scale, patient-reported outcomes represent the patient perspective, not the clinician perspective. It is for this very reason that there is a role for evaluating patient-generated health-related quality of life in interventions for stroke. I hope by the end of this presentation that you will share my perspective and will place the patient narrative at the center of outcome measurements in stroke trials.

Now referring to the CONSORT diagram, using the same methodology that I previously described to assess functional outcome, we evaluated the EuroQol visual analog scale scores and disposition of the matched survivors at three time points, day 30, 180 and 365. As shown here in the CONSORT diagram, there were 61 participants in MISTIE III who had withdrawal of life sustaining treatment and 379 survivors. Of the survivors, 90 were matched to withdrawal of life sustaining treatment patients by exact MSI coefficients. Next slide please.

Thank you. At baseline there was no

difference noted between patients who died of causes other than withdrawal of sustaining treatment, patients who had withdrawal of life sustaining treatment and matched survivors, with the exception of deep intracerebral hemorrhage location. Next slide please.

This slide shows the disposition of ICH survivors matched to patients who had withdrawal of life sustaining treatment over time. At day 30 following injury, referring to the gold bars, the highest percentage of matched survivors were transferred to a rehabilitation facility, followed by one-third remaining in an acute care facility. By day 180, referring to the blue bars, approximately 25 percent of survivors were in a long-term care facility, but 65 percent of matched survivors returned home. At one year, noted in green, a small percentage were in a rehabilitation facility, approximately 20 percent were in a long-term care facility and 73 percent of matched survivors had returned home. These findings suggest that the return to home takes time to achieve but it indeed does occur.

When we have discussions with families of ICH patients that we deem to have a poor prognosis, we often inform families that there's a high likelihood that their loved one may require care in a long-term care facility because of their expected severe deficits. Therefore, we were interested in comparing the proportion of matched survivors to patients in the general population over the age of 65 that were discharged to a long-term care facility after a major hospitalization. Using data from the Medicare Payment Advisory Commission data book we demonstrated that the proportion of matched survivors in MISTIE III living in a long-term care facility at age 65 were nearly equal to the 22 percent of Medicare recipients discharged to long-term care facilities after hospitalization. Next slide please.

Thank you. The EQ-5D instrument includes a short descriptive system and a visual analog scale known as the EQ-VAS. The EQ-VAS is a quantitative measure of health outcomes and allows the respondents to self report their health state on a vertical visual analog scale ranging from 100, best imaginable

health state, to zero, worst imaginable health state. It is patient generated, it is well validated, it is obtained in less than one minute, minimizing patient burden.

We evaluated the mean EQ-VAS score of matched survivors by time and disposition which is recorded here. At day 30 the mean EQ-VAS score of matched survivors living at home, referring to the green bars, was higher than those living in a rehabilitation facility, long-term care facility or an acute care hospital. We see a similar trend at day 180 and 365 with matched survivors living at home having the highest mean EQ-VAS score. At day 365 the mean EQ-VAS score of matched survivors living at home approached the U.S. population norm of 74.9 for age matched individuals who had never experienced an intracerebral hemorrhage. It is clear from this data that returning home makes a difference in health-related quality of life. Next slide please.

Please click further, thank you. We took a closer -- sorry, the slide before please. Thank you.

We took a closer look at the mean EQ-VAS score across three groups at day 365, and go ahead and click please. Sorry, the slide before, the slide prior, slide prior please. Thank you.

We took a closer look at the mean EQ-VAS scores across three groups at day 365, all of which displayed similar demographic and clinical characteristics. All survivors enrolled in MISTIE III had a nearly equal mean EQ-VAS score to survivors matched to withdrawal of life sustaining treatment patients. Matched survivors living at home had a higher mean EQ-VAS score. For all groups the mean EQ-VAS score approached the U.S. population norm. Next slide please. Thank you. Please click to show the material. Thank you.

When we reviewed the rationale for withdrawal by sustaining treatment from the MISTIE III case report forms, we found several factors that may have influenced decisions to perform withdrawal by sustaining treatments. Dependent outcome anticipated was the most commonly cited reason. Please click.

Having anticipation of dependent

outcomes influenced the decision to withdrawal by sustaining treatment. Please click. Among patients who died as a result of withdrawal by sustaining treatment, dependent outcome anticipated was cited 62 percent of the time as the reason to withdraw supportive measures.

Thank you, and now Dr. Hanley will summarize our findings and conclude our presentation. Next slide please.

DR. BACH: Dr. Hanley, you have -- Dr. Hanley, I'm adding a minute for injury time due to the slides, so you have about three minutes and 20 seconds.

DR. HANLEY: Thank you. This is just like an NFL game, you're doing it wonderfully.

I think it's clear that if you follow the ICH patient out to a year, and it's the same story as severe ischemic stroke, you see a lot more recovery. And the second thing that's quite clear is that health-related quality of life data is very important. We are not saying anything about decision making in withdrawal of care.

There are two major points we would like to make to CMS. One, that ICH and all

brain bleeding groups should be evaluated by CMS as a separate category since they represent the most severe category of ischemic stroke. Second, patient-reported outcomes utilized with the well validated EQ domain, whether it's the five dimensional domain or the VAS, which is very simple, should be a primary outcome of concern for CMS. The more detailed patient-reported outcomes could be a secondary outcome.

In terms of how confident we are that using the five, that, the EQ-VAS for quality of life, we believe it adequately reflects the patient experience in the context of cerebrovascular diseases and we would answer yes, it should be included as a standalone meaningful measure of health outcome research and yes, it should be included as part of composite and primary health outcome and the measures, that the detailed quality of life measures, and there are many of them, stroke impact scale, the details coming from the EQ-5D, all well validated, should also be important to CMS and its mission for the American patient.

So in summary, ICH is different from ischemic stoke and should be treated differently. Thank you very much.

DR. BACH: Next up we're going to have Dr. Michael Chen from the Society of Neurointerventional Surgery.

DR. CHEN: Clemens, perhaps you should go ahead and start?

DR. SCHIRMER: Yeah, thank you, Mike. So I'm Clemens Schirmer, I'm part of a group presentation if the chair will allow that, just confirm this. We're representing as mentioned here, five societies.

DR. BACH: Sure, so we'll pause here for a second, this is news to me. So Dr. Schirmer, who else is speaking?

DR. SCHIRMER: We were going to split this up between myself and Dr. Chen. I was going to tackle the first two questions, Dr. Chen the other two.

DR. BACH: Okay. All right, that's perfect. Why don't we start with you then, Dr. Schirmer, and the two of you have 12 minutes.

DR. SCHIRMER: Thank you.

DR. BACH: Is that okay.

DR. CHEN: That's fine.

DR. BACH: Thank you very much. So first up is Dr. Clemens Schirmer, from the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons.

DR. SCHIRMER: Thank you, yes. I represent those societies as the chair of the joint section of cerebrovascular surgery and if could just go to the next slide please, these are our other members of the group that weighed in here but as mentioned they won't all speak, and hopefully that will be to your benefit.

So going right along with what was shown before, the questions that were posed to us were about primary health outcomes. We as a group after some discussion felt mostly confident about using mRS more than three, as well as the measure of an mRS less than three or equal to the pre-stroke mRS.

We felt less confident about other kinds of stroke and also the option that was mentioned pertaining to the decrease of the mRS of more than two points.

We want to note here that the modified

Rankin score is weighted and a numerical change in the score is highly dependent on the spectrum and where the patient falls onto that spectrum. If we could go to the next slide please, it has on the positive side been found to be vary fairly reliable, as has been mentioned, it is used in daily life by a lot of people, a lot of clinicians that are highly trained and have a lot of high inter-rater reliability. It does improve with structured interviews, that has been found as well. It is not clear that structured interviews are used in daily life very much, and overall the construct and the convergence validity have been well documented as well.

DR. BACH: Dr. Chen, you might want to mute your microphone. Dr. Schirmer, go ahead.

DR. SCHIRMER: Sure, thank you, sorry about that. And we do need to consider the comorbidities and socioeconomic factors when applying and interpreting the modified Rankin score. Next slide please.

A couple of other points we wanted to make here, as a commentary, we do think that 90-day length of followup seems most

appropriate, it is a standard length of followup that aligns with some other measures and ways we think about patient followups as well. Of course the mRS cutoffs depend on the measure being studied and it should be calibrated based on the subgroup from which part of the mRS less than three group for example would indicate functional independence. Composite endpoints do include mortality but may not necessarily reflect the primary concern which is in stroke the disability that the patient incurs afterwards. To put that to a point, you know, we have lots of patients that when faced with a choice of an intervention that will leave them dead versus alive, they're less concerned about the dead part but mostly concerned about the disability part they may incur if we get them through that surgery. And better choices and better endpoints substantially strengthen the trial power of a given trial size or may reduce the sample size without loss of statistical power, and I want to make a comment about that, so with the next slide.

The mRS scores are typically not

normally distributed and the sample size calculations are sensitive to this. And there are a lot of studies that ignore this little tidbit and use normally distributed statistics to come up with sample size calculations and other analysis, and that is a hindrance to developing a valid analysis and outcomes and conclusions from said analysis. Next slide.

Delving right onto question number two, this is going to be a little bit quicker. We were most confident about the discharge disposition to rehabilitation or home versus inpatient facility. We drew a line there with our colleagues from the American Heart Association, and were less confident about some of these other measures that were mentioned as choices, hospital length of stay for the index procedure, we do believe that the length of stay is highly variable depending on comorbidities, hospital services, plus there are things like weakened effects of physician preferences. And also the number of unscheduled readmissions related to cerebrovascular disease, which we feel is a very sparse measure, it doesn't happen that

often. And next slide.

This also has been looked at before, the determination of hospital discharges and discharge disposition status at an acute admission is extremely important for stroke management and the eventual outcomes of a patient with stroke. And there's a paper cited below there that looked at the discharge disposition patterns in Tennessee, and it was associated with the key patient characteristics of selected demographics including race, clinical indicators and insurance status. So in other words, these measures may measure a lot of things about our patients but not the individual outcome related to their stroke care. It is most likely to measure the effects or the qualities of the local system of care, the local health system of care again, rather than individual systems of care.

With that I'll move on and let Dr. Chen speak to the other questions. Thank you.

DR. CHEN: Thank you, next slide. So my name is Michael Chen, I'm currently serving as the president of The Society of

Neurointerventional Surgery, and along with five other organizations we really have a joint response to the four questions posed and appreciate the opportunity to voice our input.

Now with regards to the choice of outcome measures when looking specifically between modified Rankin Score and the NIH Stroke Scale, I think we very much are much more in favor of the modified Rankin Scale. It is designed to measure disability as opposed to the NIH Stroke Scale which is initially designed to measure the severity of deficits. This has been outlined by earlier speakers in a lot of detail.

Suffice it to say from a perspective of physicians who perform these procedures and in terms of the clinical relevance to us, it's important to realize that the NIH Stroke Scale is, can very much not represent the degree of disability. For example, you could have an NIH Stroke Scale of four in somebody with a complete aphasia, or somebody who has the inability to swallow can have a score also less than four, and so those would be, you know, not well captured in terms of what meets the needs

of the patient. So as a standalone primary outcome measure, we feel that NIH Stroke Scale is not designed for this and because perhaps it has been used quite, very prominently over time, it may have over time created sort of a life of its own in terms of the amount of meaning that's attached to it, so I think that's important to keep in mind.

So as mentioned earlier, the modified Rankin Score is what we very much are aligned with, and in agreement with the previous speakers we do feel that it should ideally not be used in a dichotomized fashion but more in a weighted or utility weighted manner, to account for the varying degrees of differences and the distribution of modified Rankin Scores between each of the, you know, zero, one, two, three, four, five and six. Next slide please.

And so this is just a graphic representation of what we were talking about earlier, there's a wide variation in the sensitivity of disability measures and the categories are quite large just in terms of their meaning and how often patients are within these scores. Next slide please.

So as you mentioned earlier, there's some significant concerns with NIH Stroke Scale. Even if you were to sort of group it into different categories, say zero to ten, ten to 15, or greater than 20, I think even within those categories, or if you want to look at a delta of the NIH Stroke Scale, it may not, though it may be easy to capture because it's so widely measured in all sort of stroke accredited hospitals, it's not something that I think is as valid when the concern is for measuring disability which is, you know, generally the primary outcome measure we care most about for stroke patients. Next slide please.

So lastly, we just wanted to comment, and mostly just reiterate what's been mentioned earlier about the health outcome measure with regards to patient-reported outcome measures. We very much agree and support the importance of patient-reported outcome measures. With regard specifically to EQ-5D, we know it's very widely used and very well validated, you know, across the five domains. However, there seems to be less attention to specific realms of

speech and cognition, which are highly relevant to stroke patients. So if anything perhaps, you know, if this is used in addition to other patient-reported outcome measures, perhaps those measures which can address the concerns for speech and cognition would I think better represent the needs of stoke patients. Next slide please.

So additional points we would like to make EQ-5D is that the norms have to be established and hopefully adjust, you know, have additional measures to account for the potential deficits it has with regards to measuring the needs for stroke patients. So, next slide.

Okay, and that's all we have and we appreciate the opportunity to present our input. We do have several other speakers including Dr. Jayaraman, Dr. Milburn and Dr. Hirsch in case if we have a few more minutes if they wanted to add any additional points to what Dr. Schirmer and I mentioned.

DR. BACH: Thank you, Dr. Chen. We, just to clarify, I have Dr. Hirsch, Jayaraman and Milburn listed as speakers, so the truth is

they collectively have 18 minutes to speak to the committee. I'm not suggesting if they don't have material they shouldn't -- they should feel free to use that time, but there's no pressure whatsoever.

DR. HIRSCH: Dr. Bach, to clarify, this is Dr. Hirsch from the College of Radiology. We've ceded our time to Dr. Schirmer and Chen for the aggregated 30 minutes you just identified. I have no additional comments other than to fully support those that they've made.

DR. BACH: Okay, thank you, Dr. Hirsch. And also for Dr. Jararaman and Dr. Milburn, there's later a period where the panel can ask questions of the presenters, and you should consider yourself included amongst that group if you would like to participate in it. Dr. Jayaraman or Dr. Milburn, feel free, do you have additional comments, or not?

DR. JAYARAMAN: This is Mahesh Jayaraman and similar to Dr. Hirsch, I conceded my time to the joint presentation by Doctors Chen and Schirmer. I don't have any additional comments at this time. Thank you.

DR. BACH: Okay.

DR. MILBURN: This is Dr. Milburn. Similarly, I'm representing the American Society of Neuroradiology, and thanks for being inclusive of all these neuro societies, and I also cede my time to Doctors Chen and Schirmer, and agree with their comments.

DR. BACH: Okay, wonderful, and thank you very much for the clear presentation and the organization that clearly went into it.

This means we get to break for lunch early so everyone will have time to order the souffle. I propose we break now even though it is only 11:10 eastern right now, and we will take one hour, actually let me propose we take 50 minutes, five-zero minutes, and we come back at noon eastern time.

Is there any issue with that, that is a change in the schedule. CMS, do you have any issue with a shift in the schedule in that way? That would bring us back at noon eastern to begin questions to presenters 45 minutes early. Do any of the MEDCAC panelists, you can text me privately if that messes you up in some way and I can reconsider, or if it doesn't mess you up,

we'll just add it on the schedule.

MS. HALL: That's fine, Dr. Bach.

DR. BACH: Okay, thank you very much, I will see everyone at -- oh actually, I'm sorry, we have a panelist who cannot come back on time, can't come back ahead of schedule, so we're going to go back to our originally scheduled schedule, pardon me for saying that twice. At 12:45 Eastern we will reconvene for questions to presenters.

(Recess.)

Good afternoon, everyone, I hope everyone had a good lunch break, were able to catch up on emails and things like that if that was needed.

The next period of time which will be approximately one hour but is as needed, gives an opportunity for the MEDCAC panel members to discuss with the presenters issues that arose during the presentation, or any other questions that are relevant to the later discussions this afternoon. I encourage the panelists to ask questions that will help them eventually answer the, do the voting that's going to be required or otherwise flush out the discussion.

This is more difficult to do in a Zoom environment than it is in person where it's easy for me to identify who would like to ask questions, but for the panelists, we can do a couple of things here. If you'd like me to call on you, I think the easiest thing is to chat towards me, either towards me or toward everyone, whichever you prefer, but just so I know. You can try raising your hand as well. I found that sometimes forget to unraise their hand which can confuse me, but I'm just going to take questions in the order that they appear. I do not ask questions, I'm just here to moderate.

In terms of the presenters, it's my strong preference that you address questions to presenters, to specific presenters. In this case we had a couple of public speaker kind of groups who spoke and so in that context, those groups, there was a group of three and then there was a group of five I believe, in those contexts the group can select whom they would like to answer or address the question, but I think that will work well enough if everyone's okay with that.

So the floor is open if you would like to chat with me now or whenever that you would like to ask a question, or raise your hand and I can call you on you. And I don't have, by the way I don't have a full, I can't tell if all the presenters are on line here, I think I see most of them, and I'll go through and take a census here.

MS. HALL: Peter, I'm taking roll right now.

DR. BACH: Okay, thanks, Tara.

If you're struggling to think of questions, I'd encourage you to look at the voting questions and see if they are sparking interest in questions or things you would like clarity on.

