CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Evidence Development & Coverage

Advisory Committee

March 22, 2017

Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

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Panelists

Chairperson
Rita Redberg, MD, MSC

Acting Committee Vice Chair
Alan Hirsch, MD

MedCAC Members
Salvador Cruz-Flores, MD, MPH
Michael J. Fisch, MD, MPH, FACP
Fred Kobylarz, MD, MPH
Marcel Salive, MD, MPH
Art Sedrakyan, MD, PhD
Jodi B. Segal, MD, MPH
Julie Ann Swain, MD
Diana Zuckerman, PhD

Representatives
Eileen Hsich, MD
Lynne Warner Stevenson, MD

Industry Representative
Adi Renbaum, MBA

Guest Panel Members
Elise Berliner, PhD
Patrice Desvigne-Nickens, MD
Clyde W. Yancy, MD, MSc, MACC, FAHA
Bram Zuckerman, MD

Invited Guest Speakers
Philip B. Adamson, MD, MSc, FACC
Larry A. Allen, MD, MHS
John D. Carroll, MD

William Lawrence, MD
Ileana L. Pina, MD, MPH

CMS Liaison
Joseph Chin, MD

Executive Secretary
Maria Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:07 a.m., Wednesday, March 22, 2017.)

MS. ELLIS: Good morning and welcome, committee chairperson, acting vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, called MedCAC. The committee is here today to

discuss recommendations regarding what health outcomes and studies for heart failure treatment technology should be of interest to CMS.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflict of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate

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family owns stock or has another form of financial interest in any company, including an Internet or E-Commerce organization, that develops, manufactures, distributes and/or

markets consulting, evidence reviews or analyses or other services related to treatment of heart failure or mitral valve regurgitation. This includes direct financial investments, consulting fees and significant institutional support. If you have not already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mic, and state your name.

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For the record, the voting members present for today's meeting are Dr. Alan Hirsch, Dr. Salvador Cruz-Flores, Dr. Michael Fisch, Dr. Fred Kobylarz, Dr. Marcel Salive, Dr. Art Sedrakyan, Dr. Jodi Segal, Dr. Julie Ann Swain, and Dr. Diana Zuckerman. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including nonvoting members, will participate in the voting. The voting results will be available on our website following the meeting.

I ask that all panel members please speak directly into the mics. This meeting is being webcast via CMS in addition to the transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeness and voice during the meeting. You are also giving consent to the use and distribution of any personal 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 members of the audience, including the media, are anxious to speak with the panel about these proceedings. However, CMS and the committee will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks and at lunch.

If you require a taxicab, there are telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of this room.

At ten a.m. there will be a shelter in place exercise conducted here at CMS. It will

be announced over the CMS public address system. This will not affect us, so we will continue with the meeting so when it comes on, just keep moving. I mean, don't move, just stay in your seats, I'm sorry, continue with the meeting, don't move, stay in place.

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And lastly, all CMS guests attending today's MedCAC meeting are only permitted in the following areas of CMS single site, the main lobby, the auditorium, the lower level lobby and the cafeteria. Any person found in any other area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now, I would like to turn the meeting over to Dr. Joseph Chin.

DR. CHIN: Thank you, Maria, and good morning. We would like to welcome our panel, our invited speakers and our guests to CMS. We thank you for your participation on a topic that's very important to our Medicare

population given the prevalence of this condition. So, I think we have a very interesting agenda and I think we should proceed, so I'll turn it over to Dr. Rita Redberg, our chair of the MedCAC.

DR. REDBERG: Thanks very much, Joe, and I just want to add my welcome to all of the guests, the new panel members, the returning panel members. As Maria noted, we do have a full and will have a very interesting

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discussion today, but in the interest of letting everyone, because we want to hear what everyone has to say, one of my roles will be to make sure we all stay on time so that we'll follow the schedule and try to follow that exactly.

So I think we'll start now and just do introductions of all of the committee. Again, I'm Rita Redberg, I'm a cardiologist at the University of California at San Francisco, and

I have no conflicts.

DR. HIRSCH: My name is Alan Hirsch. I'm a professor of medicine, epidemiology and community health at the University of Minnesota Medical School, and I have no conflicts.

DR. CRUZ-FLORES: My name is Salvador Cruz-Flores, I'm a professor in the Department of Neurology at Texas Tech. I am a member of the panel and I don't have conflicts.

DR. FISCH: I am Michael Fisch, I'm a medical oncologist and palliative care physician. I'm the national medical director of medical oncology with AIM Specialty Health, which is a subsidiary of Anthem Incorporated, and I work at M.D. Anderson Cancer Center as a

clinical specialist.

DR. REDBERG: Did you state --

DR. FISCH: I have no conflicts of interest other than employment with AIM Specialty.

DR. KOBYLARZ: My name is Fred

Kobylarz, I'm an academic geriatrician at Robert Wood Johnson Medical School. I have no conflicts of interest.

DR. SALIVE: Good morning. I'm Marcel Salive, a medical officer at the National Institute on Aging as part of the NIH, and I have no conflicts.

DR. SEDRAKYAN: Good morning. I'm Art Sedrakyan from Weill Cornell Medicine. I'm a professor of health care policy and research, and I have no conflicts of interest.

DR. SEGAL: I'm Jodi Segal, I'm a professor of medicine, health policy and epidemiology at Johns Hopkins University. No conflicts.

DR. SWAIN: Julie Swain, cardiovascular surgeon, vice chair of the department at Mount Sinai School of Medicine in New York. No conflicts.

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DR. D. ZUCKERMAN: Diana Zuckerman,

president of the National Center for Health Research, trained in epidemiology and psychology, and I have no known conflicts of interest.

DR. HSICH: I'm Eileen Hsich, I'm at the Cleveland Clinic, I'm a heart failure and transplant cardiologist, and I have no conflicts.

DR. STEVENSON: Lynne Warner Stevenson, professor of medicine, Harvard Medical School, director of the heart failure program at Brigham and Women's Hospital, I'm one of the PIs of the INTERMACS registry. My division receives support from Novartis and St. Jude, and I am an unpaid consultant for St. Jude and Medtronic.

MS. RENBAUM: I'm Adi Renbaum, I'm the industry representative. I work with a variety of clinical device companies in obtaining coverage and payment, although I don't work with any involved in heart patients at this time, and have no conflicts.

DR. BERLINER: I'm Elise Berliner, I'm the director of the technology assessment

program at the Agency for Healthcare Research and Quality, and I have no conflicts.

DR. DESVIGNE-NICKENS: Good morning. I'm Patrice Desvigne-Nickens, I'm a medical officer with the Heart, Lung and Blood Institute, and representing the institute, and they're very interested in research outcomes.

DR. YANCY: Clyde Yancy, professor of medicine, professor of medical social sciences, chief of cardiology, Northwestern University, Chicago, and chair of the U.S. Hospital guidelines. I have no conflicts.

DR. B. ZUCKERMAN: Good morning, Bram Zuckerman, director, FDA division of cardiovascular devices. No known conflicts. Thank you.

DR. REDBERG: Great. So, next it's my pleasure to introduce Dr. Daniel Canos, from CMS, who will do the presentation and voting questions.

DR. CANOS: Good morning. My name is

Daniel Canos, epidemiologist in the coverage and analysis group. Currently assessments of medical technologies are made, but some evidentiary questions remain with respect to

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the clinically meaningful health outcomes for Medicare beneficiaries. Ascertainment of clinically meaningful health outcomes are essential for the CMS assessment of research studies of heart failure treatment technologies.

Given the increased focus on need of patients for new and innovative medical products, medical technologies are receiving market authorization based on less long-term data with greater reliance upon intermediate and surrogate outcomes. Innovative heart failure treatment technology studies are increasingly utilizing endpoints described by the FDA as an access pathway guidance for market authorization, including intermediate

endpoints such as exercise tolerance and symptoms, heart failure hospitalization rate, surrogate endpoints with pathophysiologic pathways leading to the clinical outcomes.

In 2012, recognizing the lack of consensus within the scientific community regarding optimal endpoints for heart failure trials, the Heart Failure Association of the European Society of Cardiology convened a group

of heart failure experts to evaluate the challenges of defining heart failure endpoints in clinical trials, and they developed a consensus framework.

Additionally, the International Consortium for Health Outcome Measurements, ICHOM, organizes a global team for physician leaders, outcomes researchers and patient advocates to define standard sets of outcomes for medical conditions and drives adoption. They have recently released their report on standard heart failure data collection

assessment. The European Society report summarized the group's recommendation for achieving common views on heart failure endpoints in clinical trials. It also outlines the areas of consensus as well as those which need further research.

ICHOM 3 is a standard set for heart failure pharmacotherapy, invasive therapy and rehabilitation, including a focus on patient-centered results, internationally agreed-upon methods for measuring each of these outcomes, and including baseline conditions and risk factors. High level treatment variables

were all considered to allow stratification of outcomes by major treatment types, and they also included a comprehensive data dictionary along with scoring guides for patient-reported outcomes.

Shown here is the ICHOM standard set for outcomes which includes patient and

clinician reported functional assessments, patient reported psychosocial outcomes, also a critical evaluation of the burden of care including side effects, treatment complications, total hospitalizations, readmission and survival. Building off this work and other work, cited materials which appear on the MedCAC website, this MedCAC panel will advise CMS about the ideal health outcomes in research studies of heart failure treatment technologies, and appropriate follow-up duration to ensure transparency of national coverage analyses and others under coverage with evidence development.

You will be hearing a clinical perspective from Dr. Ileana Pina, followed by the institutional perspective from Dr. Philip Adamson. After that we'll hear a clinical

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perspective with a focus on the use of functional assessments and quality of life measures from Dr. John Carroll, and finally

we'll hear from the Patient-Centered Outcomes Research Institute, Dr. William Lawrence.

In the afternoon session the panel will vote and provide additional discussion on the following questions. It is important to note on the first question that CMS recognizes the importance of mortality as a meaningful primary health outcome of interest in research studies. We are seeking input on what additional outcomes should be considered, as noted in the asterisk.

With that in mind, how confident are you that the following are standalone meaningful primary health outcomes in research studies of heart failure treatment technologies? A, heart failure hospitalization; B, heart failure hospitalization or heart failure hospitalization equivalent events, i.e., outpatient IV therapy for heart failure; C, total hospitalizations.

To answer this question we'll use the

following identifying scores for the level of confidence, with a score of one being low or no confidence, and five representing high confidence.

Discussion for question one: For health outcomes with greater than or equal to intermediate confidence greater than or equal to 2.5, please discuss the appropriate length of follow-up post-heart failure intervention for assessing this outcome. Please discuss important considerations when assessing the merits of composite outcomes in research studies of heart failure treatment technologies which include the combination of mortality, heart failure hospitalization, or heart failure hospitalization equivalent events.

Voting question number two: How confident are you that surrogate and intermediate endpoints are predictive of standalone meaningful primary health outcomes, e.g., reduction in mitral regurgitation, cardiac remodeling, ejection fraction or

biomarkers, in clinical research studies of heart failure treatment technologies for, A, heart failure with preserved ejection fraction;

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B, heart failure secondary to mitral regurgitation where the focus of therapy is mitral valve repair/replacement; C, heart failure with reduced ejection fraction, e.g., cardiac remodeling, ejection fraction.

Again, we will be using the scale below, identifying the level of confidence with a score of one being low or no confidence, and five representing high confidence.

Discussion questions under two are, if greater than or equal to intermediate confidence, greater than or equal to 2.5, please identify the specific surrogate or intermediate endpoints and associated disease or therapy which you believe are sufficiently predictive of meaningful health outcomes. Please discuss how these intermediate and surrogate endpoints meaningfully contribute

towards the evidence base for heart failure treatment technologies. Please discuss important factors to consider when assessing the utility of surrogate and intermediate endpoints.

Voting question three. How confident are you that quality of life measures, e.g.,

Kansas City Cardiomyopathy Questionnaire, Minnesota Living With Heart Failure Questionnaire are adequate measures, A, adequate measures which reflect the patient experience; B, should be included as the standalone meaningful primary health outcomes in research studies; C, should be included as composite standalone meaningful primary health outcomes in research studies? Use the below scale for identifying your level of confidence, with a score of one being low or no confidence, and five representing high confidence.

Voting question number four. How

confident are you that functional assessments, e.g., six-minute walk test, VO2max, ventilator threshold, A, are adequate measures which reflect the patient experience; B, should be included as the standalone meaningful primary health outcomes in research studies; C, should be included as composite standalone meaningful primary health outcomes in research studies? Using the following scores, again, identifying level of confidence with one being low or no confidence, and five representing high confidence.