DR. THOMAS: Peter, Greg Thomas here, I have a question.

DR. BACH: Sure, go ahead, Dr. Thomas.

DR. THOMAS: For Dr. Saver, thanks for your excellent presentation. One of your discussion items was using weighting utility ordinal analysis and as I recall you had some proportions potentially for weighting. How does that work, is there multiplication there

that goes on.

DR. SAVER: Yes, thank you, Dr. Thomas. Each level is given a, or each patient is given a score and then that score is averaged across the treatment group, so you have an average utility weighted score in the treatment group and in the control group and you compare those, and to some extent you can then switch to using continuous statistics if you have 15 or more many samples, which gives you more, it may give you a bit more power than ordinal statistics would. In addition, it at least weights the levels according to a patient and provider preference rather than just the simple order of the ranks.

DR. THOMAS: So you mentioned earlier that continuous analysis, and I would concur, you get more power and as I read the material, sample size is an issue here, so it seems like a continuous variable would allow one to use a lesser sample size, so is that, is the continuous variable a futuristic model or is that particularly to the weighted ordinal analysis, shift analysis, or is there another way to use a continuous variable to get more

power?

DR. SAVER: Sure. Well, the weighted ordinal analysis I think is, part of the way toward a continuous analysis but because each patient score is discrete, it becomes semi-continuous or continuous at the group level but not the individual level. There are individual measures that are continuous, for example the academic medical center linear disability scale and other measures that have tended to use item response banks to be able to cover the entire spectrum of outcomes with enough precision, you don't want to ask 150 questions of every person, so with item response banks you're able to iteratively focus in where the person roughly is and then narrow them down there, but those are a little more impractical at the bedside because you need computerized responses in real time to guide the patient or informing, so they've not had wide uptake in clinical trials.

DR. THOMAS: Thank you.

DR. BACH: Thank you, Dr. Thomas, you can put your hand down. Dr. Lahey, you're next and you can also put your hand down.

DR. LAHEY: Thank you very much. I just had a question for the group of Ms. Carhuapoma, Ms. Ostapkovich and Dr. Hanley. I think one of you talking about the intracerebral hemorrhage and the quality of life as a result of that, you gave us the impression that returning home is very very important in reaching a high quality of life as if it were an option or a decision, clinical decision whether you would send, as a physician taking care of a patient, whether I sent the patient to some inpatient facility or home. Isn't it rather that that's not an option, any patient who is well enough to be discharged to home already is in a much more favorable group, they're going to do a lot better? In other words, sicker patients go to inpatient facilities than less sick patients.

DR. HANLEY: Maybe I should answer that. Yes, that's true. We did not, and we're not suggesting that pushing people to the home improves either their function or their health-related quality of life, but in the data we showed and in other data that comes from the MISTIE and the CLEAR trials, when they are home

there is less depression and the quality of life that they self report improves. And I would point out that that quality of life is different than the utility values that we saw in ischemic stroke and have been established in ischemic stroke. That was the main point, not that going home alone makes somebody better, this is as you suggest, driven by the condition of the patient.

DR. LAHEY: Thank you.

DR. HANLEY: But let me say one other thing. The reason we focused on that is the first two questions, that the family of a brain hemorrhage patient, because the brain hemorrhage patients almost never can communicate, ask will the patient live, and then the second one is will they be able to go home, and the third one is the quality of life issues that are addressed by the first questioner, who correctly identified that continuous is better. The weighting with utility is probably quite different in hemorrhagic stroke than it is in ischemic stroke.

DR. BACH: Thank you very much.

Dr. Speir has a question.

DR. SPEIR: Yes, thank you. I'd like to address this to Dr. Ansari and then all the neurosurgeons if they have any thoughts about it. I was particularly appreciative of the focus you had on the development of the clinical registries within the neurosciences and how that has expanded over these years. As many of you may know, that's, the registry has been one of the mainstays in my specialty in cardiac surgery since 1987 and we now have 7.3 million patients or thereabouts that we analyze twice yearly by both providers of practice and then as our entire specialty. We were part of the language for the QCDRs in the MACA Bill in 2016, but the paradox is despite the support we've had toward others expanding the registries we're now finding that support waning and are pulling back in support of the QCDRs through our public policy arm, predominantly because of the administrative cost and how bulky it is within the individual institutions to maintain such a registry.

The question to you, and to all of you is as you see the registry grow within your

specialty and in others, how do you anticipate handling the size of the volume of data and the coexistent costs that are individually borne by the practices and by the hospitals as these are not made up and supported by CMS, and is there any appetite for seeking to have that? One of the goals as we're developing our recommendations here that these data points, particularly around these new and evolving technologies, can be followed as Dr. Siddiqui was making the case for over the coming years to see the success of the treatments, and can that be additionally supported by CMS, particularly in the climate where at least for the surgical practices they're seeking to decrease the reimbursement, as many of you know, between five and 10 percent.

I know that's a multiheaded dragon that I just asked, but I'd be interested to know what your thoughts are.

DR. ANSARI: Thank you for your question. Yeah, we have the same concerns, it's hard to get traction. I think as I noted in my talk, we have about 20 percent penetration of the stroke centers and I think a

lot of the resistance is the cost, not just the cost to the practices but even the hospitals, in developing enough or requiring enough staff with expertise to fill in these pretty extensive registry data points. You need, for a registry to be valuable you really need the granularity and the explicit data required as well as the followup, so it can be quite a tedious task and an expensive task as you mentioned.

And then for a lot of these practices being hospital based they don't really need to report in the mixed form because they are large group practices or they're institutional through the hospital, and so the financial benefit is not really, you know, is not really applicable to many of them.

So we saw from our sister registry, the EQI, that they had a QCDR but they stopped that as well. And so are there other roles for these registries, can they be tied to reimbursement through some type of payment additions through CMS or the government that would support this endeavor, because we know the value is there, we know that these can be

highly valuable, and with enough funding or the appropriate funds flow towards this type of true quality data, I think you can make an impact. But yeah, I think monetarily the question, I don't have any answers either.

DR. SPEIR: Just one additional point, in the Commonwealth of Virginia we took our 19 centers that perform open heart surgery in lengthy EVO-4 discharge financial data and linked it to the episode of care reported within our STS database, and we now have about 150,000 patients where we're able to see the cost benefit for improvement of the clinical initiatives that we had and whether it's in atrial fibrillation or transfusion or early extubation. Within the MACA Bill there was language that directed CMS to provide the cost data and make it available so we could link it to our STS clinical data. The problem is CMS couldn't do it or wouldn't do it, so we're trying to continue to urge them to make that available so we can show what is the real holy grail and that's value, it's showing the cost benefit for the quality improvements both for the technology as well as our clinical

outcomes, but I hope that you will be supportive of us all as we're moving that initiative forward.

DR. SIDDIQUI: Alan, I'd like to chime in there a little bit about the fact that you guys are certainly the trailblazers with the STS registry or more recently the structural heart, the way structural heart has been transformed by the work that's been done with the TVT registry, or the Society of Vascular Surgeons and how that's allowed procedures like TCAR to really become part of the mainstay. I think registry efforts are a critical component of our ability to be able to interpret data that's garnered through trials which have specific selection criteria and see how it applies to the broader populations.

I think the fundamental question about financing these data gathering exercises is a pivotal one, and that's where I believe CMS can really come into play the way that the TBT registry was covered for evidence development. I think the NVQI-QOD, which is a singular registry by all your surgical, neuroradiological and neurological

interventional societies, they all have signed on, they all contribute to it, they have a patient safety organization. If we could get support with coverage for evidence development, you would be able to gather data in a lot of these conditions longitudinally.

Because while I completely subscribe to Jeff Saver's position with mRS at 90 being really appropriate, I do believe CMS has concerns, should have concerns about what happens a year later or five years later, and the way to do that is with these registries. And the way to do that --

DR. BACH: Dr. Siddiqui, I'm sorry, just some ground rules. I appreciate the comments of course. If possible, I'd like to keep it that a single presenter answers the question and that if another presenter wants to add, that's terrific, but please try and be quite curt, brief in your remarks.

The other thing I just want to clarify, it's a subtle distinction, but the work of this committee is around evidence and coverage, not about payment policy. Everybody knows that in the real word these things

interact, including the people at CMS, but we're very much today focused on a large set of complicated questions regarding measurement and evidence, so if we can all stay focused on kind of sifting through that complicated area, that would be great.

DR. SIDDIQUI: Sure, Peter. I did, I believe Alan specifically mentioned my pitch. The point is that the data gathering exercises which are what we're talking about, trying to gather evidence, it is costly, but the best --

DR. BACH: No, I'm not disagreeing, and I'll chastise Dr. Speir later for getting us off topic.

Dr. Thomas, I don't know if you still have your hand up, or are you putting it up again?

DR. THOMAS: It's my left hand now, not my right.

DR. BACH: Sorry, it's hard to tell.

DR. THOMAS: A question for Dr. Ansari. So some of the panelists and such have, and speakers have talked about using the modified Rankin Scale at 90 days, but it looks like there's a challenge in the registries that

you mentioned trying to get that data, and maybe related to some of the comments earlier, but I think it's about 35 percent of patients not having that, and there might be a selection bias for sicker or less sick patients having that, so how do we handle that challenge?

DR. ANSARI: Thank you for the question. Yeah, I think there's two real methodologies to improve that. We've been taking a lot about that's going to be our second quality project, to actually report back to the sites, and the registry's job to identify for reporters, try to augment their participation in identifying an mRS at the 90-day mark and longer if possible, we try to recommend up to a year worth of mRS outcomes.

But the other part is certainly that, you know, a lot of institutions don't record that, even at high academic centers when stroke patients will come back and it's just not in their chart. And so again, it comes back to how we modulate that behavior at the clinical level and you know, I think actually going back to the last question really, if we had a methodology where data was important to an

institution and a practice whether private or public and that that data had to be reported for an incentive, whatever that may be, a penalty or an incentive, that you will find institutions supporting that data and having that available where in the future these registries will be provided through EMR and direct access through EMR, an ability to extract that information, and if it's in the EMR there will be an incentive for institutions to provide that.

DR. THOMAS: Thank you.

DR. BACH: Thank you. I need to interrupt also. I see discussion, I apologize for this, I see discussion going on amongst the panelists in the chat with the presenters. I don't, Tara, you can weigh in on this, but I don't think those chats are publicly available and the rule --

MS. HALL: No, you're right, all conversations about the MEDCAC needs to be done in the open forum.

DR. BACH: Sorry, we're all very comfortable chatting with each other, I hate to be a cop here again, but if you're going to

discuss the contents of the meeting in any way of substance it needs to be done verbally in this Zoom environment. Please reserve the chat for logistical things like complaining that I missed your hand being up or things like that.

So, there were important comments that I just saw, so I'd like to give a chance for people to make them. We will have a chance for the panelists to discuss things amongst themselves after this discussion with the presenters, we'll start to then just sort of speak amongst ourselves so I'll ask you to save it until then, although you can certainly weave it into questions or comments.

Dr. Stephens, I believe you're next.

DR. STEPHENS: Thank you. So this question is for Ms. Carhuapoma. I understand that you were very much a proponent of listening to the individual and their family or caregiver but I did hear, I was very struck that across all the other presentations there seemed to be a consensus that there is sort of an inherent flaw with relying on that information, either that individuals would be unable to assess their pre-stroke abilities or

disabilities, or that it just simply introduces a bias. So I wanted to understand from your perspective, one, is that the case, and two, does that in any way, if it does introduce a bias, is it mitigating some of the other biases that people are experiencing as patients in the system, so I'd like to understand your perspective and your response to that.

MS. CARHUAPOMA: Thank you for that question. I think, you know, hopefully quality of life is significantly important to patients and to families and it really informs the decision making process. So whether or not there is a baseline in terms of health-related quality of life, what really matters is post stroke, and to the comparison in terms of the general population. You know, I think that we can all agree that the EQ-5D is well used, it's well described and it is well validated, perhaps not within the stroke population. However, what people really want to know post stroke is how they're going to compare in terms of the general population, and I think that, you know, sure, that certainly introduces a bias in terms of not being able to get baseline

data in terms of health-related quality of life, but what really matters is post stroke and what their trajectory is going to look like post stroke. I hope that answers your question.

DR. BACH: Thank you very much. Dr. Miller.

DR. MILLER: Yes, thank you. I have several questions actually if that's all right.

DR. BACH: That's fine. Brian, why don't we do it, I don't know if they're all for the same person, but we'll ask a question to a person, allow for an answer, and then we'll go back to you for the next one.

DR. MILLER: Sounds good. I have one quick question first for Dr. Hanley. I heard discussions of course about embolic stroke and lacunar stroke, and then you talked about intracerebral hemorrhage and hemorrhagic stroke. Do you think that perhaps, and obviously those are distinct clinical populations and they have slightly different although maybe somewhat related time courses, but different also clinical outcomes. Do you think that perhaps different outcome measures

for those different populations would be helpful for Medicare beneficiaries, as in we should maybe look at patients with embolic strokes slightly different from patients with lacunar stroke as someone mentioned, fine motor movement being more important there versus, says a modified Rankin Scale which of course, you know, fine motor movement for intracerebral hemorrhage is probably less relevant compared to a modified Rankin Scale, so I would be interested in your thoughts on that.

DR. HANLEY: The short answer to the question is yes, and that is what Lourdes and Noeleen and I were trying to show with a small bit of our trial data. Slightly longer and I know not too long, stroke patients rightly because of the data you showed and their families, want to know will I live, will I go home, what will I function at home, and the real question is moved to the fourth question that all patients ask, and this gets to Dr. Stephens' question earlier. The fourth question is how well will I function, and the ordinal mRS done at 90 days with or without utility weighting works very well for that

question for a device or a treatment.

For brain hemorrhage where 50 percent of all patients are likely to die, the questions one wants to ask of both the healthcare system and the patients are different. You want to ask will I be well enough to go home, and what will I be like at home. The modified Rankin threes in the data that Lourdes showed were functioning independently with Barthel scores of 90. The modified Rankin fours were not fully independent as Jeff Saver said, they have Barthel scores in the 40-plus range, the range is 70 to 20. We need more data there and we need it specified by the actual type of disease, and although from a public health perspective lumping ischemic and hemorrhagic stroke together I think is very good, from a data-driven decision making, whoever is making it, the family, CMS, medical people, we need data about the specific subtypes.

DR. MILLER: Thank you.

DR. BACH: Dr. Miller, we can go back to you. Dr. Stephens, you still have your hand up. I don't know if that means you still have

a question or not. Dr. Miller, another question, and then Dr. Brewington, and then I can come back to you for more.

DR. MILLER: Thank you. This is a question for Dr. Saver and I apologize if I missed this in the presentation. So we were talking about various scales and your presentation was very helpful, it was very detailed and I appreciate that. We talked about how often, you know, when people stroke in the ER, they have a stroke on the floor of the hospital, we use the NIH Stroke Scale, and specifically you mentioned that this is relevant obviously at the time of the stroke but less relevant later because it doesn't clearly measure disability as well as the modified Rankin, and the beneficiaries are appropriately concerned about their functional status at home and in the world.

And this might be reflecting my lack of knowledge on this, but I don't believe, and I have ever seen when we do a stroke that we're doing a modified Rankin Scale, and so the question is, is it feasible from a trial perspective you think to collect, or how would

we collect that data, or like say other therapeutic areas like psychiatry where there are established conversions across scales for multiple diseases for a single disease, and is it possible to convert from the NIHSS to the modified Rankin to some degree or not, and if not, or if there is, you know, is it a validated measure, or validated conversion, pardon me.

DR. SAVER: Sure. It is a case that the modified Rankin can't reliably be scored in the first minute or hour after onset because we haven't had enough time to assess a patient's functionality as opposed to deficit in impairment. And the NIH stroke scale can be mapped to the Rankin, and our group actually did that but it is an imprecise mapping, and what instead is generally the standard in the field is to, it is recommended to compare the treatment groups using an analysis adjusted for the patient's baseline NIH Stroke Scale so it's not unaddressed in the analysis, and that takes into account without formal mapping but in much the same way it takes into account their baseline status versus their outcome.

And I will mention, one type of endpoint analysis at the time that I didn't put in the slide is a sliding dichotomy analysis, where if the patients comes in, say with a mild initial deficit, they count as a win if they have a Rankin of zero to one at three months. A moderate initial deficit, they count as a win if they have a Rankin of zero to two at three months. And a severe, they count as a win with the Rankin zero to three after three months, so that's another way of handling it.

DR. MILLER: Thank you.

DR. BACH: Thank you. I'm going to go on to Dr. Brewington. And Dr. Miller, do you have additional questions?

DR. MILLER: Not at this time.

DR. BACH: Okay, go ahead and put your hand down please. Dr. Brewington?

DR. BREWINGTON: Yes. My question is for Dr. Hanley and I'm apologizing for Lourdes because I don't know your last name, I'm sorry, I'm looking at it on the agenda, and several of our other panelists, speakers. Several of you have mentioned that there is a bias when you look at the outcome measures for quality of

life and it's been acknowledged, yet I'm not sure how we feel about it in the question. So when it comes to socioeconomic factors and diversity in the quality of life not being addressed in those quality scores, if we're going to use that as a measure for outcomes to determine whether a patient should treated or not treated, have any of you addressed that in what you're presenting? So in the MISTIE study did you try to mitigate that? I don't, I haven't heard anyone speak to the demographics of the studies.

DR. HANLEY: Lourdes, do you want to go, or do you want me to go?

DR. CARHUAPOMA: I'll let you go ahead and go first.

DR. HANLEY: Sure. Patient-reported outcomes overall correlate with functional measures but they correlate with correlation coefficients of .5 to .7 so there's unexplained variance, and that's why Lourdes and Noeleen and I think it's very important to ask the patient, and the data you saw came from asking the patients at 365 days. You can then if you have that data answer the very important

questions you're asking, which is the demographics groups, do older people behave differently, do African Americans behave differently than Caucasians or Hispanics, you can ask all of those questions. We have not seen major demographic differences in the four major questions that I told you drive our thought process, will I live, will I go home, what will I be like at home, can I have all of my functions back. There don't appear to be major demographic differences there. One that we have seen, not in MISTIE but in the CLEAR trial, is that African American families put a greater emphasis on continuous care and less emphasis on withdrawal of care and in that situation in a small subgroup, the likelihood of achieving a modified Rankin zero to three level was doubled in African Americans versus those who withdrew care, that's the one that we've seen. Remember, though, the MISTIE and CLEAR trials each are 500 patients, 250 exposed to an intervention so when you go to subgroups, the data becomes thin, which is why we wanted to present to CMS because you have a much greater set of data and I think something

simple just like getting an EQ-VAS on the patients might better answer your question. Did I miss anything, Lourdes?

DR. CARHUAPOMA: No. Dr. Brewington, did you have a question about the baseline data in terms of quality of life, the pre-stroke data?

DR. BREWINGTON: I did, but again, it comes back into play, you know, if you're not looking at the demographics when you measure the baseline then that could be a variable that's affecting the outcomes data. So all of this comes into play and even with the registries, if we're not looking at socioeconomic factors and capturing that, which I know some of the registries do not, our data is going to be -- I mean, no data is perfect but we should take that into consideration, and I don't know if you did in your baseline data.

DR. CARHUAPOMA: So we actually did not capture baseline EQ-5D data in MISTIE or CLEAR, it was only captured at 30 days, 180 and 365.

One comment to that is that even if we had baseline data, we're not really able to

capture how individuals reframe in the context of stroke, and we framed their perspective on life and what's inherently valuable to them as individuals in a social setting, so that's one thing that even if we had baseline data, there would be no way to be able to capture how people reframe in the context of stroke, and I think that's of significant importance, and when you talk to individuals with even severe disabilities, that is always a topic that comes up, is this innate ability to reframe your value system, even with severe disabilities.

DR. BREWINGTON: All right. Thank you both for your presentation.

DR. BACH: Thank you. Dr. Brewington, you can put your hand down. I only ask for that so I don't get confused. Dr. Kazerooni, you had a question?

DR. KAZEROONI: My question's been answered, thank you.

DR. BACH: Okay, Dr. Thomas, do yu have a question? I'm not sure, which hand is this now?

DR. THOMAS: So the right, thank you. The question is for Dr. Hanley. So looking at

the PROMs, which is also a part that's new, evaluating the EQ-5D, it looks like there's five measures evaluating mobility, self care, usual activities, pain and anxiety/depression. So I'd expect the precision to evaluate disability to be hindered by the pain and the anxiety/depression aspect. How do we handle that, are there better ways to measure it that are more precise to disability perhaps?

DR. HANLEY: It is an important question and it needs to be answered and I'm not sure that it is well answered yet, but EQ-VAS, which is the simplest to administer and can be administered in less than a minute, integrates all the domains and asks the single how is your quality of life question that can be baselined against the normal population, and if we had enough data could be baselined against all of the various socioeconomic and demographic information that we have. That's why we think that the visual analog scale which is continuous, a zero to 100 scale and it's simple, it's easily administered by a nonmedical person is the way to go, and we think it handles the problem that you're

talking about.

DR. THOMAS: Thank you.

DR. BACH: Okay. Dr. Miller?

DR. MILLER: Thank you. I have another question for Dr. --

DR. BACH: Brian, hold on a second. Dr. Siddiqui, I wrote to you in the chat, if you want to respond.

DR. SIDDIQUI: Yes. I just wanted to finish the stroke side of the question that Dr. Brewington asked, which is we actually have done the data on the major stroke trials, in fact multiple meta-analyses of all seven major thrombectomy trials have looked at demographics, and the two public papers that I'm aware of, one looked at patients who were over 80 years of age, so elderly, to see if their results compared favorably with those that were under 80. While there were discrepancies between IVTP and mechanical thrombectomy, there was no difference in between so this was equally efficacious therapy even for elderly populations.

The other population that was looked at were women compared to men and there was no

difference in the benefit of the therapy for acute ischemic stroke in either sex, and comparatively they were both effective.

Now racial disparities, it's not been specifically looked at in the U.S. populations but know that the seven trials were done in Australia, France, Netherlands, U.S., Canada, and so this included large populations of all demographics and the results were incredibly similar between the different trials in terms of the value of thrombectomy for mRS at 90 days.

DR. BACH: Thank you very much. Now Dr. Miller, sorry about that.

DR. MILLER: That's all right, thank you. Dr. Saver, another question for you. I think you were looking at, I believe it's slide 16 through 18, where you talked about the modified Rankin score and you had an excellent table looking at the different ways of assessing it, and you noted importantly that inter-rater consistency varies depending on how the metric is assessed. I imagine that for a lot of them, a lot of these measures that that is the case. Are there, do you think more

accurate or preferred ways of accuracy in assessing this and other stroke measures in a trial, for example, you could imagine that at a 90-day outcome that a patient goes to a clinic and they're assessed by their neurologist or whomever, but also a video is taken and that is sent remotely to be reviewed later by a blinded neurologist who doesn't know the patient or the data to score them for example, so it's sort of two questions.

DR. SAVER: Yeah. You know, in clinical trials I think it is generally the case that one of the formal methods of assigning a Rankin grade is employed that is known to have better inter-rater reliability than the intuitive method. Often in clinical practice they are intuitively assigned and that introduces some noise but the clinical trial data is stronger. The two approaches to insuring, especially in device trials, that unmasking doesn't lead to the rating of the outcome, one has been to send videos of the patients to a central scoring panel who have had no other contact with the patient, and that helps to give a uniform method of scoring

across all sites that's completely blinded. However, that does have the drawback of the raters having an impoverished amount of information compared to a rater who has the patient in front of them and has done the exam themselves.

So, the other approach has been to have an onsite blinded observer who's had no prior contact with the patient do the rating in person and that has worked well. It's been shown that central audiotape readings are imperfect and have not held up, central videotape or blinded onsite assessments both work well.

DR. MILLER: Thank you.

DR. BACH: I have Dr. Lahey next and please, if I'm missing you, please chat with me.

DR. LAHEY: Thank you. I have a question for Dr. Hanley and your group. I guess I'm asking a rather simplistic question, being a cardiac surgeon we can't get too complex, but I just want your opinion on what you think, EQ-VAS, do you think that healthcare consumers or patients are better served by

EQ-VAS being a primary outcome, or would it be more appropriate to think of it as a secondary outcome or part of a composite? I'm not saying we minimize the importance of it but just in your opinion, would you push very hard for it to be a primary outcome, standalone as it is, or adjunctive with other measures?

DR. HANLEY: I think it's of equal value to the modified Rankin, it correlates with it but it captures other dimensions as several of the questioners have asked. It would be, as you suggest, it could become a composite as well.

DR. LAHEY: Okay.

DR. HANLEY: And I can say as a patient, I would much rather have that than have a healthcare professionally derived utility value generalized to my situation to measure the value.

Can I make one clarification to what Jeff said? I agreed completely with how he answered the question. Within the MISTIE and CLEAR data where we use a blinded international committee who didn't know the patient and a scripted five to ten-minute modified Rankin,

this appeared to be more precise if you took the committee's coherence than the Rankin as obtained by a skilled physician or nurse examiner who was trained in the Rankin, and there's about a 30 percent scatter in the onsite obtained Rankin with 15 percent rating the patient higher by one Rankin legal and 15 percent lower. There was, only two percent were people off by two levels in the Rankin, so that is one measure of accuracy.

DR. BACH: Thank you. I don't see any other hands up. Dr. Lahey, I still see your hand up, but I assume that's -- I do see, Dr. Saver, do you want to make an additional comment?

DR. SAVER: Yes, I'll follow up on Dan's comment, and please know that Dan and I are very collaborative and have the same general sense, but we are proponents of different ways of rating the Rankin for the ultimate level, even though we like each other. And a problem with the central interview method is it converts the Rankin to a patient-reported outcome because the raters are not examining the patient, they're looking at the medical

record, and the comparison that Dan mentioned was to, not to the best of the onsite measures, and I think in another trial, in the RABASCA trial, that there was equal or better specificity and precision with the onsite, but minor technical point.

DR. BACH: Thank you very much, very helpful. Are there other questions for the panelists? Dr. Waldren, do you have your hand up?

DR. WALDREN: Yeah, thank you. Dr. Saver, you had mentioned in your kind of response in this Q&A talking about using the NIH score to kind of, I don't know if this is the right term, but more or less stratify people based on the severity of the impairment and then the outcome being different for the different types of modified Rankin score, and then we heard Dr. Hanley talk a little bit about the EQ-5 being more granular and more patient oriented than maybe the mRS. And then lastly, sorry about all this sort of context here, but lastly there was a conversation about intracranial hemorrhage versus ischemic versus embolic as being different.

So with all that context, one thing I'm wondering about is would you think it makes more sense to, if you could only stratify patients for stroke, would you do something like the NIH stratification or would you do it by pathogenesis of the stroke as a way to say like, that's the one way more likely to think about how you would then figure out what outcome measure goes with what category, if that makes sense?

DR. SAVER: Sure. I do think this is an important distinction on the front side of stratification versus the back side on the outcome, and on the front side one of the stroke subtypes, subarachnoid hemorrhage, has a very different clinical presentation than ischemic stroke and the intracerebral hemorrhage, much more present with diminished consciousness, coma and a paucity of focal deficits, whereas ischemic stroke and intracerebral hemorrhage is more focal, ICH somewhere in between the two. And so you can say better initial severity instruments for use in the subarachnoid hemorrhage are the Hunt and Hess Scale that the World Federation of

Neurological Surgeons provides, and the NIH Stroke Scale is not really appropriate for them. The NIH Stroke Scale works pretty well for intracerebral hemorrhage although that only was found fairly recently, there was another scale developed for intracerebral hemorrhage, the ICH score and several others that are more widespread in use. And so I think it is important to make sure that the stratification test is appropriate to the nature of the disease.

For the outcome it's a little different. You know, we're assessing, the outcome is driven by what you're trying to assess, is the patient back in the world, how are they functioning, and it doesn't matter if they have bleeding in the brain and they can't work, or if they had a bland infarct in the brain they can't work. It is important if they have a minor motor deficit at day ten and you're trying to improve that with a recovery intervention that you want a fine motor skill, but again, it doesn't matter if that happens initially because of hemorrhage or ischemic stroke, so I think the outcome measures should

be topic, should be focused on the domain you're trying to measure.

And let me also mention one other item that has been alluded to but not, a question hasn't been put about it and that is -- or partially put about it, that is the, that we are not getting the Rankin at the 90 in clinical practice and in clinical trials we do try to get these patients down but in clinical practice sometimes even with three calls the patient was moved and it's hard to find the patient, but the multiple imputation of a 90-day Rankin based on the patient's status at discharge and other factors is pretty good at predicting what the 90-day Rankin is, so a 90-day Rankin, missing this can be pretty well handled with that, but Medicare with its knowledge of whether patients went to skilled nursing facilities or acute rehab, can do that imputation even better.

DR. BACH: Thank you, Dr. Saver. Dr. Hanley, do you have more to add?

DR. HANLEY: Yeah, just one. I think it's a great question and as Jeff said, we agree on almost everything. I think he

precisely described the difference between a baseline and late, but I would answer the main part of that question slightly different. You should segregate by disease because the treatments are different and the treatments have different effectiveness, and I don't think the current supportive care and investigative treatments for ICH want to be evaluated in terms of the benefit they do provide or not in the same way that treatments for ischemic stroke are evaluated, because the goals of the patients and the families are often very different.

DR. BACH: Thank you, Dr. Hanley. Dr. Speir also has a question for Dr. Saver. Dr. Saver, I think you get to charge more for your per diem for this meeting at this point.

DR. SPEIR: If I'd known that I would have been a lot more vocal. Dr. Saver, I wonder if you could clarify please what you said regarding the word domain because I was trying to keep here, but it seems like with all of the variations of the different outcome measures and the fact that they are looking both at time and at functionality in subsequent

outcome, it's cumbersome. Does it make any sense to subdivide these into the etiology of the pathology that's being measured? Because the 30, 60, 90 days, 180 days for a modified Rankin may be vastly different in a subarachnoid hemorrhage and intracranial hemorrhage or embolic stroke perhaps than it may be for some of the other etiologies. But it's hard to differentiate this, particularly with prognosis, except including the etiology, is it not?

DR. SAVER: For baseline stratification the etiology is very important to include, absolutely, and it is the case that stroke severity is a driver of what parts of the outcome scale is going to be informative. If you have a severe hemorrhagic stroke you're going to be at the lower Rankin scores, three, four, five, six, and movements among them are going to be very important. But if you have a major ischemic stroke and have to have a hemicraniectomy, that's also where your endpoint is going to be, and the same if you have a severe subarachnoid hemorrhage.

On the other hand, some intracerebral

hemorrhages are quite small and those patients are going to end up at the, especially if we are treating them early as in blood pressure lowering trials, those patients are going to end up more likely moderate to mild in the Rankin Scale, just like the mild ischemic stroke. So it's vitally important to include etiology in the stratification and then also to design your outcome measures around the expected degree of disability and treat what's appropriate for each population.

DR. SPEIR: Thank you.

DR. BACH: Dr. Miller, you have a question as well and then we're going to, after this we're going to wrap up this section of the discussion. If anyone else has a question, please text me or please chat with me.

DR. MILLER: Thank you. A quick question for Dr. Saver just to try and see if I'm bridging correctly between his and Dr. Hanley's thinking. It seems like you're saying splitting by etiology matters in that the clinical condition is different, their expected course is different, but if we're going to measure a domain even across different

etiologies, we should have the same scale but just expect a different performance for the populations on that scale.

DR. SAVER: Yes, at a first pass I think that is my perspective. You know, if we have some very fine aspects having more differentiation per etiology may matter, but for the first general measure of how patients are doing, the broad disability, global disability and generic health-related quality of life instruments are designed to measure all of these sources and work well once you focus in on where they can be informative for each patient subset.

DR. MILLER: Thank you.

DR. BACH: Thank you. I think, barring any other questions, I think we'll draw this section to a close. At this point the presenters will no longer, I believe you are free to stay in the environment, of course, but the rest of the discussion will be amongst the panelists. We're going to discuss, we're going to have a discussion about the questions. I'd like to, it's not scheduled right now, but I would like to propose a no more than

five-minute break. It is now 1:43 right now, we're going to start again at 1:48.

(Recess.)

Okay, we're going to get started again now please. Thank you, everyone, I hope everyone appreciated having a moment.

We're now switching to the discussion among the panelists, Joe Ross is going to help me guide this discussion. The first thing, just to bring the panelists back to the task at hand, which is very much focused now around the voting questions and the discussion that goes in with it, I would like to propose that everyone takes a moment, maybe two minutes here just to read through the voting questions that we will be expected to discuss to get reoriented, and then we can have a discussion around those questions and the topics that have come up today.

DR. ROSS: Peter, this is Joe. If I could make a suggestion, which is to start actually with the agenda, the three paragraphs above the voting questions, for the context in which we're voting.

DR. BACH: Yes, that's great, Joe,

thank you.

Okay, with some context then, I would like to open up the discussion regarding the questions that are in front of everyone and the context as Joe has pointed out, and so we can voice, or so that you can all collectively interact over your thinking regarding the presentations from this morning and the other materials. And the floor is open to panelists.

Dr. Lahey, you can just go ahead, you can raise your hand and I can call on you, or you can just speak up.

DR. LAHEY: Okay. I have a little problem with question number 1.D and I wonder if people could help me understand this. It's referring to other kinds of stroke such as ipsilateral stroke or morbid stroke. I'm not sure I understand what you mean by morbid stroke, it seems to me that every stroke is morbid, and what are you trying to get at by saying an ipsilateral stroke? Is this a second stroke after the initial index stroke that you're looking at?

DR. KAZEROONI: I have an additional question that's related to that other kind of

stroke. Is this where hemorrhagic stroke comes into play, or not?

DR. BACH: CMS, Dr. Chin, we can go either way here, we can have the panelists seek to define that collectively, or we can get input from CMS if CMS has it. Your preference, Joe.

DR. CHIN: I think at this point given the discussion that we have been having over today, it may be more helpful for the panel to reinterpret that and whether it's an appropriate distinction or not given the presentations that we heard.

DR. BACH: Okay. Then the floor is open, and this happens periodically, in fact with some regularity during MEDCAC committee meetings. The questions are written honed to the questions that CMS anticipates are, you know, that are properly stratified and are relevant to their decision making, and then as information comes in and presentations present information, different categorizations, we sometimes, we don't rewrite the questions, but the discussion around them allows us to interpret them and if you will, kind of

re-weight them.