Discuss questions for question number four. Please discuss whether additional patient-reported measurement, e.g., Short Form 36, EuroQol five-dimensions questionnaire, should be considered to capture burdens associated with the heart failure therapy under study.

Please discuss the appropriate length of follow-up post-heart failure intervention

for assessing patient-reported measurements.

For some studies of heart failure treatment technologies it may not be practical for patients to be blinded. Please discuss the impact of unblinded study participants on patient-reported measurements and functional assessments.

Please discuss how to best consider the impact of adverse events associated with heart failure technologies while balancing the potential for improvements to meaningful health outcomes.

Please discuss how to balance the benefits and harms of therapies which may improve near-term patient-reported health outcome assessments or clinical measurements,

e.g., 6MWT or symptoms, but may decrease length of life.

This additional discussion topic includes: Please discuss health outcomes of

interest and appropriate follow-up duration in studies of technologies designed for diagnosis of acute heart failure. With the health outcomes and information that we have discussed today, how confident are you that there will be enough accurate information provided to patients for them to make informed decisions? Please discuss how studies can be designed to accurately capture patient preferences and their preferences can best be considered and operationalized once the study has concluded.

Thank you.

DR. REDBERG: Thanks very much, Dr. Canos. Next up is Dr. Ileana Pina, who is a professor of medicine, epidemiology and population health at Albert Einstein College of Medicine, and associate chief of academic affairs at Montefiore. She will talk about this from a clinician's perspective.

DR. PINA: Good morning, everyone, and I want to thank CMS and the panel for asking me

to be here, it's quite an honor. These are my disclosures, but I want to make sure, some of you identify me as a consultant for the FDA, and today my comments are purely my own as a clinician, and I do not represent anybody but the clinical community in something that we do every day.

I've been doing heart failure transplants for over 20 years and at my institution we have 2,500 admissions for heart failure a year. So is it a problem? The answer is yes.

So, Daniel gave me a long list of things to do, these are basically what he just reviewed, but it's a little bit daunting. So I thought I'd start with having the patient in front of me and asking the question, what makes me happy, and what makes the patient happy. And I think probably what makes me the happiest is when I look at the patient and I see that the ventricle is essentially getting better, which translates to I don't have to give him an ICD, which means that I've probably medicated them well enough that they feel better and are

doing more, and that's my happiness.

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What makes the patients happy is when I walk in and I say to them your heart looks better and you don't need the ICD, and now maybe I can stretch out your visits, and maybe I can cut back on some of your what I call the junk medicine, my patients know I call it the junk medicine, and then the important medicine.

But when I put all this together, we really have arrows for everything. What makes them happy, what makes me happy may be the physiology of their interpretation but they're pretty much the same goals, and keeping them out of the hospital is a huge part of my goal. I don't like the patient in the hospital unless there's some patients that are absolutely necessarily having to be in the hospital, and that is a lot of our population today. And I think we forget. You know, we treat the admissions in the hospital as if it were this

whole separate thing, and it's really a comma in the whole care, and that's how the patients see themselves. They see themselves as moving through their disease process and these are time periods, but we seem to categorize them with all this separateness. It's the same

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thing, same disease, just differently manifested.

And I stole this slide from Gregg Fonarow, not that you need to read it in detail, but we've just failed, we've failed in a lot of ways. And we're still failing in not giving the right medications at the right time for the right reasons, not recognizing patients early enough when they're sitting right in our wards and not knowing what's going on with them. So it is a failure.

So let me talk about hospitalizations. I don't have a lot of time and I want to cover as much as I can. Hospitalizations are darned important to me because of many things. I know

that it increases mortality, and I'll briefly show you these data. It's a revolving door. Very often the good drugs, our house staff, the first thing they do is they stop everything, and then I've got to start all over again. But sometimes bad drugs are given during that hospitalization.

We only see about 20 percent of the heart failure patients at our institution, they're being seen by internists or being seen

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by hospitalists, many of whom are excellent doctors but don't have a lot of experience in the heart failure world. Once you're putting them to bed, and Clinton Brawner today is going to talk about that, they lose function, it doesn't take long to lose muscle function. Now somebody who's functioning at home needs to go to a SNF because they can't go back home again, they're not rehabbed enough. We're not doing good physical therapy, we're not sending

the patients to cardiac rehab, and so the length of stay business which has been threatening us, and I get the care managers on my head, get the patient out, the patient has an extended stay, and sometimes what I need to do in the hospital needs an extended stay, and I can't get them out and I can't get it done in four-and-a-half days.

So I believe hospitalization should be an outcome, I believe heart failure hospitalization should be an outcome, and hospitalization equivalence, because I as many of my colleagues who are sitting here avoid the hospitalization. If I have to give IV Lasix in the office, I will, and I try to keep them out

of the emergency room and out of the hospital. So those are important events in places such as ours who have high volume and high levels of experience.

We've known this for a long time, this isn't new. Everybody thinks this is something

new and shattering. We've known that being in the hospital is bad for the patients and that they have a high mortality within a year, within six months, it doesn't take long to see it. So outcomes don't have to be two years for hospitalization, you're going to know what you need to know within 90 days because that's where the highest rates are.

And when they say well, come on, you know, this is heart failure, they're supposed to be sick, they're supposed to die, but when we put them into trials, they actually do pretty darned well in trials with a very controlled setting.

I also know that the more they get hospitalized, the more the mortality. We don't need to do these experiments, we know this, this has been well known, but I want to give you reality. This is a list of medicines that

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an average patient leaves the hospital with, I

counted them, it's 13 drugs. By the time we see them in our short-term clinic which is very successful, nor run by me, it's run by pharmacists, we get readmission rates down to 80 percent and we get rid of what I call the junk. The junk medicine includes the laxative, the stool softener, the sleeping pill, the pain pill, everything they got in the hospital is totally unnecessary. How confusing, how many of you can take 13 drugs in a day? I don't think the patients can, but this is a real list of what the medications are, taken from our patients. And by the time they leave us in that post-discharge clinic, especially since they're diabetic and they have coronary disease, I have the statins, they're down to about eight drugs.

So what gives me confidence that I can get them on guideline-directed medical therapy? It's not totally impossible, and that reverse remodeling should mean that the outcome is going to get better. Every time we've done anything that causes reverse remodeling with beta blockers, the patients actually have a

better outcome. And exercise therapy is safe, we've done this, we've done the trials, and it should be added. Capturing health status can be done and I do it clinically, and I'm going to show you the data.

And so I put the post office box here, because I tell the patient, you're like the little cubby holes, and I put all this information into little cubby holes that will give me the total picture of you, and you where you are now and where you're going. They don't want to see the Kaplan-Meier curves, they want to hear what I have to say about how they're going to do.

So why do I insist on guideline-directed medical therapy? And I thank Dr. Yancy for putting that into the guidelines because I use it all the time. It works, it actually works. You have to be consistent, you have to be patient, you have to know the drugs you're using, you have to be

confident, you have to have self-efficacy that you know how to do this. And we do follow biomarkers.

The inability to medicate, and this is

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Lynne Stevenson data, right here on the panel, it's a bad outcome. If I can't get the patients medicated, that is a very bad prognostic sign, but by people who do this all the time, not the check box. Good, I did it, I gave an ACE inhibitor, check. Can it be done, yes, it can. Gregg Fonarow's data from the IMPROVE Heart Failure trial is real world data where the addition of the medicines, every time you add one you have different outcomes. So we've got plenty of proof, we don't need any more proof in here.

Reverse remodeling, we can use anything we want, LVEDV, LVEDVi. I'm liking LVESVi because I'm seeing a lot of consistency in the literature. Ejection fraction alone may

not cut the mustard although it may lead to eventual changing, so reverse remodeling should be linked to a favorable outcome and there should be some causal relationship. Should that be an outcome? Yes, I think so.

This is stats from when I was at Case, our heart failure clinic, showing you that when patients are under a team approach to care, guess what? We have very few admissions when

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they're coming to clinic, and this is a large number of visits by year, and yet very few hospitalizations.

And take a look at these. These patients were sick, New York Heart Class 2.4. We have a lot of women absent in many of our trials, and some of you know that's one of my pet peeves. And beta blockers, well done, well titrated, can actually remodel. Not everybody, but there are patients that can do it, and you need to give them the chance to do it.

So this was from our old clinic. We

had a group of patients that had a significantly improved ejection fraction with peak O2s of 13.8, which is low, and an initial class of 2.4. Changes in ejection fraction were remarkable, as there were changes in ventricular dimensions.

And guess what? When we did this statistically, the most prominent finding was the dose of the beta blocker, 139 in patients who improved from a Metoprolol equivalent, and 98 in those that did not.

What about health outcomes? I already heard Daniel present that you want to hear more

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about health outcomes. This is from our HF ACTION trial that I know Chris O'Connor is going to be talking more about. We can use the KCCQ to show about exercise, what did exercise do to these patient-reported outcomes? And even though we've had a statistically significant benefit within three months that

persisted for two years, more and more patients shifted to a higher number, so we had proof that exercise actually does improve health outcomes.

And this is, again, in the clinic. I've been using these for years when the patients come to clinic because I want to know what their status is when they walk in the door, but you've got to do it the right way. There is a process to get this, even in an unblinded trial. It's not the people that are taking care of the patients who gives them the questionnaire, it's somebody in the front office. I don't want to be involved when they're filling it out, because I don't want them to feel that, patients actually try to protect us, they don't want you to think that they don't like what you're doing or that they

feel bad. So we give it by somebody who's totally outside of their daily care, and I'm not even in the room, I don't even want to be

in the room, and so when we take this questionnaire, we do it as unbiased as possible.

So here's a population with an EF of 19.8 percent, this is real, this is our clinic at Case, and here are the results. And for those of you who don't know the cases too well, the higher the number, the better the health status, not quality of life, health status. And you can see that the New York Heart class just really goes right down the line with the value of the physical limitation and the total symptom score. So that if I break it down, we have a pretty good sense besides that New York Heart class, which is so imprecise and so subjective, but yet, pretty darned good to look at outcomes, that it tracks exactly as the questionnaire does.

And this is now today, this is now ten years later in my clinic at Montefiore where the KCCQ overall score is 52. That's pretty bad, and those are patients leaving the

hospital with a pretty bad health status, even though there's some wide variability and a high standard deviation.

HFpEF, very quickly, I have no idea what to do with these patients. I try to get their blood pressure down, I try to get their diabetes controlled, I try to put them into exercise programs, I don't want them to have atrial fibrillation, so I'm going to leave you with a new outcome, atrial fibrillation, a very bothersome, very common comorbidity that we're seeing in this population. The treatment guidelines are kind of non-very specific, they tell us to treat blood pressure, and then the new ones will be hitting the door, and Clyde may be able to talk a little bit more about that.

But what do I have a problem with? It's that all the trials are different, the entry criteria's been different, the ejection fraction's been different, the way the ventricle looks is different. How are we ever

going to get to this when we don't even have a very good solid definition of HFpEF? And atrial fibrillation is very often the

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presentation, and I find my colleagues running to take care of that atrial fibrillation, let's control the ventricular rate, but what's underneath, which is the heart failure, very often gets ignored, so perhaps more often incidents of atrial fibrillation could also be a health outcome.

And yes, I use spironolactone because right now that's the best data that I have from the NIH-sponsored TOPCAT trial.

Exercise, highly ignored, and yet we do have data, they're smaller trials, they're not the big large randomized trial, but we do have data that the HFpEF patients do well with exercise, and I've got some of them walking in the hall, walking around their dining room table, because in the Bronx at this time of the year you can't always go out and walk, it's a

little cold now with ice and snow on the streets, so I have them walking around the dining room table and telling me how many times they can go around. It's still exercise, it's just not on the treadmill.

And then my key points for outcomes in HFpEF, reduction in all cause hospitalization;

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improvement in objective function, their ability to actually rehab; well captured symptoms, which is very hard to do; and the absence of AFib.

And then finally, devices for HFpEF, what do I want in a device? I want it to have biological plausibility, I want it to improve physiologic parameters, and notice, I'm not that interested in long-term mortality but I am interested in hospitalizations, and my ability to up titrate drugs and to continue therapy even with the device on board.

So let me finish up here, because I

don't have a lot of time. ADHF, acute heart failure, again, a comma in the process of care where we deal with the iceberg, and there's so much more going on underneath. Why do we think that 48 hours of a treatment is going to reverse this? We have failed in many of our acute heart failure trials, and it's time to look at it appropriately. Again, it's a comma in the whole disease process and when we ignore the disease process, we're ignoring everything that has gone on underneath until the patient now comes in with orthopnea and fatigue.

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So with those thoughts, I leave you there. Thank you, Danny.

DR. REDBERG: Thanks so much, Ileana, a great perspective from a clinician. Next we'll hear from Dr. Philip Adamson, vice president of medical affairs and medical director at Abbott, which was formerly St. Jude Medical. He's representing AdvaMed.

And I'll just add that we'll have a

few minutes at the end of all the presentations for any Q&A from the panel. Thank you.

DR. ADAMSON: Thank you, Professor Redberg, members of the coverage committee, particularly Dr. Canos and Dr. Chin for this invitation. I'm honored to speak in front of such distinguished folks on a committee and a panel.

Ladies and gentlemen, I'm here to express the opinion of industry on behalf of a common group called AdvaMed that represents all of industry that is responsible for the development of novel interventions and technologies for patients with heart failure. I'm Phil Adamson, I'm a heart failure cardiologist, and as Dr. Redberg mentioned, I'm

medical director at now Abbott, and involved in many clinical trials to evaluate novel technologies to improve outcomes in our patients with heart failure. And really, my

task here is to describe the industry's scientific rationale for identifying appropriate endpoints for clinical trials, and it's clinical trials testing novel interventions to benefit Medicare patients.

We are focusing on which meaningful patient-centric outcomes are appropriate to evaluate new interventions, because we are actually seeing some improvement in longitudinal care and disease management of patients with heart failure, and this is giving us new goals, it's giving us new therapies and new ways to allow patients to remain stable in their own homes and avoid hospitalizations.

Today is very important. The assessment of endpoints and outcomes will help us to maintain the progress that we've been seeing in management of these patients, and to ensure that success will continue as we manage these very very symptomatic and difficult patients to manage. And frankly, we all know

that heart failure is an exploding pandemic, with expectations of the prevalence to double within the next 15 years. So we really, I think, have to have a concerted effort to guide how we develop novel tools to manage patients with heart failure and deal with the problems that are associated with this chronic disease.

You know, I spent the last, nearly half my life as a cardiologist taking care of heart failure patients, and those patients have taught me a lot about how this disease affects them and what they want, and I've had innumerable lessons taught me from my patients. And I've also learned in the last two years a lot about industry. As a member of industry, I've learned that one of the most important things is that industry finds really no value in innovation that's made just for the sake of innovation. In fact, our goals align with CMS and other organizations such as the American Heart Association. Our purpose is to provide solutions for unmet clinical needs, providing the highest levels of patient-focused scientific evidence to improve the quality of

health care for Medicare beneficiaries. And in

fact we agree with CMS, and we agree with the American Heart Association, that heart failure hospitalizations are very important, and this is a very important clinical endpoint to manipulate and to change as technology improves.

Frankly, heart failure hospitalizations are horrifying to patients, they're potentially deadly, and these patients who otherwise have reasonably stable heart failure syndromes are faced with the possibility of death, drowning in their own juices, and this stress and trauma doesn't just affect the patients, it affects their families, their caregivers and their long-term outcomes, their psychology, their socioeconomic status. Heart failure hospitalizations are devastating, and worthy of our attention.

As Dr. Pina mentioned in some of her

slides that were published, patients when asked if they could stay out of the hospital and avoid symptoms, would that be better than staying alive longer, most answered yes, please make my symptoms better and keep me out of the hospital, don't just prolong my life.

Therefore, I think there's clear alignment between CMS and AHA and the most important group, our patients, that preventing hospitalization is a worthy endpoint to validate novel clinical technology.

I want to spend a little bit of time going through the process, because successful innovation processes must first focus on the end result. The end result is the ultimate use of clinically meaningful and appropriately validated tools. Industry is called upon to produce the highest level of scientific evidence to satisfy rigorous regulatory, reimbursement and coverage approvals. The process involves discovery and clinical

development, which for most technologies culminates in a pivotal trial that evaluates the novel innovation, and it's important to note that in these clinical trials many times the control group itself receives better care than in the community.

That's why discussing endpoints is so important, and why the common goal of assessing safety and effectiveness is a rigorous process. However, it is important to note that industry

continues to gather data after FDA approval and after CMS coverage, and uses that information from this period to ensure that ongoing safety and effectiveness in generalized use of the new intervention is present, and to use this information for revision, rediscovery, redesign, which are mandatory for any product that's designed for the benefit of the heart failure population, because many breakthroughs are concomitant and simultaneously occur over

time, so where you end up may be different than where you start, so it's an ever-changing landscape in health care delivery for patients with heart failure that's very important to assess and reassess. So with this in mind, the proper selection and agreement on appropriate endpoints for validation of novel clinical tools is critically important to the sustainability of this traditionally successful cycle of development.

You know, heart failure is really a syndrome that can be described as a journey and is associated with several different phenotypes which we all know, several different etiologies and comorbidities, and unfortunately there

really isn't a one size fits all endpoint that applies to all aspects of this heterogenous journey.

This figure actually outlines a very simplistic view of heart failure progression, but might be useful to identify where some

unmet clinical needs exist, it shows how endpoints are dependent upon where the patient is in the journey. So let's start at the beginning with a hemodynamically stable ambulatory heart failure patient with reasonable functional capacity, reasonable quality of life, and mild to moderate persistent symptoms, and actually this represents the vast majority of patients with the diagnosis.

And you know, we've learned a lot, we've learned a lot over the years about this phase of heart failure, and at least for patients with reduced ejection fractions, guideline level evidence supports drug and device interventions to prevent disease progression. Unfortunately no clear guidelines exist, as Ileana just mentioned, for patients in this Phase I portion of this journey who

have preserved ejection fraction heart failure,

despite several clinical trials evaluating promising interventions.

Many patients eventually experience worsening symptoms and transition to seek urgent care, and many times are hospitalized to receive the IV rescue therapies. And, you know, we've learned a lot about this transition period from hemodynamically stable ambulatory patients who transition into the decompensated state requiring hospitalization. In fact, it's a process that takes much longer than what we originally thought. It's characterized first by early increases in filling pressures that can be detected weeks before patients develop symptoms, leading to a presymptomatic congestion, hemodynamic congestion phase which is associated with changes in cardiac autonomic control, and eventually interstitial edema, shortness of breath, lack of rest, pulmonary edema and the need for hospitalization. And in fact, over 90 percent of patients who are hospitalized for heart failure exhibit severe symptoms of congestion in the presence of excellent perfusion of their body, so it's the

congestion that tends to drive hospitalization.

Unfortunately, consistent prospective randomized clinical trial outcomes testing a variety of methods to monitor patients using daily weights and early detection of symptoms with the hopes of preventing hospitalizations in this transition period have failed, and it's probably due to the fact that the transition from stable ambulatory to decompensated is characterized by this significant presymptomatic stage in which we can't see with signs and symptoms that the patient is worsening, and the patient doesn't know because he doesn't have symptoms developing. Weights change, symptoms develop, but they may be too late to provide effective guidance to prevent hospitalization.

A clearer understanding of this transition from stable to decompensated discovered an unmet clinical need. New interventions tested in this transition phase

should be expected to identify patients when they develop hemodynamic compromise without the development of symptoms, and should have the goal of preventing subsequent hospitalization.

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So when we test things in the transition phase, knowing what we know now about that process, heart failure hospitalization prevention is a very important outcome of those evaluations.

Now once hospitalized, patients transition to Phase II in this diagram, in which typically high dose IV diuretics are delivered as rescue therapy, and again, multiple clinical trials evaluating several promising interventions at Phase II, once patients are acutely decompensated and in the hospital, have consistently yielded negative results, and Ileana touched on that in her talk. Even recent trials testing novel matrix proteins have failed to impact clinical outcomes, so it seems that stage two actually

may be too late in the course of this progression to congestion, and little can be done to alter the course of progression.

As patients transition then into the number three there, we've unfortunately learned that after about an average of five days in the hospital for rescue therapies, over half the patients are discharged with continued congestion, the same that brought them into the

hospital. This Phase III transition from discharge to home is an incredibly important time because 25 percent of patients who are discharged are actually readmitted within the next 30 days. In fact if you look longer term, 50 percent of patients are readmitted in six months, and over 70 percent of those patients are readmitted after a year. Clearly stage three of this journey represents an unmet clinical need to more appropriately discharge patients and provide more effective followup. New technologies introduced at this time point

to demonstrate a reduction in readmission rates is a meaningful outcome.

Frankly, this admission-readmission cycle is difficult to stop, and each time the patient cycles through this process their disease worsens and progresses. Many patients who repeatedly decompensate eventually transition into a totally different pathophysiology we now call advanced heart failure or refractory Class IV Stage D heart failure shown as number four in the diagram.

Heart failure pathophysiology now changes to include poor systemic perfusion,

which is a very serious problem requiring very serious interventions. Therapies and outcome testing for this phase are completely different, and include providing implantable mechanical circulatory support systems or transplantation for appropriate patients. Importantly, for patients unable to receive

advance therapies, identification of them as an advanced patient should provide an opportunity for palliative care, as near-term death is really hard to avoid.

So the ultimate goal, then, for management of patients with chronic heart failure is to manage and maintain stability, and avoid decompensation. Novel interventions being tested for this purpose should prevent the ill effects of decompensation, which include progression of cardiovascular remodeling, leading to chronically elevated cardiac filling pressures and poor systemic perfusion with progression of their disease.

Clearly, as Ileana has mentioned, we've been shown this data from Professor Stevenson's lab and led by Dr. Setoguchi. Patients who have multiple hospitalizations are

at higher risk for mortality. In fact, patients experiencing just two admissions are nearly twice as likely to die compared to

patients admitted only once. More recently, though, very interestingly, it became clear that no matter how decompensation was treated, whether it's in the traditional hospitalization or emergency department visits, or even outpatient intensifications of therapy, decompensation leads to higher long-term mortality.

This data from the PARADIGM HF trial demonstrates a threefold greater mortality in patients experiencing decompensation regardless of the venue for rescue therapy, and let me orient you to this slide. The solid black diamonds represent death rates in patients without a clinical decompensation event, and that's compared to the red diamonds, which are patients who had intensification of therapies, the green diamonds, ER visits with IV care, and the blue diamonds are traditional hospitalization.

And look at the mortality associated with these events. The mortality differences

between no events is dramatic, but the mortality difference between experiencing decompensation are very similar, regardless of the venues in which rescue therapies are delivered. In fact, in this trial which ended somewhere in the 2014 range, it became clear that clinical practice is evolving to rely on more extended outpatient hospital visits to provide IV therapy, which is represented on the second bar of each of these pairs. So you can see over time that clinical practice patterns have evolved to rely on less hospitalizations and more outpatient-based rescue therapy treatments of decompensation.

The decision, then, about what endpoints are appropriate, is dependent upon where the patient is in their journey, and when the innovative treatment is introduced. Clearly heart failure hospitalizations and decompensation events are associated with very poor long-term outcomes, but let's focus more closely on the components of the journey. It's

certainly desirable, and a patient-preferred outcome, to maintain stability and avoid decompensation altogether.

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As mentioned, multiple interventions tested in clinical trials while patients are acutely decompensated and already hospitalized have produced really consistently disappointing results. The benefits of maintaining stability are now clear, and it should be apparent that heart failure hospitalizations are important targets as primary endpoints in heart failure clinical trials.

And as clinical practice evolves, another important measurement of success may be to prevent ER visits requiring an IV rescue therapy in short hospital stays that do not qualify as traditional hospitalizations as we've defined them in the past.

As is always the case, clarity of endpoints that depend upon exercising clinical judgment can only be achieved with careful

evaluation of each event. This requires thorough unbiased blinded expert adjudication of events as part of the routine clinical trial design, and it should include confirmation of the patient's clinical status at the time of the event, documentation of all therapeutic interventions provided, additional -- and

interestingly, additional careful medical record review should identify investigator involvement in the decision to administer IV diuretics or provide hospitalization, especially in single blinded trials.

I think it's important to capture all-cause hospitalization and include them either as secondary endpoints or used as observational data, to ensure that a change in heart failure hospitalization is not really just a shift in resource utilization or diagnostic coding.

Finally, combining decompensation

events with mortality as a composite endpoint is reasonable. However, if mortality is not included in a composite primary endpoint, mortality rates must be monitored to ensure complete assessment of competing risks.