So with that in mind, I think Dr. Lahey, you started the ball rolling here. Do you have more, do you essentially have advice to the panel regarding how to interpret or how the panel should collectively answer these questions, or in this case that bullet D?

DR. LAHEY: No, I truly don't know what that question means and I was asking for somebody to help, I need some clarity on that. So I have nothing to offer, other than help.

DR. ROSS: Peter, this is Joe Ross, maybe I can jump in here. Because I think we can all understand what a major disabling stroke would be, I think what came up a lot during the panel from the presenters and speakers was whether we should be considering different stroke types differently in terms of outcomes. There was a little bit of discussion of ischemic versus hemorrhagic, but more often it was the lacunar versus the other types. And so should we be thinking about the use of the modified Rankin scale differently by stroke types, that's how I think we might want to reinterpret it. I'm a general internist so I

defer to you all who are more specialists in this area, but I think that may be a way to think about reinterpreting the question.

MS. XIUFEN: This is Ms. Xiufen. We are looking to define the morbid stroke as a stroke with a worsened mRS.

DR. ROSS: Right, that I think is what we would consider a major disabling stroke, any stroke with a worsening mRS. The question is, should we be thinking about that measure differently if it's a lacunar stroke versus an ischemic or hemorrhagic stroke.

DR. MILLER: My answer would be yeah. I mean if you think about it, a modified Rankin is probably not a sensitive enough tool to detect some of the deficits from a lacunar stroke, nor would that have enough diagnostic performance to measure between various patient populations with lacunar strokes, so it's probably not a great measure for that.

DR. SPEIR: This is Alan Speir. I really appreciated that perspective because in essence there were probably four of us who were asking the same question that you just posed and just phrased it differently, but I really

appreciated the presenters that were clear and concise and laid it all out, but conversely, they were pretty quick to shift back and forth between the different etiologies as you just said. I'm not going to waste everybody's time in repeating what you said, but I was struck in reading through the supportive literature the plea to make the definitions more granular and to clarify those better. And I think this is an example of trying to extrapolate our answers across each of these questions, because I was interpreting everything people were saying in preparation for answering the questions, but yet the answers were differently viewed dependent upon etiology, which is in essence what I just hear you say, unless I misinterpreted it.

DR. KAZEROONI: Well, involved with that, are we saying that if we identify subcategories of strokes that we will be rating each of A, B and C against, for those specific stroke types, because the way D is written really doesn't even talk about how to rate the outcome measures above, it just simply says other. So Peter, maybe that is a point of

order, is it our intention to identify subgroups like within the other and rate them separately for these measures?

DR. BACH: So there's two opportunities on the kind of point of order kind of issue, there's two opportunities, there's the vote and then there's the discussion. CMS will consider those two things in tandem, so I don't know, Ella, if this solves the problem, but you can vote and then you can, also if you recall, I will poll each of you and when you explain your vote you can also give clarification there, so there's two opportunities to provide more granularity, at least two. And this discussion is also being, you know, is part of, is going into CMS's thinking as well.

DR. SPEIR: Peter, given the charge to review those three paragraphs before the questions, the underlying indications for use of the new technologies are going to be also different and then trying to anticipate the usefulness or what the indications for use are going to be will be different in the embolic large vessel versus the microvascular

thrombolytic type of approach, so that weighs in as well, does it not? So we've got etiology into the anticipated usefulness of these new technologies.

DR. BACH: Yeah, there are, I don't think, I mean throughout the morning, I don't think there's any question that there are several dimensions to be considered here, and this is why I hope through a combination of voting and discussion that it can be conveyed.

DR. LAHEY: Yes, I would -- I generally always defer to my colleague Dr. Speir, who is always right on the money, he always is, I always follow his lead, and I think he is touching on a very very important and unavoidable topic, and that is the different etiologies, and everything changes. In our world what we think of is, for example looking at mitral regurgitation, there's mitral regurg and there's mitral regurg, and sometimes when I'm at the RUC, at the update committee, it's hard to convince people that there's complete difference in mitral regurgitation, there's quick grab mitral regurgitation or a person with Barlow syndrome with a faulty

mitral valve, that's one thing and it's a fairly straightforward case for us to do if you have to do a mitral repair or replacement, but then there is the ischemic mitral regurgitation with somebody who has had multiple, multiple infarcts and their ventricle has just dilated to a complete bag, the mitral valve itself is quite normal but it's stretched out. So it really, I think when I'm thinking of intracerebral hemorrhage versus ischemic strokes, it seems to me that they are quite analogous to talking about the two types of mitral regurgitation where the treatment and the prognosis is wildly different. Maybe I'm being too simplistic.

DR. BACH: No, I think it's a useful analogy.

DR. ROSS: Peter, this is Joe. I would agree with that. I would just remind us that we're trying to help CMS determine what types of measures they should be looking for in clinical trials or registry of data that's going to help them make evidentiary and coverage decisions. And so while obviously there may be nuance depending on the etiology

or the stroke type, we're attempting to help them make these types of decisions. We're not designing a trial, we're just helping them essentially justify whether or not an endpoint should be included.

DR. CHIN: Right, I guess to give some context to that is when, in some instances we may actually not know some of the background in terms of patients, and then if we were presented with an outcome such as a major disabling stroke or an ipsilateral stroke or something that actually worsens with treatment, how do you capture that and is that relevant. So sometimes it's not necessarily what the patient initially starts with, and it may be, you know, getting to is it an adverse event or a harm that occurs with the treatment that you really can't characterize.

DR. SPEIR: Dr. Chin, as an expansion of that, in the second paragraph that we were rating, there's a little bit of a disconnect and almost a plea that we're not looking at the short and intermediate goals as was requested by the FDA, rather the longer-term follow-up results of such therapeutic interventions. And

so in our, and this goes back, Peter, to what you were alluding to, does it not make some sense in our discussions that we have clarification on the length of followup, is that appropriate?

DR. CHIN: I think length of followup is an important consideration and we welcome your input onto that factor. I think -- has it been captured in the other questions? Because I mean, that is an important consideration as to really when we do the measure, and I think during some of the presentations this morning there was some reservation as to at what timeframes.

DR. BACH: Let me just throw in that the discussion around some of the metrics does include length of followup as one of the dimensions that's to be discussed.

DR. KAZEROONI: So I was just going to say, I was a little confused by some of the discussion about timing of outcome measures, measurements, because it's not a specific rating question that we are ranking on.

And my other point of confusion, and even just looking back at it again now, I don't

see time in any of the specific questions for the recommendations, but certainly it's important to discuss.

In the presentation earlier this morning that looked at the outcomes and motor dysfunction, I think it was Dr. Saver, presented a paper where he drew a line on the graph and said, you know, we're trying to focus on the three-month outcomes. But there is definitely a subcategory of patients that longer-term outcomes showed recovery closer to those other first outcome recovery groups. So my question is to try and ask, is to understand better that particular group and is there, are there features of that group that require longer-term outcome assessments, because that benefit that we're seeing, that outcome improvement would not be captured at the three-month mark. I'm going back to the paper, I pulled that paper actually out and read it over the break.

DR. WALDREN: I saw that same thing, but then I also heard when they were talking about the registries and you know, this gets into kind of my area, that the longer you go

out the more difficult it is to get a good data set for that too. So for me it almost seemed like, you know, 90, 180 and 365 were kind of just going to have to be the ones that we capture, because there's the large change up in the first 90 days, but then you have to capture later but you may not be able to.

And I missed, Dr. Saver mentioned too, there was some proxy measure for that functional status at 90 days that was shorter too, but I missed that.

DR. SPEIR: The only thing, Dr. Waldren, it looked like there was about a 30 percent drop-off on the data that they were tracking, and let's not miss all the different studies, there was relevant lost information, unless I missed it.

DR. MILLER: The other thing I wanted to point out as Dr. Saver noted, which Dr. Hanley I think talked about more extensively, is that for intracranial hemorrhage that a year, six months or a year is more relevant. So it sounds like for some subtypes, 90 days captures most but not all patients, whereas for other types you

absolutely have to go at the 180-day or 365-day mark.

DR. CHIN: A suggestion to actually incorporate the timing of measurements, in question one as we talked about the outcomes themselves, if during the discussion you have identified what you believe would be the most important particular timeframes to capture, and incorporating it specifically in question one.

DR. MILLER: I think at least me, it was relatively clear that for intracerebral hemorrhage you have to go out as far as a year. I think it's probably similar for subarachnoid hemorrhage. It sounds like our debate is about embolic and thrombotic strokes, and also noting lacunar strokes as a specific subpopulation.

DR. WALDREN: I have the same thoughts. Dr. Siddiqui, though, also talked about clipping versus the coil and that the outcomes were very similar at five years, but in the shorter period of time there was differences between the two too, so as we think about registries and stuff, do we need to think about a longer term? I don't think it's primary, but would that be a secondary type of

outcome that we'd want to consider?

DR. BREWINGTON: I thought he actually said that as you went further out with the clipping versus the less invasive that they ended up being more similar as you got further out, right, or is that what you were saying?

DR. WALDREN: Yeah, that's what I would say, so I think again, if you think about coverage and you know, if you looked at shorter you may say okay, I want to cover the one that has the better outcome in that shorter period of time because we didn't look at the five-year outcome, but if there were significant costs and other considerations you may decide that well, you know, I do want to cover clipping more than I want to cover the other because of that longer term. I don't know if that example is a great example clinically, but that's what I was thinking.

DR. MILLER: I think what you're saying is if they clip it and it doesn't hold, you find it doesn't hold after two years whereas coiling did -- I mean this is not the case, but say it did, that that would be meaningful to the Medicare population, because

that's a catastrophic event.

DR. BREWINGTON: Well, I think they actually went into that, because they said coiling you have a higher risk of rebleed and so you could have a worse outcome, but with clipping they didn't see that outcome, that's what I thought I heard.

DR. CINQUEGRANI: I think you're right, I think that clipping requires a, more likely requires a separate procedure.

DR. MILLER: So it sounds like we're talking about a multiyear outcome for that specific population, it may be an initial one-year outcome and then a secondary outcome like Dr. Waldren said with multiple years out.

DR. THOMAS: Joe, before we go too far, though, you know, we start getting into competitive cause of death and regression to the mean, it's kind of like over a period of time we lose that therapeutic look. And also particularly in registries and even in clinical trials, a loss to followup can be a big deal and if it's a death loss to followup, that can skew the data one way or another.

DR. KAZEROONI: One of these things

could be a call for administrative data, so these procedures are things that should be captured in other ways.

DR. MILLER: Yeah, specifically thinking about clipping versus coiling, I was thinking about a re-procedure, rehospitalization for a rebleed, so many people have comorbidities and that could be caused by so many other things.

DR. LAHEY: Yeah. Isn't one other issue that with clipping you're talking about craniotomy, whereas in coiling it's an intravascular procedure and that's a whole other level of complexity, and how the patient is going to feel or do well or whatever, because they've had a major procedure.

DR. TYAGI: Yeah, I think those observations of clipping and coiling are very common to what I see as a vascular surgeon doing these kind of procedures. One thing I would say is we followed aneurysm patients and I wrote a paper on this several years ago just looking at long-term surveillance and followup and maybe patients with stroke may be a different population, but I think there would

be some overlap with patients with cardiovascular disease, and the three-year compliance with surveillance and followup was pretty poor. So whenever we talk or look at following patients, I would say beyond one year, the true capture rate of that I think would be poor.

DR. ROSS: This is Joe Ross again, I just want to in terms of the steering, you know, obviously this conversation we're having has a lot of relevance to the question two that CMS has posed to us around the best use of administrative data. They've asked us to consider unscheduled readmissions but from the conversation I can already hear sort of more direction towards that, towards, you know, re-procedures of sorts, so it's just for us to be thinking in terms of the comments we are providing to CMS as they're requesting.

DR. STEPHENS: Yeah, I actually had some comments about that. You know, one of the things that always makes me hesitate when it comes to length of stay or readmissions, that I think there are so many other intervening factors. I also think that there are so many

incentives related to payment policies that we're not going to discuss here, and so it makes it challenging. But one of the things that I heard in the presentation today that gave me pause was the idea that including those items, it really focuses more on the system of health care overall versus the actual medical procedure and I actually, I don't know, I found that kind of surprising because I don't know how you can separate your clinical outcomes from the system within, you know, the system that they received the care at. And so I think that the two are always linked and I don't know how you get to equity ever if you don't consider, you know, who and where you're doing these procedures, so I'm kind of at a loss on this one, because initially my thought was there's so many other things that could influence those numbers, but in hearing them it really caused me some concern to think, well, we want to just evaluate this in a complete vacuum. I mean, I get clean data but people don't have clean outcomes, so that if you really want to understand what the outcome is for a person you have to look at things within

the context.

DR. BREWINGTON: So let me ask a question of the panel. Your question might be answered in the fact that the centers that are performing these should be certified stroke centers, and by virtue of that they should have met certain qualifications and be capable of performing at a certain level that's audited with frequency, so hopefully that normalizes somewhat some of those factors with geography.

DR. MILLER: A couple thoughts. I will say that a lot of the certification designations, not specifically stroke per se, but some of them are maybe not as rigorous as we always think they are, so I'm a little hesitant to use that as a gauging mechanism.

In terms of length of stay, I think that's probably less relevant because I mean, it's just, it's harder to measure, it's harder to replicate, and then in the real world there are all kinds of things that can drive length of stay that are unrelated as multiple of our colleagues have pointed out, totally unrelated to the technology intervening on the disease. Rehospitalization specifically for

cerebrovascular disease probably is relevant because that suggest potentially a failure or flaw in the initial therapy or something else, but more likely related to the initial therapy. And then discharge disposition, I mean, I know we haven't discussed that but just to bring it up, I imagine that that is very high on everyone's radar, whether someone is going home, home with services, going to a SNIF or going to an inpatient rehab facility.

DR. LAHEY: I agree, I think that discharge disposition is a surrogate for the really important stuff, and you can get an idea if this patient is going to do well or not. The patient that goes to a SNIF in any discipline, you know that those people are very very sick and they're not, they're totally different from the patient going home.

I would say as far as length of stay and readmissions, there are so many confounders that it almost is, I won't say it's worthless, but it seems to me that with all the pressures that clinicians are under nowadays, a lot of external pressures, there's a lot of incentives for not readmitting patients when they should

be readmitted, there's instances where patients have, well, they're readmitted inappropriately, length of stay same thing, get the patient out, get the patient out, or oh no, it's Friday, keep the patient until Monday and then send the patient out. And the other thing of course is, I don't know how good they are at censoring out deaths for length of stay data, but all this stuff, many of you know this already but we have volumes of papers in the STS database addressing each one of these particular issues and all the confounders.

DR. ROSS: So can I pick up on that comment that Stephen just made, because I want to say specifically in the language from CMS says around standalone measures, and I want to just raise for the group, if we're talking about discharge disposition as being a key outcome for patients who have undergone treatments with these technologies, whatever the technologies may be, is it sufficient as a standalone without the context of who actually survives to discharge?

DR. MILLER: I don't particularly view those as standalone measures, I view them as

partner or secondary measures.

DR. LAHEY: Yeah.

DR. MILLER: And then also adding on the readmissions, you can also avoid readmissions by having them classified as an observation stay when they come back. So there are lots of games that make that metric challenging.

DR. TYAGI: I would make two points kind of from my anecdotal experience. I would agree on the readmissions being not a very clear outcome point. I mean, there's so many patients I see that, you know, had a stroke two months ago, two weeks ago, not two weeks ago, two years ago, that sort of thing, that doesn't play into the fact of what I'm doing. I mean, if 20, 25 percent of ischemic thrombolic strokes are from carotid disease, they inherently have coronary artery disease and may be having work done for that, or peripheral vascular disease. And let's say I do an operation, the patient had a stroke three months ago and now they have gangrene and I do an operation and they're admitted for a wound infection that I caused, you know, how did that

affect the outcome for their initial stroke treatment because that was six months later. You know, I think maybe if there was a length of time, readmission is a stroke-related readmission versus not that might have some value, but I think in general it doesn't.

And another thing I would also make a point of is if we are really going to focus on disposition status of the patient on discharge and if that becomes an important metric, what does that do to help people, you know, what drives clinical care, you know, like there's going to be a drive, you know, maybe to push somebody home that maybe could require a SNIF, you know, that could be just biased by outcomes, you know, as opposed to what is best for the patient, you know, so that's another thing I just want to throw out there, you know, like the patient who gets a transplant and stays in the ICU for 30 days, you know, when they should have had a goal of care discussion three weeks prior, you know what I mean.

DR. STEPHENS: I was just going to say, that's what I was thinking of, I understand there's these perversions of the

system that are built within the system that really significantly alter these factors.

DR. BREWINGTON: I agree with that, I think that, I agree wholeheartedly with that. So going back to the question, the question is do we see it as a meaningful primary health outcome, so it sounds like the group consensus is that, you know, these with high variability dependent on other factors are really more secondary at most, so I think we all agree on that.

DR. THOMAS: I would agree, this is Greg, and I'm concerned also that CMS kind of suggested earlier, STS status determining whether someone is going home or to an inpatient facility, we already have the challenge with some of our safety net hospitals being penalized for the quality of care that may be related to other factors, and I wouldn't want to see this here as we look at the science.