So let's consider, now, patients who develop a need for an advanced therapy shown as Phase IV in this diagram. And it's important that endpoints chosen in clinical trials should be disease-specific. Patients with refractory advanced heart failure many times are acutely unstable and require prompt intervention to

survive. I think we all remember the startling difference in mortality seen in the REMATCH trial between medically treated advanced heart failure patients and those receiving mechanical circulatory support. It would be really difficult to envision another trial examining medical management in this group.

However, once the advanced therapy is delivered, then it's also important to

recognize the disease state in patients who receive advanced therapy is different, vastly different than ambulatory heart failure. For example, post-transplant immunosuppression and rejection represent many poor outcomes in transplant groups.

Patients living with mechanical circulatory support also have a unique pathophysiology which includes coagulopathy, systolic events, device-related infections and device malfunction. How do these patients start in their journey to mechanical circulatory support with totally different and severe baseline conditions, which is associated with very high mortality using medical therapy alone. In this regard, new iterations of

mechanical circulatory support focus primarily on restoring functional capacity, improving quality of life, and decreasing complications associated with the pathophysiology that's

acquired with the chronic device implantation. In fact, hospitalizations for acutely decompensated heart failure are rare after a bad implementation and may not be a meaningful short-term endpoint. Hospitalizations for bleeding, infection, device malfunction, however, would be key elements of measuring success in these patients.

Particularly important for this context is that currently available quality of life measurements are designed for patients with chronic heart failure and may not be specific to this new pathophysiology that exists post-VAD support. While established quality of life measurements document improvement from baseline in patients receiving MCS, the remarkable post-VAD clinical improvement is compared with their severe baseline. In this regard, new disease-specific quality of life markers are likely needed to evaluate the durability and the magnitude of

specific components of quality of life that capture the unique challenges of patients while they live with mechanical circulatory support.

In this regard, then, disease-specific quality of life measurements are now recognized as one of the three pillars of quality health care delivery, along with clinical effectiveness and safety. The most clinically validated instruments, as Ileana mentioned, are the Kansas City Cardiomyopathy Questionnaire, and the Minnesota Living With Heart Failure Questionnaire. Although these instruments are not perfect, favorable changes in each of them independently predict a favorable outcome, and are robust enough, in patients with chronic ambulatory heart failure at least, to represent a meaningful clinical outcome.

Longer-term assessment, however, of quality of life using these instruments becomes confounded with the comorbidities that commonly accompany the heart failure syndrome. Furthermore, questionnaires assume that the patient has sufficient cognitive function to understand and provide accurate answers, and

25 the prevalence of cognitive dysfunction in

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1 patients with heart failure may be
2 under-appreciated. Assessment of quality of
3 life beyond one year from an innovative
4 intervention is probably problematic. But
5 developing novel quality of life instruments
6 that focus on patient-specific defined worst
7 symptom or psychosocial stressors along with
8 locus of control issues are risky in the
9 context of evaluating a new technology. A
10 negative result with a new quality of life
11 marker may actually be due to the new quality
12 of life marker itself rather than the new
13 technology. So I think we need creative ways
14 of evaluating new quality of life measurements
15 that are meaningful and obligatory endpoints in
16 clinical trials that match the disease that's
17 present.
18 So how about functional assessment?
19 Changes in functional capacity are also

important markers for a successful novel intervention. All functional assessments, however, assume and are limited to patients who can participate in the measurement without confounding impairment from comorbid conditions such as arthroscopy, amputation or paralysis.

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Certainly the easiest and most widely used marker is a simple six-minute hall walk test, which remains a good measure and a good measure of functional capacity with appropriate diagnostic and prognostic value.

More sophisticated cardiopulmonary stress testing with the goal particularly of measuring VO2max provides an excellent measure of exercise capacity, but we believe should be performed under specific conditions such as core lab oversight or interpretation of borderline tests using observatory or objective methods intended to validate tests that would otherwise be considered inadequate.

Additionally, statistical analysis is

planned to account for patients who subsequently are unable to repeat the tests for reasons unrelated to the fundamental question being tested. Functional improvement is a patient-centric preferred outcome of any intervention tested in the heart failure community.

So how about surrogate markers or intermediate markers? They certainly are attractive for use in clinical trials since

shorter-term changes may reflect that the intervention is successful and may give rise to conclusions about long-term benefits. For example, it's reasonable to consider a reduction of valvular regurgitation or stenosis as an appropriate endpoint for a novel valvular intervention. Reversal of adverse ventricular modeling, as Ileana mentioned, is a very gratifying thing to see, and usually measured as an improvement in left ventricular and

systolic or diastolic indices, and directly correlated with improved survival. But reversal of adverse remodeling is known to occur with successful drug and device interventions and should be considered a measure of success.

In patients with acute cardiogenic shock from acute myocardial infarction or myocarditis, temporary mechanical circulatory support may prolong survival long enough for improvement in ejection fractions to occur, and that may be a situation in which the left ventricular ejection fraction may be an appropriate intervention.

And finally, favorable changes in

biomarkers such as NT protein, C or B type proteins, or ST2, may provide sufficient evidence to support further investigation of a novel intervention. And particularly applicable to patients with reduced ejection fraction heart failure, congruent improvement

in biomarkers, functional capacity and quality of life as a composite is now a means for expedited regulatory review and potential early FDA approval, with the expectation of further real world evidence development in the post-approval period.

In that regard, then, fairly recent development of credible real world databases in very large populations also provide meaningful opportunities for continued evidence development. Data objectively extracted from these databases have the potential to corroborate the results of randomized clinical trial data, and have the potential to provide a so-called cultivated cohort, which may provide appropriate concomitant comparison groups.

Multiple databases are now available from several sources and may provide novel means to more fully evaluate generalizability

and, importantly, clinical effectiveness of a

novel intervention after it's made available for clinical use.

In summary, then, disease-specific non-mortality outcomes are scientifically sound methods to evaluate novel interventions for patients with heart failure. Preventing decompensation events regardless of the venue in which therapy is delivered should be considered as appropriate in clinical trials, in heart failure clinical trials. The goals of allowing patients to remain stable and at home is patient-centric and appropriate. Stability many times improves quality of life and especially in those patients whose baseline condition is characterized as quite severe.

Functional improvement is an important outcome, very important assessment of innovation, and can be considered as primary endpoints under certain conditions and circumstances. And certainly combining congruent improvement in biomarkers, quality of life measures and functional capacity is a very strong signal for overall health outcomes.

We applaud the efforts of CMS in

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stimulating this discussion about how to measure success with novel interventions that are designed to improve the patient experience with heart failure. Alignment of non-mortality endpoints as a criteria for regulatory and coverage decisions is critical to ensure sustainability of clinically meaningful progress in innovation, with the hope of providing meaningful solutions for addressing unmet clinical needs. Thank you very much.

DR. REDBERG: Thank you, Dr. Carroll. I'm sorry, thank you, Dr. Adamson. Looking ahead. I would like to introduce Dr. John Carroll, professor of medicine at the University of Colorado School of Medicine, and director of interventional cardiology. Dr. Carroll.

DR. CARROLL: Thank you, Dr. Redberg. It's a pleasure to be here this morning and to share with you some thoughts on what health care outcomes should be of interest to CMS in

studies for heart failure treatment technologies. I have no financial disclosures relative to this topic. My institution and I are investigators in a variety of clinical

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trials in this space.

So, the goal is to provide CMS with the ideal health care outcomes and research studies in heart failure treatment technologies and appropriate follow-up duration, and I will try to stick to the topic. My perspective is perhaps different from others here. I'm an interventional cardiologist and my areas of expertise relative to this are heart failure-related valvular heart disease and other transcatheter approaches to valve replacement and repair, and CHF related to cardiac shunts treated with a variety of different transcatheter technologies, that's my perspective.

Clinically significant valvular heart

disease is really becoming prevalent in our aging U.S. population as shown here. Moderate to severe mitral valve disease, aortic valve disease obviously increases with age, and notice that the final age is greater than 75, and certainly now we have many many of us living beyond that point. So there are major issues that we have to discuss and make explicit that are confounding in outcome

assessments and one of them is the issue of advanced age, and the other is socioeconomic status.

And certainly in this area of heart failure in general and also in the areas I work, the focus is on the elderly, it is a fast growing segment of the population. Cardiovascular disease is the leading cause of morbidity and mortality in these people and they have the presence of significant comorbidities and different forms of cognizant dysfunction, social support, diminished

functional status. All these things influence our decision-making and treatment outcomes.

Furthermore, we have to deal with certain realities that life does have a finite expectancy and as we age, that the expected life expectancy drops, and that's relevant when we talk about therapies that apply to 80-year-olds versus 50-year-olds. And the survival benefits of some of these treatments do have, and have been shown in randomized clinical trials, are important, but the other benefits are extremely important in predicting the value of transcatheter therapies, such as

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clinical status, quality of life, and freedom from hospitalization.

And these outcome assessments must be put in a broader context of the patient's daily existence, and there are a variety of social determinants of risks and outcomes for cardiovascular disease that we all confront on

a daily basis, and include some of these items demarcated on the left, and these markers of socioeconomic position often are not captured when we do clinical trials and we assess long-term outcomes, and are key issues that are under appreciated but have a huge impact on outcomes.

So in preparing for this, I tried to be very explicit about the different domains about things that need to be considered, survival but also objective assessment of the disease-specific anatomical physiologic variables that the treatments address. The presence or absence of treatment complications. The improvement, or lack of, in patient-reported health status. The objective functional assessments and the freedom from hospitalization, and lost of independent

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living.

So in terms of the objective assessment of disease-specific anatomical

physiologic variables that the treatment addresses we have to have a time frame, and typically the time frame for assessment is immediate to 30 days. One year is important if durability is a central issue for the treatment.

I always hesitate sending movies as part of the talks, but on the left is a patient with an aortic bioprosthesis that has generated severe regurgitation and on the right is after the implantation of a transcatheter valve within that, and the two videos show severe aortic regurgitation on the left and the absence of aortic regurgitation. So that's the assessment of the treatment effects.

We can further assess the outcomes directly related to the disease process by other measures noninvasively or invasively, and this shows the pre and post impact on cardiac aortic pressures, also respiration of the competent aortic valve.

Outcome assessment like cardiac

ultrasound is central in the heart failure and the transcatheter and surgical valve area. The preprocedure documentation has severe mitral regurgitation that must be paired with the postprocedure documentation with the degree of reduction using standardized methodology that we have arrived upon.

Next, we must assess the presence or absence of treatment complications and the time frame of that is really throughout the patient's life, but starts with the immediate to 30 days. One year is important because there are some late complications that are unique to different treatment modalities.

So we've learned a lot about assessment of physician and hospital performance that's relevant to looking at outcomes, as CMS wishes to do, for example an isolated surgical valve replacement with a composite score based solely on outcomes. We have risk standardized mortalities but we also have to look at the alternate to know the

stress-patient morbidity occurrence that is very important to our patients and for us as clinicians. We note the sternal infection,

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reoperation, stroke, renal failure and prolonged ventilation, and this drives some of the work in the STS crew.

Next, we have to get an idea of whether patients' health status is improved from their own perspective, or has not improved, or potentially has deteriorated, and there the time frame is obviously prolonged. It starts with the establishment of baseline measurements that serve as an index for the individual patient to see to what degree they improve or not, and it's particularly important in the elderly or those with comorbid conditions that could impact on the benefit from the treatment.

So, the importance of measuring patient health care status is outlined here by my colleagues, and some of them are at

Colorado, like Dr. Rumsfeld. So we are talking about living longer, living better. We are talking about patient-reported health status, which includes not just quality of life but the symptom burden, the functional status, both social and other validated patient health care surveys that need to be disease-specific but

sometimes need to be broadened to patients with multiple forms of cardiovascular disease and allow for quantification of these critical patient-centered outcomes. And these patient health care status surveys have been used to successfully document the impact of treatments and certainly we use them in long-term follow-up in clinical registries like TVT that I'm involved with. And it's also a baseline marker for adverse outcomes and health care costs.

So here if we look at this spectrum of patient-reported health status, we start with

the disease and treatment, and assessing symptoms, functional status, and health-related quality of life. And we see, as shown below, all the different things that impact on how a patient may respond to a questionnaire and come up with different answers, different variables.

So specifically within the TVT registry when we were developing the basic data elements that needed to be gathered, we decided on the KCCQ as a health status measure that integrates multiple aspects of symptoms, functional status, and quality of life, into a

single measure, and it has been documented to be reliable, patient-centered, and easily collected in routine clinical practice after adequate education.

And this shows some of the impact that we've been able to assess using the large number of patients entered into the TVT registry, which is approaching 100,000 patients who've undergone FDA-approved commercially

available transcatheter therapy for valvular heart disease, and what do we see here? We see there are patients who fortunately have large improvements in the KCCQ, we see those with moderate improvement, greater than ten, which seems to be an objective realistic goal, but then there are patients who have no improvement, no change, or decreased at 30 days. What does that mean and what can we do about it?

Here we see transcatheter aortic valve replacement according to baseline health status, so it has prognostic value, not just looking at deltas, but it helps us assess what might come down the road, what are the chances of patients benefitting from these therapies,

something very very important as we go forward trying to predict in whom is this treatment going to be beneficial, and that helps inform patients to make their decisions about whether

or not to undergo a treatment.

And the ability to develop conceptual frameworks of describing tests as not necessarily failure but lack of success when it comes to various treatments is shown here, a publication from Dr. Arnold looking at the interplay of both KCC score but also patient survival, and trying to identify in whom, is there not either individual patient marks, in whom is there a poor outcome, and can we predict it, and a reasonable definition of a poor outcome, what is that? And we have certainly persistent low KCCQ as a reflection of the patients' health status, and further decrease in that score of course is not something we like to see when we're trying to help people.

We're entering an era where we want to be able to predict outcomes and then assess what happens in terms of testing the validity of predictive tools, and that's where so much

effort is going into risk model algorithms to predict mortality, immediate treatment related but also long term, and if we can do a better job of predicting who responds and who does not respond to a treatment, wouldn't that be fantastic, to not only bring the therapy to the people who respond, but not subject other people to treatments that they may not respond to, and the associated huge health care costs.

So we need objective functional assessments, and the new metrics for success are in front of us and shown here with this individual undergoing a functional assessment of not only how they report the success or failure of how they're doing and using more than the simple classification of the New York Heart functional class, but looking at six-minute walk tests, which can be done in the majority of these patients, but some cannot due to orthopedic and other issues that prevent them from walking.

When we look at new therapies like mitral valve clipping procedures and looking at changes in the New York Heart classification,

baseline versus 30 days, we see significant

improvements in their functional class affecting the majority of patients but not all.

Certainly great emphasis has already been placed on the freedom from hospitalization, but also the loss of independent living is as important as many other parameters for our patients. The time frame of assessment is important, it can be done early on, but we really have to, again, look in many of these therapies beyond the immediate procedural results and look at outcomes at one year. They are a reflection of many things, not only the procedure, but the quality of care subsequently.

And after transcatheter aortic valve replacement in the TVT registry, we're able to see what happens to these patients when they're discharged, do they actually go home, do they die, are they transferred to a rehab institute

or do they go to a nursing home? We need to look at these parameters of what happens to patients after therapy, that is an important metric.

Certainly one of the benefits of the stakeholder engagement and participation of CMS

and FDA in the professional registries like the TVT registry that's jointly sponsored by STS and ACC is the ability to link patient records with long-term CMS data and look at rehospitalization rates as shown here. This helps us further refine the benefit of therapy and patient selection criteria, and identify some unmet needs and how we might improve things.

So in conclusion, the assessment of outcomes must address these six major domains that I've identified here. Survival is one. The second is objective assessment of the disease-specific anatomical-physiologic variables that the treatment addresses. And

16 third, the presence or absence of treatment
17 complications. Fourth, the improved
18 patient-reported health status. Fifth,
19 objective functional assessment. And sixth,
20 freedom from hospitalization and loss of
21 independent living.
22 The timing of the assessment of the
23 different domains of outcomes should include
24 baseline assessment for comparison to post
25 treatment. Immediate to 30-day survival, but

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1 also objective assessment of the
2 disease-specific variables that the treatment
3 purportedly addresses, and the presence or
4 absence of treatment complications. At one
5 year, survival, improved health status,
6 objective functional assessment, and freedom
7 from hospitalization and loss of independent
8 living are key. Thank you.
9 DR. REDBERG: Thanks very much,
10 Dr. Carroll. Next we'll hear from Dr. William

Lawrence, who is associate director of clinical effectiveness and decision science at the Patient-Centered Outcomes Research Institute, and Dr. Larry Allen, who is associate professor of medicine and medical director of the Advanced Heart failure at University of Colorado Denver, a colleague of Dr. Carroll.

DR. LAWRENCE: Good morning, and on behalf of both Dr. Allen and myself, I thank you for having us this morning. So, first, just disclosures for myself. I'm an employee of PCORI and have no other conflicts.

So, this is a co-presented presentation, and just a brief overview, I'm actually going to give just a very brief

introduction towards patient-centered outcomes, and then Dr. Larry Allen will talk about his work working with patients on LVAD decision-making.

So first, just a couple words on Patient-Centered Outcomes Research Institute.

I've got here our mission and goals. Really the big thing I wanted to point out is that our mission is to help people make informed health care decisions by producing high integrity evidence-based information that comes from research guided by patients, caregivers and the broader health care community, so my main point today is to make sure that our stakeholders are involved in the research from the start.

So, we fund patient-centered outcomes research. This is a form of comparative effectiveness research that, what we're really interested in is that it considers the patients' needs and preferences, and the outcomes that are most important to them. We're also interested in what works not only for the whole population, but what works for whom and under what circumstances. And then finally, interested in helping patients and

other health care stakeholders make better

informed decisions about health and health care options.

So just a couple of things. We're interested in the concept of patient-centeredness, so we are actually interested in basically answering the questions or examining the outcomes that matter to patients within the context of their own preferences and that, our proposition is that research questions and outcomes should reflect what is important to patients and the caregivers.

And the other thing is that we're interested in patient and stakeholder engagement, so stakeholders should be involved from the start of the research and not just basically the subject of the research. So with that introduction, I'll turn it over to Dr. Larry Allen from the University of Colorado, to talk about his work with LVAD patients.

DR. ALLEN: So, thanks, Bill, and thanks to PCORI for inviting me, and thanks to CMS for giving me the opportunity to hopefully

contextualize this discussion about outcomes from the patient perspective, and today I'd like to use what we've done with left ventricular assist devices, but I think it applies to a variety of cardiac devices.

These are my disclosures. I do some consulting for Novartis, Janssen and ZS Pharma that's funded by the AHA and PCORI.

So, I think this is a good way to think about how outcomes inform what we do. So here you have a doctor who's saying hmm, when a patient asks Doctor, I want to choose how I'm treated, the doctor says hmm, you're not just ill, you're deluded, but I actually think this sets up the framework for how outcomes really help us deliver good health care.

The first thing is that outcomes help us decide what are medically reasonable options for this patient. I don't know whether I can recommend one or two or three options to a patient, or say that's not an option, unless I

have good quality data that tells me whether that's good for the patient or bad for the patient, what the balance of that is. But rarely do I come to a conclusion where I know

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exactly one thing is right for this one patient, so we also need outcomes presented to patients in ways that they can understand which option among the ones that may be medically reasonable is actually right for that individual patient. So as we consider the outcomes for measuring, we need to think about not only what's good kind of from a standard or societal perspective, but how do we help individual different people sort through those options in a way that they can then decide.

I think outcomes also help us decide or approach the way that we present medical options to patients. So sometimes we use behavioral counseling, when scientific evidence for benefit strongly outweighs harm. So in

smoking cessation or a beta blocker for heart failure with reduced ejection fraction, and then decision support designed to describe, justify, recommend and engage is most appropriate.

At the end of the day, even when we think that smoking cessation is the right thing to do and that's the one option in front of this patient, patients still have to appreciate

that that's right for them, and then feel motivated to move forward. And so if we can't present that the outcomes show the benefits vastly outweigh the risks for that patient, then it's hard for us to do behavioral counseling. We've got to be able to have these outcomes in a way that allows us to do that.

Increasingly, though, especially with medical devices, I think we fall into the second category, where shared decision-making is most easily applied to preference sensitive decisions, where both the clinician and the

patient agree that equipoise exists between different options, and decision support helps patients think through, forecast, and deliberate those options.

So at the end of the day, we may not have outcomes that tell us exactly what is the right choice for this specific patient. What we want to do is be able to help create a discussion around whether a treatment that may be good for one person may not be good for another, and be able to have the data to do that.

I also think that the concept of

outcomes also applies to, do we have kind of the data to be able to engage and then activate and help patients deliberate and discuss what are valued important decisions for themselves. And we actually have measures for levels of engagement, levels of activation, and those are important.

So I'm going to talk about left ventricular assist devices or artificial heart technology, because I think it's a great case study to illustrate with medical devices for heart failure how the outcomes are so important. So you know, 50 years ago, artificial heart technology was pie in the sky, and here we are today where left ventricular assist devices are now done in over 4,000 patients a year in the United States, which has outpaced transplantation, and even one of our vice presidents has benefitted from this technology.

This is a fast moving field, which also challenges the data collection and outcomes measurement. So, this is from the New England Journal of Medicine in February of this year, and you can see that there was one

article on the new Heartmate 3 device which was studied in the MOMENTUM trial, there's a second article on the HVAD device studied in the

ENDURANCE trial. So this field, again, is moving forward fast and we need good data.

The other reason mechanical circulatory support, left ventricular assist devices are such a great place to study outcomes measurement is that there is almost nowhere where there is such high risk, high reward, right? This is where the benefits are huge and the risks are huge, and so being able to measure those and convey those in a way that people can kind of weigh is critically important to the therapy and the way that we counsel people.

So let me give you some examples of how we've tried to take the outcomes data from the scientific community and digest it in a way that patients can potentially comprehend the gist, and then make a decision about. So, left ventricular assist devices for people essentially dying of heart failure can have fairly significant survival advantages, so when we did a systematic review of the data

available which, most of it only goes out to a year, so we really can't even say what happens at five years very well, but there's data out there that without therapy, about 80 percent of people will die and 20 percent will live, and with the therapy, about 20 percent of people will die and 80 percent will live. And the way that this looks on a Kaplan-Meier curve, which I think would be difficult for a patient to understand, is that at a year we really move people so that their survival more than doubles, so the number needed to treat at one year, that if we put in two LVADs, more than one life is saved on average. That's pretty impressive and that's pretty important to most patients.

However, patients not only want to live longer, they want to live better, and so how do we convey that to patients as well? Well, we also provide quality of life information. We're going to have some discussion today about what are the best

quality of life measures in terms of general
quality of life measures, disease-specific
quality of life measures, as well as functional

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outcomes and other things that should amount to
quality of life and independence. But what we
found when we went to patients is that
presenting a whole slew of scores with scales
that are not necessarily easily digestible is
actually very challenging.

And so we ended up with this figure
here, which essentially takes the KCCQ data
from the trials and shows that on average
patients move from a KCCQ score of 28 to a KCCQ
score of 70 among those who live. So, a couple
of key points about this. One is that I think
this is a very digestible way for people to
take in that information and it's on a scale
that I think makes sense, rather than 105 down
to zero, it's zero to 100, which I think is
important.

And then the last is, we spend a lot

of time trying to parse out very minor differences between outcomes, and what we find from most patients who are trying to take in all this information is that it's actually the big picture that's far more important than the very minute details. And I think a lot of times we split hairs over which quality of life

measure we want to use, and if you actually look at the data for all these diverse measures that kind of map the quality of life domains or health status domains, they actually kind of all move in the same direction, and that's what patients care about.

The other is that there are always tradeoffs and there are always downsides and always risks. And so we present on the top, what are the average benefits, but people also care about what are the individual bad things that might be able to happen to me, and we need to be able to convey that as well. So with

left ventricular assist devices, there are plenty of bad things that can happen even though the benefits are quite impressive on the whole. So we talked about hospitalization, because it is important to people, it maps the independence, it maps the symptoms, and it also maps the prognosis, and then it maps the costs, not just for Medicare or for society, but it also maps the out-of-pocket costs for patients.

Bleeding is a major problem for these patients, and so understanding what are the specific things that could happen and what are

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the frequency of those is important to patients. Stroke is a big downside and a major cause of death for patients who do get a left ventricular assist device, and so talking about this is important, and most people think differently about stroke versus bleeding even though they both may decrease quality of life and even survival.