DR. SPEIR: I think the only caveat to that is the term inpatient facility because of the differentiation, particularly mortality, around a SNIF versus a rehab facility, because

we know at least that the mortality is much higher in the SNIFs, they could skew some of these follow-up results as opposed to going to rehab, which I think Dr. Brewington, you alluded to, and I think your point that I still haven't gotten away from is the sophistication of, you used the stroke centers, and I think that that, is that an unrealistic expectation with a lot of this technology, that it's not going to be, the differentiation between stroke centers I would assume, while we wish it was not going to be the case, is going to be much broader across many centers, and the only thing in my experience that I've seen in this limitation was in our transcatheter valves where they had a much more rigorous restriction on the rollout of that technology that had to do with volume training and number of facilities down to about 40 across the country. In the technologies that we're anticipating, is it going to be that strident? I'm not sure that that doesn't fall into what Allison was saying before, it would be more influenced by the real world than the limitation. I didn't say that very well, but you'll get what I'm

saying.

DR. ROSS: This is Joe Ross and I don't mean to divert the conversation. I do just want to make sure, CMS is a large organization, we are not speaking up to the group that's in charge of quality and payment to hospitals, we're speaking to the coverage and evidence group, and we're talking about the measures that they can use to understand the safety and effectiveness of the technology, right, and how well they work and whether to provide coverage for them. I just want to make sure that we're focused on that, not what's sort of fair or appropriate. I heard somebody bring up the readmission measures that CMS uses around hospital payment and quality measurements. This is very distinct from that, this is whether specific types of readmissions may be a measure of the technologies' safety or the technologies' benefit, not of the hospitals providing the care.

DR. KAZEROONI: So Dr. Ross, I just want to ask you for a clarification of what you just said. So are we trying to evaluate the technologies in their purest sense, in which

case you want to get rid of all these things that could be providing variables toward outcomes, are we trying to evaluate these technologies when administered in clinical care? So are we trying to evaluate them for the purpose of an ideal research trial, are we trying to evaluate them for the purpose of a clinical trial in real world practice which cops with all these variabilities that people have been talking about?

DR. ROSS: That's a great question. I don't know how CMS would answer that and I don't know if Joe Chin wants to jump in. I would guess that they are making decisions on what type of evidence they want to see collected either as part of a coverage decision or after deciding to cover the product and looking for secondary, so all of these surrounding things matter, but it's a little bit of a knock-knock thing.

DR. BACH: Joe, I'm going to dive in on that one.

DR. ROSS: Please, save me.

DR. BACH: Well no, I don't know if I can. I'm going to first of all postulate that

CMS won't answer that question as precisely as you've asked it, so I'm going to take a shot here.

The general approach to coverage focuses more, I think what most of us would traditionally refer to as effectiveness rather than efficacy, and I think the distinction you're making, Ella, is that exact one. So this is a question of kind of what will, if covering this item or service for Medicare beneficiaries will improve their health, their health outcomes or net outcomes, whatever you want, so it is, all the real world elements need to be incorporated.

We've had a number of questions about variability by age, by sex, by race or ethnicity. I think all those things are real world contemplations for the Agency. The other dimension of this which has come up a number of times, a number of the panelists raised these kinds of general points, it is not outside the Agency's purview to limit the scope of the delivery of services, just like they did in CT screening for lung cancer for example, and so those are dimensions where if there are, if

there's evidence of important variability by, you know, site of care, type of provider, experience, whatever it is, those are all things that they would like to hear from the panel regarding. And so that was a very long answer, I know, but I hope it was useful.

DR. MILLER: I may -- go ahead.

DR. BREWINGTON: I go back to the questions the way that they are posed. You know, the questions are asking about primary outcomes and then what we've been able to agree on is a lot of these ones with variables should be put into a bucket of secondaries, and I think if we keep going down that pathway it will guide us into what we think is more subjective and what's objective, with the objective being those things that have a scale, so going back to the Rankin score as being more objective measures, and I think that might help us as we go through these questions if we think of it that way.

DR. TYAGI: I'd like to if I can share with you guys kind of an analogy from the vascular world where I come from, just to give an example. So for peripheral artery stenting,

essentially every industry person that comes up with a stent to place in a superficial femoral artery, their outcome is they'll put on a poster that will be in a magazine or whatever, will be target lesion revascularization, TLR, which means did this stent fix the lesion. That is not a clinical outcome that any of us use really. We want to know, is the life saved or what is, you know, the limb salvage rate, you know. And so that has been, and these studies are one and two-year studies for patients who have, you know, five to ten years. So the entire industry is every company has put out stents and their main outcome measures they'll put TLR, and you have to dig into the papers to find out what is the primary Phase II, secondary Phase III, or the limb salvage rate, and you look at the heterogeneity of the population. So I think having a real functional outcome be an emphasis is really important, and I've seen that go and you know, we've seen millions of dollars going in the wrong direction without I think a true outcome measure. So I think really, thanks for putting us back on the question, and I think having a

measurable outcome measure is what matters the most. I don't know what that outcome measure is, though.

DR. MILLER: I was going to say, my general comment is I think about these questions in terms of mapping efficacy in a trial onto real world effectiveness and this is for the Medicare population, this is CMS asking us how to look at what comes from FDA trial data and interpret it in a clinically meaningful context for Medicare beneficiaries to help them be, you know, meet their goals be it, you know, preventing additional diagnostic testing, improving functional status, extending lives, arresting decline and those sorts of general framing.

DR. KAZEROONI: So in that sense, I can (inaudible, multiple speakers) they're all measurable, they're objective. I think what we're discussing is whether they're primary or secondary and how important they are, are they when it comes directly to evaluating the outcomes related to a specific intervention.

DR. MILER: Right, and the question specifically as we've mentioned, if framed as

primary, and we all think that they should be secondary, there's three that we've listed.

DR. STEPHENS: One thing I wanted to just clarify is there needs to be, and I know historically there's been a focus on disability related to physical health and I guess if that's the historical, you know, interpretation, I don't know if that's the only interpretation that we should be looking at, and so I know there was some questions during the presentations about like okay, well that's just a depression/anxiety. When I think about functioning and disability, that would include both, and I guess I wonder if we're talking about CMS, are they using the federal definition of disability which would include both, you know, from SSA or ADA, and how do we integrate that to the conversation, do we really generally know at that time that's relevant? I would think it is considering it's your brain, but their mental health might be impacted in some way, right?

DR. BACH: I'll weigh in on that one. CMS is not in the context of measuring a health outcome using a categorical definition of

disability, it has to do with eligibility requirements which, I think that's your question, Dr. Stephens.

DR. SPEIR: I think Ella did give a pretty good direction and then with, Dr. Bach, your answer, in terms of we spent all this time looking at the subcategories of stroke and etiology but none of that matters, it's a matter of how do we perceive the technology in its purest form and what could we perceive, again forgetting all of those things that just cloud our judgment as providers on a day-to-day basis, and try to just stick to the question in its purest form, which I think is an unrealistic ask, at least for me to be honest, because I'm so influenced by what I see and how I'm trying to respond. Dr. Ross, you're sort of, you know, think without using your brain for a minute, you know, and just answer the question. So it's, the directive is pretty challenging to honest, I'm trying to stay on course here, but we can't help but try to give you back our best guess as to what is going to be beneficial.

DR. BACH: I can't understate the

value of the discussion throughout the day, including the presentations, the questions of presenters and even the discussion that you will be free to engage in in the context of a vote or after each question. So I get, Dr. Speir, I don't think anyone promised you this would be easy, but I certainly get that the challenges are considerable. So flesh out your answers and we're just going to try and provide some useful information to CAG.

DR. MILLER: Maybe in that vein we should move to the discussion of the third question and then the fourth too, looking at our time?

DR. ROSS: I think that's a great idea. Joe Chin, you had your hand up. Did you want to clarify something before we move on?

DR. CHIN: Yes, I wanted to add a comment that hopefully may be helpful to some of the discussion that we have just been having. I think perhaps taking the view of an item, device or technology if it was a little earlier in the developmental cycle, you know, would be one way to pose it. I think many of these types of interventions, devices are new

technologies, so you know, while I think many of the questions about how they actually work is a little bit, in actual practice outside of clinical trials are extremely relevant to what we would actually consider, sometimes we don't even get to that point in our considerations. The question is if you were developing a device and designing a trial, you know, what would be the outcomes that would be important in that context, which is, I think shifts your thought process, I mean, it shifts the way I think about it a little bit differently to what, you know, perhaps more of an initial question about benefits of the device itself or the intervention itself.

DR. ROSS: I was just going to say, I think that actually sets up well discussing questions three and four around functional assessment and quality of life, the discussion of EQ-5D, mRS and the NIH Stroke Scale as functional measures. But I'm sorry, Michael, you were going to say something?

DR. CINQUEGRANI: I was going to say that, you know, questions, you know, if we're talking about new device development, those are

really issues that are solved by the FDA approval process, are they not? And so I have a little bit of difficulty reconciling the questions we're posing here as it relates to a device that might be approved by the FDA through the usual mechanisms of clinical trials that are vetted, that are approved under the auspices of the FDA for their execution, and then the presentation to the FDA and subsequent approval by FDA, the question then is how CMS uses that data I suppose for payment purposes. And I know that's not the direction here, but it's a little hard for me to understand the answers to these questions in the context of approval processes that are under the auspices of the FDA.

DR. CHIN: You mentioned, I think you actually highlighted a distinction there, so I think perhaps the example that Dr. Siddiqui mentioned earlier might be helpful in that context where we look at the, and we don't have a coverage decision on these devices, but as an example the drug eluting percutaneous stent, how they were actually approved with sort of a functional or an outcome that looked at

patients that did nothing versus, you know, something that, in the questionnaire that gets back to really outcomes that would be important for, health outcomes that would be important for the Medicare population and in that context, and I think typically when we approach interventions, I think more of an outcome in our thinking would be amputations, mortality, or in that context. So I think there is a distinction that you've highlighted and I've tried to, I guess tried to use that example as something that may help in discussing the answers and how we actually might consider what a health outcome is.

DR. MILLER: If I may, the way I look at it is FDA clearance or approval of a device is based upon standards FDA sets for safety and efficacy for market entry. Our specific question is what is useful for the Medicare population and what's most effective in the Medicare population, which could help potentially by informing CMS about that, that could also inform device manufacturers as they design trials for FDA approval and clearance, so that way a trial could be designed to meet

FDA standards and also potentially meet what CMS is looking for, rather than getting a device approved and cleared and then having the Medicare program say oh, these are very different things that we're looking for, sorry. So the idea is to make this distinction clearer for device manufacturers in this particular space, at least that's how I see it.

DR. CINQUEGRANI: The question you raise --

DR. SPEIR: There are different processes but in order to clear the FDA there had to have been both clear outcome measures that do show safety and efficacy that were, those hurdles were already cleared. This isn't a peripheral stent or a coronary stent, so how many of the measures that we're looking at that answer these questions may have been already used and looked at through the FDA process that rather than reinventing the wheel, we're raising something that is perhaps conflicting that we're going to be measuring it differently, does that not have a role here that we could use in our decision?

DR. MILLER: Go back to the prompt

before the questions where it talks about devices specifically through the investigational device introduction pathway, which is a shorter pathway to market.

DR. CHIN: I guess I would suggest in general that we don't specifically address the safety and effectiveness, which is really the FDA, and focus onto what actually you believe would be important for the Medicare population in terms of the outcomes that we are typically looking at.

DR. KAZEROONI: It sounds like, Joe, from your comments and others, it's a step towards effectiveness from FDA efficacy that we may be looking for here?

DR. CHIN: Yeah, I think so, and I think there could be synergies and actually ideally there would be synergies there with outcomes. I would like to take the FDA factor out of the question as much as possible.

DR. MILLER: So I guess maybe onto question three where we're looking at the modified Rankin Scale and the NIH Stroke Scale, it sounds like from our guest speakers that the NIH Stroke Scale might not be a great measure

because it doesn't measure disability and that's more of an immediate measure?

DR. BACH: Brian, you're raising that for discussion instead of an assertion?

DR. MILLER: Yeah, there was a question mark at the end of that sentence.

DR. BACH: Right, I added it.

DR. BREWINGTON: There were a couple conflicting statements when the presenters were talking about the modified Rankin Scale and the NIH. I wrote in my notes and then I drew arrows because they were in conflict. On the NIH Stroke Scale there was a statement that it was widely accepted as a measure of preventing severity, and then when they talked about the modified Rankin Scale they said it was the most common used in acute stroke, but then there was a statement that it can't be used immediately in acute stroke. So can someone reconcile those statements for me?

DR. CINQUEGRANI: I went back over Dr. Saver's slides during our break and what I gleaned from it was that the modified Rankin Scale was really applicable about, in the first seven days, not day one or day two perhaps, but

you know, during the course of the initial evaluation and treatment of somebody with stroke you do a modified Rankin as an assessment and then it would be applicable again at a later time, say 90 days later where you would measure the difference or change, the improvement or worsening over time. That's what I gleaned from it.

And that the NIH Stroke Scale, you know, is really something that is of short-term evaluation at the time of presentation in terms of assessing the severity of the acute presentation, and measuring in short term the effectiveness of a therapy like thrombectomy on an ischemic stroke patient, you could measure improvement within a day or so based on that intervention, and that's where the NIH Stroke Scale would be very useful.

DR. LAHEY: Is this a competition? I mean, which one's better, modified Rankin or NIH Stroke Scale? It's not a competition, I like both of them, I like both of them a lot.

DR. CINQUEGRANI: I think they're looking at the same problem in two different ways.

DR. LAHEY: Right. I like both of them.

DR. MILLER: Well, the NIH Stroke Scale is measuring loss of function whereas Rankin is measuring disability, which is why I think the modified Rankin Scale is useful for like a 90 or a 180-day outcome compared to a, say discharge from hospital measure or close to discharge from hospital, whereas the NIH Stroke Scale is determining severity when you have a stroke, like I think this patient has a stroke, call a stroke code in the hospital, the neurology attending or resident shows up and scores the patient and then drags him off to the CT scanner or whatever, so it's a different use.

DR. LAHEY: They're different but neither one -- I mean, they both have enormous value at different time points during the course of the patient's illness.

DR. BACH: I don't think you're being asked to choose between them, I think you can rate each of them independently and give much of the context that is coming up in this discussion when we do the actual voting.

DR. LAHEY: I planned on doing that independently, but I just thought that we were getting into a discussion of which one is of more value and I don't see that at all. I mean, I thought it was interesting that one of the presenters said as far as the NIH Stroke Scale that there was some problems with, you could have a NIH Stroke Scale of four but be completely aphasic, and that kind of shook me a little bit, but with the exception of those individual oddities, by in large I think they're both very very useful for different reasons.

DR. MILLER: Right, one is short term and one is longer term.

DR. LAHEY: Yes.

DR. THOMAS: I think the trialists in terms of evaluating the efficacy of what they're studying is pretty uniform, in that they think that the more sensitive measure is the Rankin Scale rather than the NIHSS.

DR. KAZEROONI: I don't think they're both saying that the NIH Stroke Scale is invalid but it's measuring something different, it's measuring at the time of acute

presentation the severity of the stroke. That itself is not an outcome measure, that's essentially an assessment at the time before the treatment is given, whereas the Rankin delivered towards the end of admission and then serially is looking at health outcomes over time and the NIH score doesn't do that. So it has nothing to do with validity, I don't think we're talking about the validity of each one of them, it's reproducibility, but we're talking about, the question is functional assessment as a standalone meaningful primary health outcome, whereas NIH is really not an outcome, it's part of a diagnostic assessment if this is stroke and how severe it is. So I think for entry criteria and stratification of patients, I think it's a very important example.

DR. WALDREN: Yeah, I think Sam gave us a cautionary tale that if we use the NIH Stroke Scale, that he saw an ad of it being able, the device being able to decrease the stroke score by ten points, but what does that really mean? So again, I don't think it's an outcome.

DR. THOMAS: I think another issue as

we evaluate the Rankin Scale is the usefulness of the delta. Earlier like in ISUISA I it talks about a change of two being a primary endpoint and I think when we're looking at, you know, something as, with as many strokes as we have in the United States and elsewhere that a minor change I think could be helpful, so I'm not sure why we're, why two is often used rather than a change of one.

And also, I think we may well want to weigh in on the measurement tool in terms of, for example, the ordinal shift analysis look rather than the dichotomous look, it should be using that utility weighted shift analysis to get more precision to find smaller changes, so we can, if we add up these smaller changes that can become very important for patients.

DR. BACH: I'm trying to be sensitive to time without curtailing conversation. I think there's an interest probably, I'm guessing there's some interest in discussing question four, and we have a couple more minutes left in this section as well. And then I'll remind the presenters, who I think know this, that they're not to use the chat to

communicate with panelists at any time, but certainly during this discussion. But does anyone want to start a discussion of question four?

DR. ROSS: Peter, this is Joe Ross. Before we go there, can I ask one point of clarification? This is just my lack of experience in this, but I thought NIH Stroke Scale had been used as an outcome in trials like in the early TPA trials.