Talking about device-related

infections is also relevant, as well as what might happen to these devices that could then affect the patient. And then I think it's also relevant to think about the fact that sometimes therapies, they work on average but they don't always work, and so one of the things patients have told us is that they've gotten a left ventricular assist device with the promise that their heart failure would go away, and yet about 18 percent of people continue to have very significant heart failure due to right ventricular dysfunction. So that's important because of the disappointment and the expectation management, and so measuring all of these outcomes is important to people if they're going to weigh all these tradeoffs, so

I don't think there's one single measure that's going to give us the answer or give patients the answer.

The other thing that's really

interesting about left ventricular assist devices is that caregiver involvement is really important, and patients care about that. Patients, one of the most important things to patients who are older, who are suffering from heart failure is they don't want to be a burden, and so if we don't measure what's happening to caregivers then we're not doing our job to help patients make good decisions that are important to them. And this is some work we did where we looked actually just at eight sequential patients at our institution, actually Dr. Redberg published this and championed it, but essentially what we found is that eight people with a left ventricular assist device when they died had pretty horrific deaths. I actually think that the deaths for many of them were not particularly troublesome for the patient, they were actually more troublesome for the caregivers, and so understanding how this affects the people, the

loved ones of the patients making the decisions is critical.

The other concept or contextualization I want to give you is that we like to talk in these very discrete kind of hard outcomes, and if you really sit back and spend time with patients about how they're making decisions, that's not the way that they often approach this. So as we today talk about what do we want to measure and how are we going to help patients going forward, we also have to think about what is it that's going on in patients' heads. And I think people like Dan Kahneman and the whole kind of literature around the way people make decisions has been informative.

So here you have a patient who's dying of heart failure, they're very symptomatic, they've been in and out of the hospital, and you offer them a left ventricular assist device which, like I said, on average may offer great benefit, but comes at significant cost and resources, and also may have not a good outcome for a minority of patients. This is high stakes, it's complex and it involves

caregivers, but it's also extremely emotional,

and at the end of the day there's certainly a range in these types of decisions, so we may be able to talk in averages but we also need to talk about the extremes in the individual course that each patient may undergo. And then finally, there are a lot of cognitive biases in the way that people process the information, so they may not weigh it rationally like we do, they may actually be very affected by whether they either had a relative die of a gastrointestinal bleed or had a relative die of heart failure or had a relative die of stroke.

The other thing we find is the way that people make these decisions, and in talking to patients there's kind of, there's a real dichotomy, so we have some patients who are like us, they think they're very reflective, they use a utilitarian approach, they weigh the survival data, they weigh the

outcomes data, they weigh how this is going to affect their family and how much it's going to cost, and they try to put all that together and make a decision.

But what we saw is that many people approach this kind of from a simplistic

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emotional view, and the thing that really determines whether they want the therapy or not is whether they're comfortable with death or not, and if they're not comfortable with death, survival becomes dominant over everything else and kind of fear of death can change the course of how they're deciding, so they become very automatic in their self-preservation, they're actually not necessarily interested in a lot of the nuances. And so I think that those patients still need to be counseled, they still need outcomes data, but the way that we present kind of what are the benefits and risks is important, but it's also important how we do it. So helping patients understand that just

because their average survival is better, if they get a left ventricular assist device that's a much more aggressive approach to therapy, and so while they may do well, when they don't do well there are a lot of burdens in the way that they die, and that is also something to be fearful of.

The other comment I want to make is that I really do think we're moving forward in the way that we're approaching this. So

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there's a lot of good discussion out there now that informed consent is very broken, that having the legalese kind of long paper that people sign, it really doesn't do much to help them understand the gist of what's going on with these medical decisions and the various options they're facing. I think we're moving in the right direction.

The other again is, like I had mentioned before, is Medicare cares about this.

So the national coverage determination for left atrial appendage occlusion as well as the NCD for lung cancer screening with CT, now actually mandates that shared decision-making take place, that there are people who aren't particularly biased involved in that counseling, and that patients use tools that help them kind of process this information, and those tools are specifically not in an informed consent document like this.

The other problem, I think, where Medicare and this community can make a difference is actually helping to make sure that patients are getting the right information, and to some extent I think we've

not done a good job of asking for that for our patients and the people that we either care for or we cover their therapies. So because we've said that we're not going to feel responsible for really educating our patients, what's happened is that marketing, which is fine, has

really filled the void of doing that. And so in left ventricular assist device therapy about five years ago, there was essentially almost nothing except for advertisements for people to understand their therapy and what they should do, and so we looked at what was available out there for patients a few years ago, and not surprisingly, 97 percent of the information available to patients talked about the outcomes that related to benefits but only half of them talked about the outcomes related to harm or risk. And so it's incumbent upon us not only to make sure that we're measuring the right outcomes, but that we get those outcomes out to patients and have the infrastructure to do that, and I think we all have various ways that we can help make that happen.

One of the ways that we're doing it is through patient decision aids or tools. I

think these tools take the outcomes data that

we're talking about what we should measure on today, and decide what is medically reasonable, and then make sure that that knowledge is transferred in a way that makes sense to patients and is balanced and is not overwhelming. And then also to list the patient's preferences. So one of the key features of a good decision is not only making sure that patients are knowledgeable and understand the range of outcomes, but also ask them to reflect on what their values are, and increasingly I ask patients to reflect on, is it really survival alone that's most important, or is it really living with a good quality of life that's more important. And also what maps to that is am I an aggressive person who doesn't mind interfacing with the medical community and is willing to take some risks for a possible overall average benefit, or am I somebody who is happy with life, does not want to see my doctor, does not want to be in the hospital, and does not want to take a lot of risks. And I think sorting through those values, the patient is almost as important

essentially as making sure that they have the outcomes available to them, that only in merging the values with the outcomes for the various options can really help patients make the right decision.

So, we've done this for left ventricular assist devices. This is kind of a classic approach to developing a decision aid. So first off there's a needs assessment, what's out there, what do patients need, what do providers think is needed, what do payers like Medicare actually think is needed, and then we kind of poll that information and we develop an initial kind of tool that tries to put together what is the problem, what are the options, what is the data for and against each option, and what are the values that are relevant to that information. And then we do an iterative process where we go back and forth with patients, providers, caregivers and other stakeholders, to try and distill this down into

the most important information in a balanced way that then helps people approach this, and ultimately it really comes down to what are the outcomes for each option that are important,

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and how do people use their values to sort between them.

The other thing I would say is that we're going to talk today all about kind of these formal averaged outcomes, and what's really interesting is that patients care a whole lot more about what does an individual's course look like. So I may say that your average survival increases from 20 to 80 percent and your average health status increases by, or doubles if you survive. But what patients really want to know rather than that list is, I want to see somebody who went through this and what did it look like for that person, to really ground the outcomes in what's the actual experience that people seek. And

the only way that I figured out how to do this other than presenting the data as I showed you before is actually to gather a group of different people who have taken the various options and then have experienced different courses with that option.

So you can see here, these are a couple of the patients who have agreed to be in our studies, so one patient had a very good

outcome, one patient didn't have such a good outcome from LVAD, and to show their individual experience and the contrast is helpful. But also just as important is to show people who chose not to pursue left ventricular assist device. So on the right is one of my patients who said I don't want to get a left ventricular assist device, this is why, and this is actually what my life looked like after I decided not to do that. So we need to be able to take those data and the outcomes and present them, but I think people also want to know,

what does that look like for a single individual.

I was listening to a talk actually this morning on the treadmill and they said, you know, every patient is an outlier, right, there is no average patient, so we can't pretend that if we collect a whole bunch of outcome data and just give it to people that we've actually done our jobs. And this is one of the ways to collect data I think that's important, but it's got to be balanced.

We can't do what I think sometimes advertising does, which is to say, you know, I

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bought these shoes, or I got this left ventricular device, and everybody does well. What we need to do is collect not only the outcomes for large groups of people but also, what are the specific courses that people can have after they make a decision.

So we're actually also spending a lot

of time trying to figure out once you do all that and you create these tools, how do you get them into use? And I think PCORI has really struggled with this. In the first couple years of PCORI, about 60 percent of the projects developed decision aids to create tools to help people make the right decision, but none of these tools or, not none of them, but many of them are not really being used. And so the work that we've done that's been funded by PCORI has spent a lot of time trying to think about, okay, now we've worked really hard to develop these tools with all the outcomes data that this community has collected, trying to put it in a form that's digestible and accessible. How do we make sure that that gets out to the patients in a way that's not only good for them and that they can use and is

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practical, but also doesn't add to the provider burden of trying to do what they do. Hopefully it actually makes it easier for us to have

these discussions going forward.

And so we're actually finishing up a study, we just closed enrollment in February so I don't have final results, but we had six sites with some of the people in this room and actually had an incredible experience, we actually overenrolled in this study because everybody was so excited to participate, and I think that speaks a lot to the need in terms of how do we get these outcomes out to people.

We actually used the RE-AIM framework about, you know, does the decision aid reach the patients, does it actually help improve their knowledge and their value of treatment concordance in the decisions they make, but also on the provider and the shareholder side, are people adopting this, are they implementing it in a way that makes sense and was intended? And finally, now that we've stopped the study, are people maintaining the use of these decision aids that talk about the outcomes, and I will tell you that all six sites actually are

continuing to use this, and there are really only over a hundred sites in the country that use left ventricular assist devices, and we've had organic uptake and kind of natural implementation of these decision aids at another 20 sites, so that's I think encouraging.

The outcomes are, you know, talk about knowledge, but it also talks about decisional conflict, decisional regret, stress and anxiety for patients, what caregivers are experiencing, and then control preferences. And one of the things that we see is patients will say Doc, I just want you to make the decision for me, and that's mostly out of ignorance and fear. If you engage patients with these types of decision aids, what we find is that the activation, the desire by patients to be involved in their decisions actually goes way up because now they're empowered to say oh, I actually can take all this outcomes data, understand it, and then match it to my values,

and now I no longer want you to decide for me, I want to decide for me. So we've got to be able to do that with the information that we

have today, is give it to patients in a way that they can use so that they feel empowered to make value concordant decisions.

And we see that people's values actually change. The caregivers think we should be absolutely aggressive and they fear the death of their spouse, but actually when you go through this process and show them all the tradeoffs, all of a sudden they can realize, maybe I don't want to be that aggressive, that actually doesn't match the true values of myself or my loved one. And we will hopefully have some of these results for you in the future, but I think it, even though we don't have them for you today, I think they inform the discussion going forward.

So, we've been developing these decision aids not only for left ventricular

assist devices, but we have them for implantable cardioverter defibrillators which I think are really important because they don't improve quality of life, they only improve survival, and we are also working on left ventricular -- sorry, left atrial appendage occlusion devices as well as other devices going forward, and

hopefully this will be helpful for the community.

So thank you again for letting me talk about this work, and I just want to summarize by saying, you know, if we really want to help patients make informed decisions about new heart failure technologies then we need their input from the start, we need to think about the patient perspective when we're measuring the outcomes, from the perspective of what are the patient -- the important questions for the patient, what are the important outcomes for the patient, and how can we get that data in a

form that patients can understand and incorporate into their decision-making? And I think actually, you know, thinking about the questions, the outcomes, and making sure that it is accessible to patients really should help inform the discussion later today, so thank you again - --

DR. REDBERG: Thanks so much, Dr. Allen and Dr. Lawrence, and you've really given us a lot of new information to think about for this and other technologies on patient decision-making and we look forward to

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hearing more from you.

And also, I have to thank all of the speakers for not just staying on time, but some people were ahead of schedule, and so we will use that time to stay ahead of schedule. But I think we can now take, it's a few minutes before ten, we'll come back at 10:10 and then we'll start with the public speakers, scheduled and open public comments. Thank you.

(Recess.)

DR. REDBERG: We're going to start again, so I would like to welcome everyone back from the break. Will the panel please take their seats. And we now have scheduled speakers for public comment, they have seven minutes per person, and the first speaker will be Clinton Brawner, who is a clinical exercise physiologist from Henry Ford Hospital, and he is representing The Cardiovascular Research Foundation. Dr. Brawner.

Okay. If he's not here, maybe we'll go to the second person. If Dr. Brawner is not here, then I'm going to go on to --

DR. BRAWNER: I apologize for that, thank you. It got quiet and I knew I was in

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trouble.

Good morning. It's my pleasure to be here on behalf of my colleagues here to talk about exercise as a measure. We really

appreciate the opportunity given to us by the panel to present here today.

So, here are our conflicts. For myself, I'm employed at Henry Ford Hospital, I perform cardiopulmonary exercise tests, and I also serve as a core lab for multi-site clinical trials and our current contracts are shown here.