DR. KAZEROONI: Yeah, and I thought one of the presenters today actually used a combination of the two as being better than the modified Rankin score alone, so it's not to say that it's not valid and not measurable, but if I were to rate the two as a primary standalone healthcare outcome measure, as I read the language of the question, it's just toward the modified Rankin Scale.

DR. CINQUEGRANI: I think they're not mutually exclusive, I think they are measuring effectiveness, NIH I think is measuring the effectiveness of an acute intervention as it relates to how patients respond to interventions, whereas the Rankin scale is sort

of the measure of how people do functionally over time.

DR. ROSS: So that might have some bearing if the technology is an acute treatment technology.

DR. CINQUEGRANI: Yes, and the stuff we're talking about, some of it is.

DR. ROSS: All right, that's helpful, thanks.

DR. KAZEROONI: Thank you.

DR. STEPHENS: I guess I'll start with number four. I think, this is a little bit challenging for me but at the end of the day I think that it's always important to get the perspective of the individual and their family or caregivers, and it sort of seems like this would be the only opportunity to do that in this process really, I don't think that you can evaluate any outcome without asking the person how he feels and, you know, are you having a better quality of life based on your own standard.

And I will bring up the issue of health equity again because I do believe that the concept of, you know, wife and family,

quality of life, things you want to do, I think it's their own family culture and other traditions and values that they have, and I don't know how you get to that if you don't ever talk to people about it.

DR. WALDREN: I was thinking the same thing when I saw this. You know, you talk about anxiety and depression and that's one of the Ds in the 5Ds. What I was thinking of too, one of my thoughts is the Rankin, modified Rankin if it is a severe stroke, you know, a two or three or above, it seemed to be more germane than the EQ-5, where the EQ-5 would seem more germane if it was less than three, because it would need to be a little more nuanced and the patient had more facility to give their input, but that's kind of what I was thinking.

DR. MILLER: I guess that directly looking at the question, I agree that quality of life is important as the patients, the patient's the patient, they're the one we're doing this all for.

I guess I, the questions are also about the EQ-5D in particular and then also

whether primary, composite or secondary. I guess just briefly, we can use it as a primary outcome, composite outcomes have many challenges, and it can be statistically engineering, and so I would say I would use it as a secondary outcome. I'm less certain about the EQ-5B instrument itself though.

DR. THOMAS: I have a question regarding the use of the primary health outcome. When we state that it should be used, is that we're thinking that it is the primary endpoint, we're going to recommend that the, if it's a PI statistic that's used on all EQ-5s do we use that, or are we recommending that it's good as a standalone with some other primary endpoints but it's standalone as a secondary endpoint?

DR. ROSS: Greg, that's a good question. As I read it, I'll just say, and having served on these committees before, I think of it as a principal, like an important health outcome as opposed to this should be the primary endpoint in the trial outcome.

DR. THOMAS: Okay. So we can put, we can use a synonym of important or principal as

an addition to primary then, okay.

DR. ROSS: Unless someone from CMS wants to clarify.

DR. SPEIR: Really C and D are competitive, it's either the primary or the secondary, right? I didn't totally -- you were making a point that I was waiting until the end, so if, do we view this as a standalone primary outcome or a standalone secondary outcome?

DR. LAHEY: I think Joe said it could be either one.

DR. SPEIR: I know, but they're competitive.

DR. THOMAS: I think that we -- I don't -- but on the other hand, I think that it would be up to the folks putting the protocol to determine where they rank it depending on the type of strokes they're looking at the intervention, so I think we'd want to give them that flexibility.

DR. STEPHENS: So I'd like to, because I'm not a physician, kind of understand what that would look like in an example. So I'm thinking as an individual, I've had a stroke,

I'm going to be given a treatment, and maybe clinically we can look at certain outcomes to say yes, I have problems, but I've got 12 other things that went wrong that have made my life hell, which one becomes primary? That's just my kind of nonclinical and patient advocate role on this committee, just putting it out there.

DR. LAHEY: You know, I asked Dr. Hanley this question, and I said in your opinion, do you think it would be -- well, actually it was the EQ-VAS, what do you think, is it a primary or is it a secondary? You know, I think we were on the same page that it's extremely important but it's more adjunctive, it's not -- I mean, I would like to have a clinical physician assessment of the patient at a certain time, but I also want to know how the patient perceives his or her own condition, and I'm realizing that it is going to change over time, so I thought of it as more adjunctive and so I didn't want to put it in the primary outcome. That's not to say it's not important, it's extremely important, but built on other data that we're getting.

DR. BREWINGTON: Doesn't that place it into C? I mean, C puts it in as a composite but meaningful primary health outcome. So the way I'm reading go that question, and someone correct me if I'm misreading it, as part of a composite of a meaningful primary it becomes weighted, right?

DR. MILLER: I would look at it slightly differently, so a secondary health outcome you could be looking at four or five different things including, you know, complications, et cetera, and quality of life, so those are important secondary outcomes that would be assessed in a trial. A composite outcome is saying like does this affect disability, quality of life, plus mortality, plus et cetera, and so any one of those individual outcomes might not be significant but the composite combination of them is, which is why I'm extremely hesitant about including or recommending composite outcomes in this setting, because we want to know if technology is useful for the Medicare population for a specific primary outcome and a specific series of secondary outcomes, because we need to

completely answer that question.

DR. TYAGI: I too would agree with that because when it comes to composite outcomes it's almost kind of in this realm of, the CREST trial had a composite outcome of stroke and MI, although the stroke was around four percent, and two percent were cardio endarterectomy, and combined it was MI with a similar composite outcome, but it really wasn't comparable.

DR. CINQUEGRANI: A lot of times composite outcomes, you know, death, cardiovascular death and MI, so all these things are really, the positivity of the measured outcome is driven by one of the factors or the options, so it can be a little misleading. I think, you know, this is obviously very important. The question is, you know, if you're designing the trial to see how people do in response to some stroke therapy obviously you have to have a primary outcome if it works, did it work or not. But it's also incredibly important given the nature of stroke and its impact on peoples lives over time, how does it affect their quality of life, so this

is a very important question. I don't think it's a standalone primary outcome of the trial unless the trial you're looking at here is quality of life, but if it's a therapeutic intervention which we're supposed to be addressing, new devices or whatever, then this would be a very important secondary health outcome related to the impacts of stroke over time.

DR. MILLER: And having it as a secondary outcome allows it to stand cleanly on its own rather than getting washed away by other effects. So that way you know, you could know if a device improves someone's quality of life or not, versus if you mix that with other outcomes, it's harder to answer that question.

DR. CINQUEGRANI: You can get lost.

DR. BREWINGTON: All right, I agree with that perspective, because I think at the end of the day when you do get to a longitudinal review of this device, which is what we're talking about, you know, if you found that, hypothetically that you had an improved survival rate but at the end of the day all those patients that survived, this

being extreme, said but I wouldn't want to live like this, then we'd go back and we'd change whether it's this device, or this treatment should continue.

DR. BACH: Dr. Brewington, speaking of the end of the day, we're rounding out towards the end of this discussion section. I don't want to ignore an important points that people try to make. Although, Joe Chin, I think I saw your hand up but I don't know if was residual, so do you have something you want to say now? Otherwise I'm going to move us to a shorter than scheduled break, I apologize for that.

Dr. Waldren, do you have something to say also?

DR. CHIN: Not at this time, thank you.

DR. BACH: Joe Chin, you have nothing. Dr. Waldren?

DR. WALDREN: Yes, just one, I guess one question since it's been a long time since I've been really in the clinical research space. So it seems like when we look at all of these measures in regards to what a primary measure should be, there's significant

limitations for all of them. So I guess, can you have a study that just has a bunch of secondary measures then there's no primary, or do you have to have a primary measure?

DR. BACH: I'll try to take that. I think that's probably beyond the scope of this discussion, or a discussion that would be particularly useful for CMS. I think sort of the Stats 101 answer would be no, because you have to have a power calculation for a study, which means you have to have a primary outcome to design it around.

DR. WALDREN: I'm sorry, Peter. I guess one reason I was asking that is like if you have to have one, I guess that's what I was trying to weigh in on thinking about these is like okay, the ones we've discussed, would I move up my confidence because of all the ones that we've listed, it's the worst least option, so anyway, thank you.

DR. BACH: Fair enough. I think there is a score for least bad options that will come up in the voting.

Can I bring this section of the discussion to a close at this point and bring

everyone back, is there any objection to a five-minute break so we can stay on schedule? I mean, we're a little behind but not bad. Then we'll come back at 3:06 eastern for the voting and a couple of remarks. Thank you.

(Recess.)

So, I think there's been a reasonable amount of discussion regarding how the voting works at this point. I'm happy to go through the ranking of the answers but those have also been reviewed. Are there any questions? I certainly don't want to belabor the Likert scale that's in front of you. Are there any questions about it?

Okay, so the order of events is I'll read the question, you will all vote. As the votes are given there will be that little thing where we figure out if everyone has voted. As soon as that is done we'll look at the distribution of scores, at that point you cannot change your vote. Actually you can't change your vote as soon as you enter it, you won't see anyone's vote until all are entered, I apologize if I misspoke. And then I'm going to poll each of you, you're going to speak

verbally your vote. I'm going to say your name, I'm just going to go alphabetically down the list, you'll say what your vote is, and that's a moment where you can give explanation but you are under no obligation to do so. And then we'll go through each of the questions as it played out in the votes and we'll have a discussion again, if needed, if not redundant, it supplements. So again, there's no requirements on any of those things except for the votes themselves.

DR. LAHEY: What is the session ID?

DR. BACH: Tara, do you want to put it into the chat again? I have it. For anyone who hasn't --

MS. HALL: Please don't say the session out loud. Who asked for the session ID?

DR. BACH: Dr. Lahey.

DR. LAHEY: Oh, I had it on my iPhone, it says hello, put in session ID.

MS. HALL: Okay. I'm going to send you a message, I'm going to sent you an email and in the chat room.

DR. THOMAS: This is Greg Thomas, I

would like the same thing.

DR. STEPHENS: And Allison Stephens.

DR. LAHEY: I got nothing.

DR. THOMAS: I see it on mine now.

DR. LAHEY: I see it, okay.

DR. BACH: Allison, do you have it?

DR. STEPHENS: I do, and yet it's the same one I had before, for some reason it's not letting me in, so let me try it again. Voila, thank you.

DR. BACH: Okay. Is there anyone who is not logged in?

DR. LAHEY: Just me, I'm trying to do the user name, is that from our previous?

MS. HALL: It's your first name, your last name and your email.

(Inaudible colloquy.)

DR. THOMAS: I got it, okay.

DR. LAHEY: Bingo.

DR. THOMAS: I've got a number associated with the ID.

MS. HALL: There shouldn't be.

DR. BACH: Who is still not in the system? I'm going to take it that everybody is logged in; is that correct? Is there anyone

not logged in?

DR. THOMAS: I'm good.

DR. BACH: Okay, great. I'm going to commence with the first question. Question number one, how confident are you that the following are standalone meaningful primary health outcomes in research studies of cerebrovascular disease technologies:

So the first question is, A, major disabling stroke, defined as stroke in the treated vascular territory that results in a modified Rankin Scale of greater than or equal to three? Please go ahead and vote.

(The panel voted and votes were recorded by staff.)

DR. STEPHENS: I tried to vote but it kicked me out, so I'm going to try to log back in again.

DR. BACH: Thank you. CMS, this is not, there's something wrong with our system it looks like, so I'm going to ask everyone to vote, while voting please don't look at the screen, none of the votes are supposed to be revealed until all the votes are in.

MS. HALL: As people vote, the number

show you who voted but they don't tell you exactly who pressed what.

DR. BACH: It's still not -- but the way we had it set up last time, it's not supposed to show any results until all votes have been collected, so I'm going to, if we can't fix that I'm just going to ask the panelists to do their best not to look at the screen while they're voting, to complete your vote before you look at what the results start to come in as. CMS, if you can fix that, that would be terrific. Okay. And also we have one too many votes, we should have only ten, I believe. Oh no.

MS. HALL: No, we have 11. Everyone has voted.

DR. BACH: I didn't count Joe, thank you. Okay. We collected the votes, I'm going to go down and poll each of you for your, if you would announce verbally, state what your vote was and if you want to add clarity at any time, this is an opportunity to do so. Dr. Ross?

DR. ROSS: I voted a five, with the idea that it would be used for intermediate and

longer-term outcomes.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: I voted four.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: I voted four.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: I voted five.

DR. BACH: Dr. Lahey?

DR. LAHEY: I voted four.

DR. BACH: Dr. Miller?

DR. MILLER: I voted four.

DR. BACH: Dr. Speir?

DR. SPEIR: Four.

DR. BACH: Dr. Stephens?

DR. STEPHENS: Four.

DR. BACH: Dr. Tyagi?

DR. TYAGI: Four.

DR. BACH: Dr. Thomas? Dr. Thomas?

DR. THOMAS: Four.

DR. BACH: Thank you. And Dr. Waldren?

DR. WALDREN: Three.

DR. BACH: Okay.

DR. WALDREN: Mostly for the etiology, I think these might need to be changed, but

three is my highest.

DR. BACH: Okay. Let's go on to question B, 1.B. CMS, can you clear the screen? And again, I'm going to ask the panelists not to look at how the results are coming in until you have voted. This same question one would be B, the outcome is decrease in the modified Rankin Scale of greater than or equal to two points compared to baseline. (The panel voted and votes were recorded by staff.)

MS. HALL: Everyone has voted.

DR. BACH: Thank you. Dr. Ross?

DR. ROSS: I voted a two.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: I voted two.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: I voted four.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: Four.

DR. BACH: Dr. Lahey?

DR. LAHEY: Two.

DR. BACH: Dr. Miller?

DR. MILLER: Four.

DR. BACH: Dr. Speir?

DR. SPEIR: Three.
DR. BACH: Dr. Stephens?
DR. STEPHENS: Four.
DR. BACH: Dr. Tyagi?
DR. TYAGI: Five.
DR. BACH: Dr. Thomas?
DR. THOMAS: Four.
DR. BACH: Dr. Waldren?
DR. WALDREN: Two.
DR. BACH: Okay, we can go on to the next, 1.C. CMS. You're capturing these mean values?
MS. HALL: Yes.
DR. BACH: Okay, great. 1.C, modified Rankin score of less than or equal to two, or equal to the pre-stroke modified Rankin score if the pre-stroke modified Rankin score greater than two.
(The panel voted and votes were recorded by staff.)
MS. HALL: We need one more vote.
DR. BACH: Great, we have all 11. Dr. Ross?
DR. ROSS: I voted three.
DR. BACH: Dr. Brewington?

DR. BREWINGTON: I voted three.
DR. BACH: Dr. Cinquegrani?
DR. CINQUEGRANI: Three.
DR. BACH: Dr. Kazerooni?
DR. KAZEROONI: Three.
DR. BACH: Dr. Lahey?
DR. LAHEY: Two.
DR. BACH: Dr. Miller?
DR. MILLER: Four.
DR. BACH: Dr. Speir?
DR. SPEIR: Three.
DR. BACH: Dr. Stephens?
DR. STEPHENS: Four.
DR. BACH: Dr. Tyagi?
DR. TYAGI: Five.
DR. BACH: Dr. Thomas?
DR. THOMAS: Four.
DR. BACH: Dr. Waldren?
DR. WALDREN: Two.
DR. BACH: And if we could go on to 1.D? Okay, other kinds of stroke such as major ipsilateral stroke or morbid stroke.
(The panel voted and votes were recorded by staff.)
Great. Dr. Ross?

DR. ROSS: I voted a four. I interpreted it as using the modified Rankin Scale for other types of stroke, that's how I interpreted the question.

DR. BACH: Great, thank you. Dr. Brewington?

DR. BREWINGTON: I voted three.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Four, I interpreted it the same way as Dr. Ross.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: Three.

DR. BACH: Dr. Lahey?

DR. LAHEY: Three.

DR. BACH: Dr. Miller?

DR. MILLER: Three.

DR. BACH: Dr. Speir?

DR. SPEIR: Three, for the reasons noted above.

DR. BACH: Thank you. Dr. Stephens?

DR. STEPHENS: One, due to the ambiguity of the definition.

DR. BACH: Dr. Tyagi?

DR. TYAGI: Three.

DR. BACH: Dr. Thomas?

DR. THOMAS: Three.

DR. BACH: Dr. Waldren?

DR. WALDREN: Two.

DR. BACH: Great. We can pause here. Thank you, CMS. We can pause here, so we're asked for each health outcome greater than or equal to an intermediate confidence, please discuss the appropriate length of followup post intervention for assessing this outcome. So of these, CMS, which ones achieved greater than two-and-a-half? I think it was the first three but I'm not certain of that. Tara, did we have, do you have the averages from these votes?

MS. HALL: I'm not keeping score, I'm reaching out to the person who is, they can answer it.

DR. BACH: All right, I'm confident the first one had an average greater than three, so if we can start with the first one, which is major disabling stroke, the question is the appropriate length of followup post intervention for assessing this outcome.

And I can float the idea if we focus on for example, 30 days, 90 days or one year

for example, as alternatives for length of outcomes, since those appear to be the ones that show up in the various trials.

DR. ROSS: Peter, this is Joe Ross. I can start by saying that based on the presentations we heard there was a lot of confidence around using it at 90 days and longer, so that's how I made my vote, that was my qualifier.