So, the earlier presenters did a lot of my work. 20 slides -- I'm not going to cover that in seven minutes -- and it appears I'm not the only presenter that has kind of set that model up. Heart failure is a challenge, these are patients that a cardinal symptom is exercise intolerance. They come into the clinic saying I can't do this, I can't do that, I can't do what I used to be able to do. So, we've heard quite a bit of that thus far. That means they're affected by their activities of daily living, they can't do what they used to be able to do.

Heart failure trials have done a great job. We've got smart people working on this challenge, as we've heard already this morning. Mortality rates have gone down, but are still high. Continuing to use hard outcomes like hospitalization and mortality is a challenge, it takes a lot of patience and it takes a lot of time, which is putting a lot of demand on both health systems and patients.

The current presentation over the next six minutes or so is addressing question four, how confident are you that the functional assessments, six-minute walk test, the VO2max, and it's been thrown out already a couple of times, I'll give it at least a very quick definition for those that may only know it cursorily, and ventilatory threshold.

Six-minute walk test, we've kind of heard this a bit, it is a fairly simple test, but a simple test can be confused and done wrong. Dr. Pina talked about how she delivers the KCCQ in her clinic, that she has someone unfamiliar with the patient, unfamiliar with the care of the patient, deliver that test to

them. The same kind of challenges are

presented with exercise tests like the six-minute walk test. The six-minute walk test is done in a hallway, there's very defined standards on this, and we simply ask the person to walk as far as they can over the course of six minutes, with the idea being if your symptoms are so limiting, they may limit your ability to walk at whatever your normal pace might be. Originally developed in patients with pulmonary disease, it's been applied to patients with heart failure, pulmonary hypertension and others.

The cardiopulmonary exercise test, has gone by a couple of names, but this is a more formal test. We bring the person into the lab, we put them on a treadmill and potentially ride a bike, and we have a mask or mouthpiece on them. And the best example I can give you is if you've seen the Gatorade commercial where

they've got athletes sweating different colors; there's a couple images of an athlete running on a treadmill with a mouthpiece in. That's what we ask some of our most severe patients with heart failure to do.

And I've heard some of the critics in

the past, patients will do it, it's putting it in the context of, maybe a patient-centered context that describes the what and why what we're doing, whether it's for the clinic or for the research for clinical trial.

Not only are these two tests very different in their conduct but they're different in the measures they might be presenting. The six-minute walk advocates would suggest that it's more representative of daily living. This is how people live throughout their day; the pace they walk at the grocery store, how fast or slow they walk to and from their car in the parking lot. And then those who are in the cardiopulmonary

exercise test camp would say it's much more objective, we get a lot more physiologic data. Both might be true.

So for the cardiopulmonary exercise test, it's been thrown out already, I'd like you to think about for a moment, Dr. Pina threw out an example of a patient with a VO2 of 14. VO2 is the volume of oxygen the patient can consume. The more oxygen -- we're back to high school biology -- the more oxygen you use, the

more energy you create, and we need oxygen to work through energy.

DR. REDBERG: Two minutes remaining.

DR. BRAWNER: Thank you. A patient with a VO2 is very limited, just imagine a VO2 of 14, they're working at 50 percent of their ability just to walk down the hall.

Does VO2 correlate with, improvement of VO2 correlate with outcomes? It does. HF action shows that a six percent increase in VO2

when adjusted for other independent predictors was associated with a five percent lower risk for all-cause mortality, real important, many trials have shown improvement in VO2 is also correlated with outcomes.

VO2 as well as six-minute walk requires professional oversight, most commonly done with a core lab. There are other measures of the cardiopulmonary exercise test, the anaerobic threshold and ventilatory anaerobic threshold is one of those, and they also can be used to show important outcomes.

DR. REDBERG: Okay, thank you, Dr. Brawner.

DR. BRAWNER: Thank you for your time.

DR. REDBERG: The next speaker is Biykem, I hope I pronounced that correctly, Bozkurt. He's the Mary and Gordon Cain Chair at the DeBakey VA Medical Center and director of Winters Center for Heart Failure Research. He's representing the American College of

Cardiology. Dr. Bozkurt. Oh, she -- I'm sorry.

DR. BOZKERT: No problem. I'd like to thank CMS for the opportunity to present on behalf of the American College of Cardiology, I'm hoping to have my slides up on the monitor. In terms of my employment which has been already stated, I work at the VA in Houston and I do enrollment in clinical trials, and the American College of Cardiology has no conflicts to disclose regarding the presentation.

In the next few sessions we're going to collaborate. I, as the representative from the American College of Cardiology, will tackle question one, and representatives from SCAI, AHA and HFSA will be tackling some other questions in detail.

And the first question, hospitalizations, are they important, the

answer is absolutely yes, they're the home run

of the endpoint in our heart failure clinical trials, but I'm going to take it another step. We have to define as to what we demand according to the patient's journey and the device type. This is in the literature for a patient who undergoes a technology or device that may be associated with morbidity or even mortality, or a long hospital stay. They may not have time to be readmitted. Thus, they realize perhaps it may be a better concept of, freedom from hospitalization, that overall survival may be a better concept.

The second concept, a mixed component Coumadin to help treatment strategies with IV diuretics as an outpatient is critical. Especially when we have an admission or are giving the treatment as an outpatient. So the middle silo, which is heart failure hospitalization or equivalent events would be critical for individuals with congestion and where treatment strategies are being deployed more at the urgent care setting.

The third silo, all-cause hospitalizations are critical when we have

devices that may be associated with morbidity or even other comorbidities such as hypertension or renal failure, bleeding or fibrillation, and this may be an important concept in HFpEF.

And the patient's journey is critical because if the patient is in shock, which is on the left side of the panel, with critical heart failure, what's the duration? Should we call it perhaps short, maybe in-hospital mortality, or six-month rehospitalization rates. Whereas for a patient hospitalized without shock, perhaps we need to add a 30-day admission rate or a 60-day. For a patient with Stage C, we look at up to one year in that rate. For Stage D, end of life may be at shorter endpoints.

The next concept that we questioned was combining endpoints. It's important perhaps when the event rate is low for us to be able to achieve a sample size, but the

direction of the endpoint needs to be concordant. The other reason that we combine the endpoints is it's a more holistic perspective, not so one endpoint from the

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patient's perspective is a bit better. And a global ranking approach, where is the hierarchy of events, will need to be taken into consideration. And for valuing that, there will need to be a higher ranked endpoint than the others (unintelligible).

The other needed component of devices, there needs to be definitely a reflection of the device's efficacy, not solely in heart failure hospitalizations, so we need to be able to see that the device is actually performing what it's supposed to be doing, freedom from complications, along with maybe clinical endpoints.

And under these three examples as to when the hospitalizations may not be adequate

enough, this is perhaps a busy slide reflecting the summary of what we know with shock recovery gadgets in the acute heart failure setting, most of which have not looked at heart failure hospitalizations but were developed to demonstrate survival benefit, but was able to demonstrate hemodynamic benefits.

Second, we have devices out there that are targeting heart failure hospitalizations.

A few things need to be kept in mind, it is not going to be as simple as an insertion. That is going to make probably the reduction in hospitalizations, but the effort that goes behind the monitoring in outside continuation of medication, that's when Medicare looks at the concept of reimbursement for these entities, the effort and all the outside application of the medication has to be taken into consideration.

Another concept that we need to be taking into consideration is the secular trend

of what's happening in the technology. The clinician initiated -- this is an ICM slide -- are moving very rapidly in revising and refining their technology that will look similar to the other perhaps approved devices. They will be able to do certain entities without other sensors or upgrading, so the Cadillacs are moving very rapidly and not to be taken into consideration in the background. So we need to be cognizant, and we are only looking at hospitalization which in an observational trial was not able to be demonstrated in an NIH sponsored trial. We

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were able to see a signal from the adverse events when combined with the clinical events, and we had other primary endpoints such as looking at the rise in creatinine and white loss.

So we need to go out of the box with technology and see what the technology is

positing, which is the device's initial efficiency, and then we set clinical endpoints in conjunction with perhaps the adverse outcomes. Safety concerns mandate the necessity of controlled trials or controlled settings because in the background, as seen on this slide, due to a variety of other interventions, the heart failure hospitalizations are going down, and maybe the opposite thing or urgent care setting is going up.

This is a slide from Lynne Stevenson Warner's group showing that the patient's journey matters, even though it has a hospitalization, perhaps end of life which is seen on the right side of the panel, is (unintelligible) this is also here and now that we're transitioning to outside (unintelligible)

may not be presentable, and maybe that's not what's meaningful for the patient or for the health care providers.

DR. REDBERG: Time to wrap up.

DR. BOZKERT: And to finalize for acute heart failure shock, we may need to have in-hospital events, maybe look at a six-month follow-up, or without shock, maybe a longer follow-up; chronic heart failure patients maybe freedom from hospitalization and survival, they do need to have a functional assessment.

So in summary, one endpoint would not be appropriate for all technology. Technology needs to focus on device safety and function according to the technology target profile and patient stages. Composite endpoints need to be concordant. A time to event approach may mask later events. And outcomes should be comparable in direction in magnitude, and safety and efficacy should be considered as well as efficacy. And background changes in care, many are starting look at what community we're going to target, both for clinical trials and for reimbursement. Thank you.

DR. REDBERG: Thank you, Dr. Bozkurt.

Next is Srihari Naidu, who is director of hypertrophic cardiomyopathy and an interventional cardiologist at Westchester Medical Center. Dr. Naidu is representing the Society for Cardiovascular Angiography and Interventions.

DR. NAIDU: Thank you for having me. It's my pleasure to be here and represent the Society for Cardiovascular Angiography and Interventions, and my name is Srihari Naidu. I'm a little bit, I guess unique in the field of interventional cardiology in that I think I wear two hats and that's one of the reasons that I'm here today, is that I run a hypertrophic cardiomyopathy program, which obviously is a form of heart failure with a preserved ejection fraction, and I'm an interventional cardiologist. So a lot of what I do in my day-to-day life is really understanding the effect of both heart failure and interventional cardiology, and looking at interventional cardiology more in terms of

advanced hemodynamics and techniques that we could promote to improve the heart failure state, that's where my career has gone.

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I have some advisory boards that are fairly modest, they all relate to heart failure.

These are the questions you guys already know and we have very little time so I'll move past.

So I want to talk about the Interventional Heart Failure Work Group. This is a group where we discussed this topic and I was very happy CMS was looking at this topic because it's fundamental to the reason that interventional heart failure is here. The concept was enlightening to me that many times interventionalists have been viewed as individuals that approach things anatomically; we see a blockage, we fix the blockage; we see a valve leaking, we fix a leaky valve.

But fundamentally I think we have to

change and I have been promoting this among our colleagues, that we are really interested more in the heart failure state. Many people on medications are surviving their heart attacks, they live with their heart failure but it may not be a very good quality of life, in fact it's a miserable quality of life depending on

what medications they take, which is true, that is a morbidity for the patients, and we've also heard about how they struggle with these hospitalizations. So interventional heart failure is a concept that there are oftentimes device-based strategies that we believe can minimize the medications, improve the anatomy, and ultimately lead to meaningful improvements in outcomes, and importantly, not all those outcomes are mortality.

So we believe that most therapies that have improved mortality results in more patients living with heart failure. Current

and future therapies must focus not only on mortality but perhaps on heart failure related outcomes. Patients and physicians value quality as much or more than quantity of life, especially as patients age. We must be working as part of a team, not just as interventional cardiologists. And advocacy, which we're doing here, education on that sort of research are necessary to help foster technological advancements to reduce the burden of heart failure.

So, the search for meaningful

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endpoints. When death occurs with high frequency, it's very obvious that we can improve the mortality. Many of our therapies have markedly reduced mortality, but those ICDs are often leaving the patients with ongoing and progressive heart failure. Clinical events related to the heart failure state have emerged as accepted secondary targets. It's very easy to see how this is the case in aortic stenosis,

where one's symptom's emerged within three years, they're falling off a cliff, and so therapies that can improve that will obviously have an impact on patient care.

As you see here, this is data from the Sapien XT and Corevalve trials looking at pattern in AS. We very clearly have a mortality benefit that approaches three percent within the first 30 days and then actually enlarges as time goes by, so that's a very obvious benefit. But the story is different for other technologies.

This is mitral valve disease, and is it reasonable to use mortality as a surrogate? Probably not, because you see surgical approaches have really not improved survival in

the case of mitral regurgitation, but that doesn't mean it's a failure. If you look at secondary MR, we have lots of reasons why if you fix the MR, you may not see an immediate

benefit in these patients in terms of mortality.