DR. MILLER: The same, 90 days for embolic-thrombotic, and then probably, intracerebral hemorrhage probably a year. And unclear, lacunar would probably fall under embolic-thrombotic.

DR. KAZEROONI: I agree with that statement.

DR. SPEIR: I agree with that statement.

DR. THOMAS: I'd add also that for the severe strokes and the nonischemic category that they also be considered useful for 180 or one year.

DR. WALDREN: I agree with Dr. Thomas on the 180 just because of the follow-up concerns at one year, if you have that data.

DR. MILLER: Agreed.

DR. BACH: Okay. And on the decrease in mRS of greater than two points compared to baseline -- all four of these scores were greater than two-and-a-half by the the way so we're going to discuss all four of them. The decrease in mRS greater than two points compared to baseline.

MR. MILLER: I imagine it would be similar to our prior metrics.

DR. BREWINGTON: Agree.

DR. BACH: And for Item C?

DR. ROSS: Can I just note, Peter, that there was some reluctance among the presenters around using the baseline measure of the modified Rankin, we didn't discuss that, but I'll just raise it here so that they have it.

DR. MILLER: Well, my thought there was as long as you do a modified Rankin prior to discharge and then compare it to that and have that be the baseline, or the also question about cross-matching the NIH Stroke Scale which is done at the time of diagnosis or for diagnosis, to the modified Rankin, so that's

another measure alternative.

DR. ROSS: That's helpful.

DR. BACH: Okay. And for the modified Rankin of less than or equal to two, or equal to pre-stroke modified Rankin if the pre-stroke modified Rankin was greater than two?

DR. MILLER: I imagine they're similar timeframes.

DR. KAZEROONI: Agree.

DR. BACH: And D, I don't want to lead you, but the same for D for different for D?

DR. STEPHENS: Well, I'd like to say, I would say they might be truncated a little bit more for people who already were at a greater than two level, because I would think that, I don't know, things might be exacerbated or there, you know, there just might be needs to follow up on if a person is already starting and walking into this, or having a stroke with already having that two or greater.

DR. MILLER: A modified Rankin of two is a slight disability, unable to carry out all previous activities but able to look after their own affairs without assistance, so I'd say maybe for two, and then that might be

truncated for higher than two.

DR. STEPHENS: I can see that.

DR. BACH: Great. And for other kinds of stroke such as major ipsilateral stroke or morbid stroke?

DR. SPEIR: I'd put it the same way as we did for the disabling strokes, the number one, or the A.

DR. MILLER: I agree.

UNIDENTIFIED SPEAKER: Agree.

DR. THOMAS: Peter, is it appropriate the composite outcomes here?

DR. BACH: Sure, you can.

DR. THOMAS: Sure. I would hope that as raised earlier, composites are important if they give a study power and again, these studies are hard to do, hard to get consent, et cetera, et cetera, but I would hope that with composites that the trialists tried to group endpoints that are fairly equivalent so we don't have a, you know, a weak endpoint that's not that important to the patient or the clinician driving a composite being favorable, for example.

DR. MILLER: I share that, I would say

that if there were a composite endpoint it should have the same sort of measurements or similar types of measurements as opposed to sticking in combating factors to overpower the trial to find the positive primary outcome, that would then be less meaningful to Medicare beneficiaries.

DR. BACH: The next bullet is for each health outcome greater than two for all of the outcomes above, discuss the appropriate cutoff points for either modified Rankin or the NIH Stroke Scale for assessing these outcomes. So for major disabling stroke?

DR. SPEIR: Doesn't the question define that cutoff?

DR. BACH: I think it does.

DR. MILLER: I think A through C, correct me if I'm wrong, defined the cutoffs for the modified Rankin, not for the Stroke Scale, because the Stroke Scale as we discusses is a diagnostic tool as opposed to an outcome assessment tool primarily.

DR. BACH: Do you think it can be applied to D?

DR. MILLER: You mean the NIH Stroke

Scale applied to D?

DR. BACH: Well, there's no modified Rankin in the cutoff in Item D either.

DR. MILLER: I would posit that it's a similar cutoff, but it would be either at the two-point transition or a major disabling -- well, you wouldn't want to duplicate the measurements, but it would probably be either any of the -- it could also be used to classify with lacunar strokes looking at other functional outcomes. I think the Question, D is a little unclear in this particular context, to me at least.

DR. SPEIR: Granted the modified Rankin is a whole other question, A through C was for modified Rankin.

DR. MILLER: Right, so unclear what D would be in this context.

DR. LAHEY: That's reasonable.

DR. BACH: There was, the next discussion point relates to considerations when using composite outcomes. I think Dr. Thomas, or maybe it wasn't you, I apologize if I got it wrong, already brought up some of the concerns or questions about composite outcomes. Are

there other comments related to the outcomes in this question or related ones in terms of combining them in research studies of cerebrovascular disease treatment technologies?

DR. MILLER: Again, I want to echo Dr. Thomas's comments, but composites should be different ways of measuring the same thing as opposed to like measuring a decrease in modified Rankin plus, say rehospitalization, which is not necessarily, that would not be a good composite outcome for example.

DR. BACH: Other comments?

DR. LAHEY: I agree, composites are fraught, it's could be problematic for the reasons mentioned earlier.

DR. BACH: Okay, I propose we move on to question two, if we can bring up the survey tool again. How confident are you that the following are standalone meaningful primary health outcomes in research studies of cerebrovascular disease treatment technologies: Question one is hospitalization, length of stay for the index procedure.

(The panel voted and votes were recorded by staff.)

Dr. Ross?
DR. ROSS: I voted a two.
DR. BACH: Dr. Brewington?
DR. BREWINGTON: Two.
DR. BACH: Dr. Cinquegrani?
DR. CINQUEGRANI: One.
DR. BACH: Dr. Kazerooni?
DR. KAZEROONI: Three.
DR. BACH: Dr. Lahey?
DR. LAHEY: One.
DR. BACH: Dr. Miller?
DR. MILLER: Two.
DR. BACH: Dr. Speir?
DR. SPEIR: Two.
DR. BACH: Dr. Stephens?
DR. STEPHENS: Two.
DR. BACH: Dr. Tyagi?
DR. TYAGI: I voted three. It didn't really say primary or secondary outcomes so I found it could be somewhat important.
DR. BACH: Dr. Thomas?
DR. THOMAS: One.
DR. BACH: Dr. Waldren?
DR. WALDREN: One.
DR. BACH: The next question, 2.B, the

number of unscheduled readmissions that are related to cerebrovascular disease.

(The panel voted and votes were recorded by staff.)

Dr. Ross?

DR. ROSS: I voted a five, particularly with respect to repeat procedures.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: I voted three.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Two.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: Three.

DR. BACH: Dr. Lahey?

DR. LAHEY: Two.

DR. BACH: Dr. Miller?

DR. MILLER: Two.

DR. BACH: Dr. Speir?

DR. SPEIR: Two.

DR. BACH: Dr. Stephens?

DR. STEPHENS: Three.

DR. BACH: Dr. Tyagi?

DR. TYAGI: I voted four. I mean, if it's directly related to cerebrovascular disease it should be important.

DR. BACH: Dr. Thomas?

DR. THOMAS: I voted two.

DR. BACH: Dr. Waldren?

DR. WALDREN: Two.

DR. BACH: And then, okay, and Item C, discharge disposition to rehabilitation, home versus inpatient facility, and I will add more texture to this question which is, there's obviously a broad range of hospital discharge types, but I think the general dimensionality is clear in the question.

(The panel voted and votes were recorded by staff.)

MS. HALL: Waiting on one vote.

DR. BACH: There we go. Dr. Ross?

DR. ROSS: I voted a four, I would recommend that CMS consider other dimensions like actual death as well as socioeconomic status.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: I voted three and agree with the socioeconomic considerations that need to be put in.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Three.

DR. BACH: Dr. Kazerooni?
DR. KAZEROONI: Three.
DR. BACH: Dr. Lahey?
DR. LAHEY: I voted four and also agree that it's very important to account for the socioeconomic factors.
DR. BACH: Dr. Miller?
DR. MILLER: Three.
DR. BACH: Dr. Speir?
DR. SPEIR: Three.
DR. BACH: Dr. Stephens?
DR. STEPHENS: Three. I also agree with the socioeconomic factors and want to highlight that there are other intervening factors that are, or that may not be positive, and that could change the discharge plan.
DR. BACH: Dr. Tyagi?
DR. TYAGI: I voted three. I would have voted higher but for all the reasons stated above I felt like there were other factors than just looking at this alone, and that's my vote.
DR. BACH: Dr. Thomas?
DR. THOMAS: Two.
DR. BACH: Dr. Waldren?

DR. WALDREN: Two. I was concerned about the confounding factors in the steering but I feel this would be a very important secondary, and I would have voted five if it were a secondary measure.

DR. BACH: Thank you. We're now going to move to discussion on question two where the second two measures, the B and C measures qualify for discussion. So for each of the health outcomes B and C were greater than or equal to intermediate confidence, and please the appropriate length of followup post intervention for assessing this outcome although this, to be clear, this only applies to B in this phrasing, the number, so this is a question about the duration of measurement for unscheduled readmissions that are related to cerebrovascular disease.

DR. ROSS: This is Joe Ross. I guess I would say for safety-related cerebrovascular disease like a complication of sorts, short term would be useful within 30 to 60 days, but I think the idea of needing to redo procedures would be a longer time period, I'd just defer to those specialists who actually do those

things.

DR. BACH: And actually an item of clarification, Joe. In that answer, are you starting the timing at the date of admission, index admission, or the date of index discharge when you say 30 days?

DR. ROSS: I probably would have said discharge.

DR. BACH: Okay, fair enough.

DR. LAHEY: I would say discharge as well and I would go to 90 days. I think beyond that you have other reasons why people are admitted and the data gets kind of noisy.

DR. WALDREN: I want to say 90 days for those situations, and that's in keeping with our responsibility to CMS.

DR. BREWINGTON: I agree with the 90 days as well post discharge.

DR. WALDREN: I actually had a comment about the index, I wonder about that index, you know, at the time of the intervention, just in case there's a subsequent intervention that has to be done before discharge.

DR. KAZEROONI: I guess I would add the time needs to coincide with the other

three-month measurements that are being taken, so we should be consistent across the timing.

DR. THOMAS: And I considered more 30 days because so often these measurements are 30 days, typical of other evaluations.

DR. STEPHENS: Yeah, I think in my experience 30 days is typical, and I am guess concerned about the idea of not going past 90 days, I do think that there is somewhat of an obligation, there are comorbidities where everything's involved, it can't just be I did my small part and left out there, so I would like to extend that a little bit although I can understand, you know, that the obligation at this point is 90 days.

DR. MILLER: Even though I didn't support this measure, one thing I think is worth pointing out is it's a question that says primary health outcome, so I think as a primary health outcome going longer as opposed to shorter would be more appropriate. I think if it were a secondary outcome, it could be shorter.

DR. CINQUEGRANI: I think the 90 days makes sense.

DR. BACH: Okay. And then the next question is, relates to composite outcomes that I think are intended to incorporate more these measures of the 2.A, B, C, although we're really only focusing on B and C in this case, but either way because of the scoring, but the question to you is to discuss important considerations when assessing the merits of composite outcomes in research studies of cerebrovascular disease treatment technologies, which include the combination of mortality, stroke, healthcare resource utilization for index procedures, post procedure and rehospitalization, and neurologic functional evaluation.

DR. MILLER: That sounds like you would view functional evaluation as a separate question from utilization of additional resources or required re-procedures, so I would not combine them, because they're measuring different things.

DR. BACH: Others?

DR. BREWINGTON: I think we discussed this, I mean for the reasons we discussed before about composite scoring and how they

carry equal value, I mean, I think we covered that in that discussion earlier before we started answering questions.

DR. BACH: Agreed.

DR. THOMAS: I think there's too much noise in these measurements to put them together, I think we would be adding noise to noise, so I'd suggest they be standalone.

DR. BACH: Anything else? Okay, I'd like to move on to question three please, if we can bring up the scoring thing. Question three reads, how confident are you that each of the following functional assessments are standalone meaningful primary health outcome measures in clinical research studies of cerebrovascular disease treatment technologies, the first one, A, the modified Rankin Scale?

(The panel voted and votes were recorded by staff.)

Dr. Ross?

DR. ROSS: I voted four.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: Five.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Four.

DR. BACH: Dr. Kazerooni?
DR. KAZEROONI: Five.
DR. BACH: Dr. Lahey?
DR. LAHEY: Five.
DR. BACH: Dr. Miller?
DR. MILLER: Four.
DR. BACH: Dr. Speir?
DR. SPEIR: Four.
DR. BACH: Dr. Stephens?
DR. STEPHENS: Four.
DR. BACH: Dr. Tyagi?
DR. TYAGI: Four.
DR. BACH: Dr. Thomas?
DR. THOMAS: Five.
DR. BACH: Dr. Waldren?
DR. WALDREN: Three. Four, I'm sorry.
DR. BACH: That's okay, thank you.
Question 3.b, the National Institutes of Health Stroke Scale, or NIHSS.
(The panel voted and votes were recorded by staff.)
Dr. Ross?
DR. ROSS: I voted a four, I wasn't really wasn't thinking it would be used explicitly for technologies being used acutely,

ou know, for a rapid treatment.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: I voted five for the exact same reason.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Four, for the same reason.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: I voted a four, thinking more about treatment outcomes that go beyond the immediate post-procedural timeframe.

DR. BACH: Dr. Lahey?

DR. LAHEY: I voted four, realizing there are some limitations to it, but it's still very important.

DR. BACH: Dr. Miller?

DR. MILLER: I voted one, viewing it primarily as a function as a diagnostic tool rather than as an outcomes assessment tool based upon our prior discussions and the multiple guest speakers.

DR. BACH: Dr. Speir?

DR. SPEIR: Four.

DR. BACH: Dr. Stephens?

DR. STEPHENS: Two, for the same

reason that it seems to be more of a diagnostic tool.

DR. BACH: Dr. Tyagi?

DR. TYAGI: I voted one. I think this is a poorly worded question, I think we all kind of similarly are thinking it, our voting is across the map.

DR. BACH: Dr. Thomas?

DR. THOMAS: Two, suggesting that it's more something to stratify patients on rather than an outcome measure given what the trialists commented about it, and --

DR. BACH: Dr. Waldren? I'm sorry, I didn't mean to cut you off.

DR. THOMAS: Imprecision of measurement, with the aphasic patient with a score of four for example.

DR. BACH: Dr Walden?

DR. WALDREN: Two, for the same reasons that others mentioned for two.

DR. BACH: All right. For each of these that received a score of greater than two-and-a-half, so for each of those, please discuss the appropriate length of followup post intervention for assessing the outcome. Let's

start with the modified Rankin Scale.

MS. HALL: Could I interject real quick, this is Tara Hall. When you are discussing, please say your name before you start speaking so we can keep track.

DR. BACH: I'm sorry about that, I should be enforcing that. That's great, thank you.

So this is Peter Bach, and I'm calling the group, let's first discuss the appropriate length of followup post intervention for assessing the modified Rankin Scale.

DR. MILLER: This is Brian Miller. I think based upon our prior discussions in question one, it's sort of where most people think it probably is, I agree.

DR. BACH: It's Peter Bach. Just to clarify, the discussion about these endpoints was, the length of followup was covered in some detail in the discussion for question one, CMS. Is that discussion satisfactory for this purpose?

DR. KAZEROONI: This is Ella, I agree.

DR. LAHEY: This is Steve Lahey, I think that would be sufficient.

DR. BACH: Okay. If there is, without any objection, if there is any objection to moving onto the second outcome measure, which is the NIHSS, which was not discussed in question one, if we could talk about the appropriate duration or length of followup post intervention for assessing that outcome. I already heard a couple people say that it was only appropriate for short time interval endpoints, but I'm not trying to lead the discussion, I just wanted to register that for CMS.

DR. TYAGI: I mean that's how I viewed it as but I didn't think the question made that distinction, did it?

DR. BACH: That was Dr. Tyagi. It's all right to add details to the answer, even if the question doesn't prompt them specifically.

DR. BREWINGTON: This is Dr. Brewington. I agree, I think it's mostly used for short term.

DR. CINQUEGRANI: Cinquegrani. I would say, you know, probably 90 days where most of the benefits accrue from interventional approaches and treatment of ischemic stroke

because, you know, if the intervention is effective it should be durable for at least 90 days.

DR. MILLER: This is Dr. Miller playing devil's advocate. The question asked about using NIH Stroke Scale as a primary health outcome, and it being an assessment tool as opposed to a measure of disability, and the issue at 90 days with the core stroke is disability, I would, recognizing my extremely low score, I would use this within a short period within hospitalization or say a week, because you don't want to measure disability with something that doesn't measure disability.

DR. ROSS: This is Joe Ross --

DR. KAZEROONI: This is Ella Kazerooni, I agree with Brian.

DR. ROSS: This is Joe Ross, I was going to say the same thing, I thought 48 hours may be a peak.

DR. STEPHENS: Allison Stephens. I think that if you have a poor assessment in the beginning it might affect the outcome, and so maybe things show up and it might be interesting to take a look at that what happens

at the 90-day mark, not to say that you wouldn't look at it earlier.

DR. SPEIR: This is Speir, seven days.

DR. MILLER: Dr. Miller again. 90 days, again, I think the question is, you're right that other things would show up, but I don't think that this tool necessarily would be the best tool to detect that.

DR. BACH: And just to add clarity here, the question, the entire question was organized around the concept that this is a primary health outcome measure in the clinical research study, just to help guide this discussion.

DR. MILLER: Right, and in that since this doesn't assess disability, as other things pop up you want to use a different tool to assess disability as opposed to this.

DR. LAHEY: Steve Lahey, I agree, seven days.

DR. KAZEROONI: So I would say seven days at the time of discharge, so seven days from the time of discharge of less than seven days.

DR. BACH: If we could go onto the

next bullet and again here, unless there's objection from the committee, I would propose we focus just on the NIH scale because the discussion of cutoffs, which is what bullet number two asks about, has been dealt with extensively with regard to the modified Rankin Scale. So the question for the NIH scale unless people want to also discuss the mRS, is please discuss the appropriate cutoff points for assessing this outcome.

DR. LAHEY: This is Steve Lahey, I would say seven days, as many of us have said.

DR. BACH: I think in this case, Dr. Lahey, the question's of cutoff of the scale, not the duration.

DR. LAHEY: Yep, yep, I see.

DR. BACH: If I'm understanding the question.

DR. LAHEY: Yep.

DR. KAZEROONI: This is Ella Kazerooni. If I'm remembering the discussion in the presentations today, there was not much focus on cut points of this variable compared to the Rankin score scale.

DR. CINQUEGRANI: Cinquegrani. The

NIH Stroke Scale went zero to four for mild, five to ten for moderate, 11 to 42 for severe.

DR. BACH: Thank you. The next bullet is on composite outcomes with the same list of potential outcomes that could be combined in some capacity by including neurologic functional evaluation, and I guess I'll ask whether or not there are additional comments now that we're at question three regarding this topic of composite outcomes, beyond those that CMS has already captured.

Barring that, the fourth bullet asks, are there any other functional assessments and there are a handful of examples given, the Barthel Index, the Fugl-Meyer Upper and Lower Extremity Scales, that we've not discussed, whose use you believe would result in important information pertaining to meaningful primary health outcomes in clinical research studies of cerebrovascular disease treatment technologies.

DR. MILLER: This is Dr. Miller. I think some of those indices or measuring tools might be useful for lacunar stroke. It's unclear which would because it would depend on what the deficit was, but having a more precise

measurement for lacunar strokes would probably be helpful and meaningful.

DR. THOMAS: Greg Thomas. I concur with giving trialists the opportunity to use these given their granularity from, you know, like the Barthel Index is one to a hundred, so that gives a really good opportunity to measure a change.

DR. SPEIR: This is Speir, I would agree with that. I'm not sure I would limit it to a lacunar report, rather giving our, those conducting the trials the most opportunity to measure depending on what their question is.

DR. MILLER: This is Dr. Miller and I agree with Dr. Speir and Dr. Thomas. I guess I was satisfying that it could be useful for all particular strokes, but in particular for lacunar strokes where improvement might not be detected by other measurement scales.

DR. BACH: I think we can move onto question four, CMS. It reads, how confident are you that using the EQ-5D to measure quality of life, Item A, is an adequate which reflects the patient experience in the context of cerebrovascular disease studies?

(The panel voted and votes were recorded by staff.)

DR. CINQUEGRANI: I'm having to log back in, just give me a moment.

DR. BACH: Dr. Ross?

DR. ROSS: I voted four.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: I voted four, with commentary that socioeconomics, again, should be taken into consideration.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Three.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: Also a score of four, and I agree with Dr. Brewington.

DR. BACH: Dr. Lahey please?

DR. LAHEY: Four.

DR. BACH: Dr. Miller?

DR. MILLER: Two, with the caveat that this might not have the granularity that is needed for this question.

DR. BACH: Dr. Speir?

DR. SPEIR: Four, agree with Brewington.

DR. BACH: Dr. Stephens?

DR. STEPHENS: Four.
DR. BACH: Dr. Tyagi?
DR. TYAGI: Four.
DR. BACH: Dr. Thomas?
DR. THOMAS: Four, and I agree that there may be other scales that for different types of stroke maybe have more granularity and precision measurement.
DR. BACH: Dr. Waldren?
DR. WALDREN: Four.
DR. BACH: Let's move onto 4.B, should be included as standalone meaningful primary health outcome measures in research studies.
(The panel voted and votes were recorded by staff.)
Dr. Ross?
DR. ROSS: I gave it a three.
DR. BACH: Dr. Brewington?
DR. BREWINGTON: I gave it a two, I think it should be a secondary.
DR. BACH: Dr. Cinquegrani?
DR. CINQUEGRANI: Two, for the same reasons as Dr. Brewington.
DR. BACH: Dr. Kazerooni?
DR. KAZEROONI: Three.

DR. BACH: Dr. Lahey?

DR. LAHEY: One. I guess I really think it should be a secondary.

DR. BACH: Dr. Miller?

DR. MILLER: Two, it should be a secondary measure.

DR. BACH: Dr. Speir?

DR. SPEIR: Three.

DR. BACH: Dr. Stephens?

DR. STEPHENS: Four, because I do think that there's quality for a particular tool that's used, but I also am going back to the question of needing to identify did it work yes or no, and I think if someone were to say what Dr. Brewington said is it may look like it works but I wouldn't want to live like this, then the answer is it didn't work.

DR. BACH: Dr. Tyagi?

DR. TYAGI: Three.

DR. BACH: Dr. Thomas?

DR. THOMAS: Two, it should be secondary.

DR. BACH: Dr. Waldren?

DR. WALDREN: Three, for non-major disabling strokes.

DR. BACH: Thank you. 4.C, should be included as a composite meaningful primary health outcome in research studies.

(The panel voted and votes were recorded by staff.)

Dr. Ross?

DR. ROSS: I gave it a four with the logic from the prior question around mortality or other disability with the composite.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: I gave it a two for the same reason.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Three here.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: I'm simpatico with Dr. Brewington on this one, I gave it a two for the same logic.

DR. BACH: I think we may have to review what the Likert scale is here, but anyway, Dr. Lahey?

DR. LAHEY: I gave it a two.

DR. BACH: Dr. Miller?

DR. MILLER: A glass is half empty and emptying, I gave it a one, and the primary

reason is that I think it should be an individual secondary outcome.

DR. LAHEY: Dr. Bach, this is Steve Lahey.

DR. BACH: Yeah?

DR. LAHEY: I read my thing wrong, I gave it a one for the same reason I gave it a one on the previous one.

DR. BACH: Got it, okay. CMS, did you capture that?

MS. HALL: Yes, we got that, thanks.

DR. BACH: Dr. Speir?

DR. SPEIR: Three.

DR. BACH: Dr. Stephens?

DR. STEPHENS: Three.

DR. BACH: Dr. Tyagi?

DR. TYAGI: Three.

DR. BACH: Dr. Thomas?

DR. THOMAS: Three, and I think that the PROMs are so new, I think they should be part of an exploratory endpoint and putting them together makes sense with other PROMs essentially.

DR. BACH: Dr. Waldren?

DR. WALDREN: I gave it a three

because it said should instead of shall. Sorry.

DR. BACH: No, thank you for making that comment. Okay, home stretch, people. Question 4.D, and thank you for keeping your sense of humor at this hour. Should be included as secondary health outcome measure in research studies.

(The panel voted and votes were recorded by staff.)

Dr. Ross.

DR. ROSS: I gave it a five.

DR. BACH: Dr. Brewington?

DR. BREWINGTON: Five.

DR. BACH: Dr. Cinquegrani?

DR. CINQUEGRANI: Four.

DR. BACH: Dr. Kazerooni?

DR. KAZEROONI: After a five, this is a five, I think that's where the sweet spot is.

DR. BACH: Dr. Lahey?

DR. LAHEY: I gave it a five. I think it absolutely should be a secondary.

DR. BACH: Dr. Miller?

DR. MILLER: I gave it a three. The rationale is I think quality of life should be

a secondary outcome as a five, but this particular measurement tool might not be the best for this circumstance, hence a three.

DR. BACH: Dr. Speir?

DR. SPEIR: Four.

DR. BACH: Dr. Stephens?

DR. STEPHENS: Five.

DR. BACH: Dr. Tyagi?

DR. TYAGI: Five.

DR. BACH: Dr. Thomas?

DR. THOMAS: Four.

DR. BACH: Dr. Waldren?

DR. WALDREN: Five.

DR. BACH: Terrific, thank you for your votes. The remaining discussion questions relate to this general category but they are not of exactly the flavor of the prior discussion questions.

The first one is to discuss whether additional patient-reported measurements such as the SF-36 or the Stroke Impact Scale 16 should be captured burdens associated with cerebrovascular disease treatment therapies under study.

DR. SPEIR: I think the SF-36 is a

good tool, I'm not familiar with the Stroke Impact Scale 16 unfortunately.

DR. THOMAS: This is Greg Thomas. I took a look at the Stroke Impact Scale and it looks very disease specific and I like it as that because I have some concerns about things that are measuring things other than neurological function.

DR. LAHEY: And I agree, I think the SF-36 is so broad, it's used so often that it kind of loses a little bit of its impact and I think the Stroke Impact Scale is a bit more relevant for this issue.

DR. STEPHENS: I think it depends on what you're looking for, what kind of information you're trying to check.

DR. BACH: The next question is, please discuss the minimal clinically improper differences for the instruments. I think here we're looking primarily at the EQ-5D, although comments about the other instruments I'm sure would be welcomed.

DR. THOMAS: I don't recall in the presentations, people discussed that aspect of this particular measure.

DR. MILLER: I don't think it was discussed.

MS. HALL: Please remember to state your names when you're speaking.

DR. THOMAS: Oh, that was Thomas.

DR. MILLER: And Dr. Miller. It's going to be hard for me to describe that --

MS. HALL: Go ahead.

DR. THOMAS: Like I said, this is Thomas. It's going to be hard for me to describe it without the expertise of someone, one of the presenters or more of the presenters.

DR. ROSS: This is Joe Ross. I also do not know the measure of specifications but I would fully encourage CMS to consider the minimally clinically important difference when using the instrument.

DR. BACH: The next and final discussion point is, please discuss the appropriate length of followup post intervention for assessing patient-reported measurements such as, they don't say it here but for example the EQ-5D.

DR. BREWINGTON: This is Brewington.

I think we should go back to the original statement of assessing them at the same time intervals for quality of life, so going all the way out to a year if we go out to a year on the other measures.

DR. BACH: Thank you.

DR. KAZEROONI: This is Ella Kazerooni. I think we had I think recommended one year for the major disabling strokes and for hemorrhagic but not for the other categories of changes in modified Rankin score, and I would support doing that in parallel with this measure.

DR. SPEIR: This is Speir, I would make it a year.

DR. THOMAS: This is Thomas, I'd recommend 90 days because I think you have a lot of, between that and the 360, a lot more reframing potentially of what's acceptable, and I want to look at the measure, the acute aspect of the measure.

DR. MILLER: This is Dr. Miller. I agree with Dr. Thomas.

DR. LAHEY: Steve Lahey. I think it should go out to a year, I think there's a lot

of valuable information that we could get at one year.

DR. KAZEROONI: This is Ella Kazerooni. Just for clarification, so in some of the earlier measures when we were discussing outcomes we said three months, and for another subset we said three months and one year, so would this supercede those measurements where we only said three months for some of the other variables? So we had said for decrease in mRS greater than equal to two points per the baseline and for mRS less than or equal to two or equal to pre-stroke mRS, and we said three months unless it was a hemorrhagic stroke, where we said add one year. So we didn't use one year for all of the other time points, I'm just bringing that up.

DR. THOMAS: Yeah, we kind of said for the severe strokes and the bleed strokes se said a year, but for the fixed strokes a typical time is 90 days.

DR. KAZEROONI: Right, so would we be saying we recommend the EQ-5D at one year for everybody, or stay with the same recommended timeframe that we had for the other measures?

Is it important enough to add it for all the others, for one year for all the subcategories we discussed earlier?

DR. THOMAS: I'd suggest a 90 days, because the study could end earlier that way if there's only one measure at a year, and that delays by nine months reporting the study.

DR. BREWINGTON: I'd say I intended for it to be congruent with the other measure, so if we said 90 for something, then I'd say measure the quality of life out to 90; if it was severe stroke and we went out to a year, then I would say measure the quality of life out to a year, because the assumption would be that we were measuring a shorter period of time because this was a, I guess a more immediate fix.

DR. KAZEROONI: This is Dr. Kazerooni. I agree with Dr. Brewington.

DR. LAHEY: This is Steve Lahey. I'm not looking for congruence here, because I think this is a PROMs as opposed to clinician-generated data that, I mean it's totally different. I'm very interested in what the patient perceives as his or her health

status out to a year, which can change quite a bit.

DR. STEPHENS: Allison Stephens, I'm in agreement with Dr. Lahey.

DR. BACH: Okay, I think this concludes the voting and discussion of the vote section of the MEDCAC meeting, which is the last formal part of panel input. We now have a period where we can have an open discussion if there are lingering issues or for whatever reasons the questions or discussions didn't touched on, other issues that are felt to be by any of you of importance. So I would just say that for the panelists, the floor is open.

DR. THOMAS: This is Thomas. I would like to comment, in the 40 or so years since internship in cardiology I've seen the risk of in-hospital death for acute myocardial infarction go from 25 percent to five percent and that was done with research studies that showed that as much as one percent decrease in mortality, for example PPA versus (unintelligible) the AUGUSTA trial if I got the name right was just one percent. So I encourage as we try to do similar things with

stroke to look for small improvements and use the best statistics we can, the most granular opportunities, the utility brain shift for example to, you know, look for small changes, because small changes end up being big changes if we add them together.

DR. BACH: Thank you for that comment.

DR. SPEIR: This is Alan Speir. I really appreciated being a part of this panel and I've learned a lot today, I'm confused a lot as well, but I've learned a lot. I do think, Peter, and I appreciated you keeping us on task, particularly your admonitions around costs and around finances. I do feel that it is in this day and age restrictive of CMS to not include this in our conversations and in our assessments, because particularly as we're looking at new technology and the cost of new technology and the impact it has, we ought to have that as discussable points, so I found that quite restrictive. But that's, I know you wanted to admonish me for bringing it up, so here's your chance.

DR. BACH: I certainly was not admonishing you, I was rearticulating the

domain of statutory authority that the guide in the Coverage and Analysis Group, and I think the simpler answer is if you feel that way you should tell your congressman and if enough of us do that, then maybe things will change.

DR. LAHEY: I can assure you that Alan Speir and I do speak to our congressmen quite a bit.

DR. THOMAS: I think we might have a legislative day coming up.

DR. BACH: I have to warn you, the MEDCAC meeting would be longer if we also had a section on costs, so it's something to think about in terms of caring about your chair.

Are there any other topics? I want to, I'm going to give Joe Chin a chance to say something, but I want to thank you all for your perseverance, this is much more difficult on Zoom than it is to do in person, and it's, the level of focus and seriousness with which you've taken this task, which is at times quite difficult, is deeply appreciated. I just want to thank you all for your collegiality and for your participation. Joe?

DR. CHIN: Thanks, and I would like to

echo that thought. It's been a long day, I think it's a lot of information for us, it's extremely helpful. I think as we heard mentioned earlier this morning even though we don't have an open coverage determination on any of these types of devices, the discussions and the presentations and the input are extremely important to other aspects of our work, including a review of similar files, and also provide clarity, I believe, to providers, clinicians, innovators as they really look at these devices and try to develop them perhaps. And also in that sense helps us, you know, provide an opportunity for input, particular input in an open transparent manner that you see at MEDCAC.

I think much of the discussion during the discussion of the questions did mirror actually some of our internal discussions, because it is really complex issues on some of these aspects of the testing, so I think all that discussion will be very helpful to us.

I would like to highlight one point that I think has been raised a number of times during the day and I think we are strongly

encouraging that as these studies are developed that we do actually include unrepresented populations in these trials of these devices so that we actually do have a better sense of what's going on. I think that's a priority for CMS and I think that's really important at this point.

I would like to, you know, thank of course Dr. Bach and Dr. Ross for chairing the meeting and getting us through the meeting on time. I also want to acknowledge Tara Hall as our primary point of contact and Michelle Atkinson, the division director for the division that organizes the MEDCAC, and I see many of the names of our staff on the screen that actually have been working very hard to make sure things go well.

And in addition, I have to end these with an award we presented this morning to Dr. Steven Chu, who is really our primary, and our subject matter experts who have provided a lot.

So with that, really, thanks everyone, I hope everyone has a nice evening, and I'll turn it back over to Peter.

DR. BACH: I have no more housekeeping really. Thank you all for your time. I do want to also acknowledge CMS staff including Tara Hall. It's probably apparent to you the amount of work that goes into preparing for this meeting and scheduling it and arranging for speakers to present a diverse and educated set of viewpoints in their data rich presentations, and also there's a great deal of work that will now come afterwards where all of the input and comments will be incorporated into CMS's thinking going forward.

So just thank you all again for all of your time, and I'm going to call the meeting to an end.

(Whereupon, the meeting adjourned at 4:18 p.m. EDT.)