Looking at the EVEREST 4 trial for mitral assist, we saw the same thing. Death is not impacted in the near short term, MR is impacted in the near and short, short term and near term, and it is done with less risk because these are percutaneous procedures, but the benefit is quite meaningful. You see improvements in New York Heart Association class that are comparable to surgery without surgery, and this is seen at 48 months, which I think is a reasonable short-term horizon.

In terms of the path forward, we do need novel hard endpoints that are required, and I use hard in quotes because they're not mortality oftentimes. Maybe we should look at days alive and out of the hospital, or heart failure rehospitalizations, or total hospitalizations as a measure of efficacy, and this has intrinsic value to all parties

including everybody in this room, we are all patients, we are physicians, we are family, we are the health care system, and we are responsible for all of this.

And the surrogate endpoint doesn't make sense, we have to show effectiveness. This is device and disease-specific, for example reduction in MR in the mitral set.

And importantly, I think, we are at a stage where we must face the consequences, or the point here that not every treatment must save lives. We do have treatments that perhaps improve the quality of people's lives, and maybe are neutral or perhaps even negative sometimes in terms of the quantity of life. So, examples where mortality benefit would not be a realistic target, the ESCAPE trial, CardioMEMS, these are devices that do have meaningful benefit, we believe, but it may not be in mortality, certainly not in the near-term horizon. Appropriate targets for these would be surrogate endpoints of heart failure, which would be reasonable predictors of improved quality and maybe a reasonable predictor of

quantity of life going forward, but we cannot

power trials to determine that.

So what are these meaningful surrogates in our world? For heart failure with preserved EF, perhaps six-minute walk test, biomarkers, and whether you escalate or deescalate therapy, medication therapy, I think that's important, if it leads to deescalation that should be considered. Heart failure secondary to MR, reduction to trace for one or two plus MR, the same other markers, perhaps LV volume is very important mechanistically in that situation, and the same with reducing ejection fraction where volumes become important, as well as deescalation of therapy.

Surrogate endpoints should ideally be part of combined endpoints and are generally not sufficient as standalone benefits, and you should ideally demonstrate congruence between hard endpoints and surrogates to confirm safety

of devices.

So further discussion, it's important to note that the aforementioned surrogates in general have not been proven prospectively, and I think it's very important to pick some of these and determine which ones we're going to

make the gold standard going forward so that we can continue to innovate, and we would encourage those trials that define these variables, and stand behind them as important variables for all of us.

So to summarize, except for heart failure etiologies with high mortality, most others affect quality of life primarily and this is a very very important target. Hard endpoints will need to include novel endpoints such as rehospitalization or days alive and out of the hospital, meaningful to every stakeholder. Additional surrogate endpoints as part of combined endpoints will be necessary to prove improvements in heart failure syndrome

that are technology and disease-specific.

Importantly, there is no one size fits all, and a tailored approach to selecting surrogates will be required, understanding that devices should maintain low procedural risk. So that means that as you're looking at different devices in this space, we need to look at how they may work and how they may impact heart failure specifically.

And finally, effects on mortality

should be tracked as registries over the longer term, understanding that the goal of days alive and out of the hospital may not always relate to reduced mortality.

So the conclusion, I do believe that we all want to applaud, SCAI applauds MedCAC and CMS for looking beyond mortality as a meaningful endpoint to address the main clinical outcomes in heart failure, i.e. morbidity rather than mortality in today's

world; to prioritize quality of life as much as, and perhaps more than quantity of life, consistent with palliative care principles; and to facilitate advances in technology.

And that's why I'm here today. At SCAI we work hand in hand with our patients, with other colleagues in cardiology, and also with our industry colleagues, because we do believe that most of these will translate to mortality if we pick the right variables. Thank you very much.

DR. REDBERG: Thanks very much, Dr. Naidu. Next I'd like to introduce Dr. Nancy Sweitzer, who is from the Sarver Heart Center at University of Arizona, and she

is representing the American Heart Association.

DR. SWEITZER: I'd like to thank the panel for allowing me to be here on behalf of the American Heart Association. My goal is to discuss quality of life in particular as an endpoint. I have a career also in clinical

trial leadership so I do have some disclosures related to that.

So I'm here to address quality of life, question number three, and particularly I'm going to focus on what I would argue is our best quality of life measurement tool presently in heart failure, which is the Kansas City Cardiomyopathy Questionnaire, KCCQ. On behalf of the AHA, we believe that disease-specific quality of life measures do reflect the patient experience when they're well designed, and capture dramatically what's most meaningful to our patients and thus, represent a very important endpoint in our trials.

The KCCQ is a validated and almost all heart failure states, including HFrEF and HFpEF, it maintains validity in the presence of other morbidities which are common in our patients. A change of five points on this

scale is considered clinically meaningful, and

has been shown to be clinically significant when followed. It's the most sensitive questionnaire to change, and is certainly more sensitive than some of the less disease-specific questionnaires.

A meaningful primary health outcome must be clinically meaningful in its own right and important to the patient, and I believe quality of life outcomes meet this definition of a meaningful outcome, and are sensitive and specific tools for testing interventions. I think it's just absolutely that quality of life can be a standalone primary health outcome in some research studies, providing safety and risks of the interventions are also being measured. Symptoms and functional capacity have been standalone outcomes for therapies in other cardiovascular disease states including angina, peripheral vascular disease, and pulmonary hypertension, and certainly I think it's time to move this into the arena of heart failure as well.

Failure to include a measure of quality of life, I would say, is a failure to

comprehensively study an intervention. If we're looking at particularly technological innovations and we're not looking at the impacts of those technologies on our patients, I think we've failed our patients, so it's critical that these be included as endpoints. I don't think they should be part of composite endpoints because they are qualitatively different from less subjective endpoints such as hospitalization or death, so they should be their own standalone endpoints in our trials.

We're obligated to understand the impact of technology on our patients lives, and these sensitive and specific questionnaires that we've developed do just that. So we would strongly support an actual requirement for some assessment of impact on quality of life as an adjunct to other endpoints in design of technology trials.

With reference to the discussion questions for this particular aspect of the

inquiry, there's little evidence that other questionnaires improve understanding of therapeutic burden associated with heart failure beyond what is found in the KCCQ. The

more general questionnaires such as SF-36 and EQ5D are less sensitive in our patient population and because we have such a good tool in heart failure, I would argue that that's the appropriate tool to use.

To detect, to talk about length of follow-up, there are many device trials now, the BAB trials, the trials of CRT therapy in heart failure that show us that quality of life benefits are typically realized quite quickly in these patients, typically a six-month period would be sufficient to detect the improvements in quality of life, and in fact going beyond that period, often quality of life outcomes might be contaminated by ongoing processes that were not impacted by the technology. So

actually the short-term, six-month outcomes are probably sufficient for most technologies. Of course when we're looking at a new technology, we have to imagine how that is going to work and impact, and use that to inform our decisions in this respect, but to date, six months seems to have been adequate for most of our technology outcomes in terms of quality of life effects.

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I think when we're looking at quality of life, lack of blinding is particularly problematic because there's often a belief in the technology among all patients in the trials, and quality of life may well improve. We've seen that multiple times in heart failure trials with significant improvements in quality of life in placebo-treated groups, so if quality of life is a primary outcome, I think it can only be used as such in a blinded trial.

And then finally, in terms of the talking about balancing adverse effects,

obviously, I think as Dr. Allen illustrated very eloquently for us, many of our technologies risks as well as benefits, and it is important to understand the impact of the technology on the domains of interest to a patient. Different patients have different goals and goals change as patients age, live with disease, and develop other limiting comorbidities, so ideally a well designed study will help inform our future shared decision-making around technologies. We've seen this as illustrated by BAB, we see this daily with atrial fibrillation and decisions to

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us anticoagulation, as well as our TAVR decisions.

So, we need to design our trials so that we get as such information as possible to make these informed decisions, and at the end of the trial we should hopefully have detailed information about benefits and harms that will

enable us to have the best discussions around technology with our patients moving forward.

So in conclusion, we need to understand the impact of new technologies on the patient experience, quantify the impact of the technology on disease manifestations most important to each individual, and use that as we move forward to implement those therapies in the heart failure population. Thank you very much.

DR. REDBERG: Thank you, Dr. Sweitzer. Next is Dr. Chris O'Connor, who's the CEO and executive director of Inova Heart and Vascular, an adjunct at Duke University, and president-elect of the Heart Failure Society of America, and he is representing them.

DR. O'CONNOR: Thank you for having me here today, and I'm representing the Heart

Failure Society of America in addressing question four on functional assessment in outcomes in heart failure. Here are my

disclosures as part of being in clinical research.

Well, I'm pleased that Clinton set the stage for us already in the first talk, and so the question you're already familiar with, how confident are you that functional assessment would be an adequate endpoint, should we include them as standalone meaningful outcomes or should they be part of a composite endpoint, and I'll try to address this really through work as principal investigator at one of the largest clinical trials that had serial measurements for functional assessments, that was the HF-ACTION trial where we could actually validate and show you the results with clinical endpoints.

So, peak VO2, six-minute walk or other CPET variable that are out there, gait speed, there's even shorter durations of walk and even exercise time, are functional outcomes that could be used as important endpoints in clinical trials. These have been shown to be

prognostically important. As Clinton showed you, this is an example from Keteyian's work from HF-ACTION on peak V02 showing a nice gradient of VO2 reduction and worse outcomes.

Actually in our predictive Uber model, it turned out when we put all the variable functional testing in the model, exercise duration was the single most important prognostic determinant of the mortality endpoint. Six-minute walk correlates with outcome, we've seen this, but in an analysis where we put all the competing functional endpoints into clinical modeling, you can see here on this slide that six-minute walk performs well in comparison to peak VO2 and equally well to more complicated functional outcome measurements such as VE/VCO2 slope.

So I think these functional outcomes are highly predictive, peak VO2 and six-minute walk are the best independent predictors and as I will show you here, I'll skip over a couple slides from HF-ACTION, as Clinton showed you

earlier on this slide, the validation of peak VO2 as an intermediate endpoint, as a functional endpoint, was conducted in the

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HF-ACTION trial because we had adequate number of morbidity and mortality events to show that the change actually correlated with the composite endpoints and mortality.

So, how would we integrate this into decision-making? Could functional assessment outcomes be standalone endpoints? They could be a primary endpoint in highly prevalent disease states if we could exclude harm, but in order to exclude harm, particularly in diseases that have, where there's lots of patients, you have to do large trials, so you already then have enough information to look at the clinical endpoints.

The example of angina drugs is a good one, in which many drugs were approved on improvement, reduction in symptoms and improvement of a one-minute improvement in

exercise time, but they excluded harms in those clinical studies, and is certainly acceptable in Phase II studies.

So, the functional endpoint could also be used as a composite endpoint. Certainly in common diseases where event rates such as mortality are low, this might be a good use of

the functional endpoint as a composite. In rare diseases the functional endpoint could be standalone or could be used in a composite, depending on how sick or rare that population is. And the Phase II studies, of course the functional endpoint in a composite is appropriate.

Remember that when looking at composite endpoints, you want to make sure that all the components are going in the right direction, and that's one of the challenges. Here's an example of a study that we worked on for the last couple years, just published

yesterday actually, where we used the global rank endpoint of six-minute walk, CV hospitalization and survival, and it allowed us to do a smaller sample size and look at a device in decompensated heart failure. And in this study we were able to detect a signal in the HFpEF population which is allowing us to plan for larger clinical studies. Could this be used as a primary indication, I think would have to be discussed further.

So in conclusion, I think as standalone acceptable in the small population,

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for sure, you could never get morbidity mortality in this population. So what I would like to say to the panel is that six-minute walk and peak VO2 are probably our best functional studies that we could offer possible indications for use as a primary standalone endpoint in highly prevalent diseases if we could rule out harm. Certainly a reasonable endpoint in rare cardiomyopathies or very

advanced disease, such as varied Class IV heart failure, and the composite endpoint I think is an intriguing endpoint, particularly in the global rank and low mortality conditions and in special subgroups, perhaps in the very elderly or other conditions. Thank you.

DR. REDBERG: Thanks very much, Dr. O'Connor. Next, our last speaker is Dan Schaber, PharmD, vice president of heart failure clinical research at Medtronic.

DR. SCHABER: Thank you, Dr. Redberg, and thank you to the panel for the opportunity to be here and discuss Medtronic's view about heart failure trial endpoints. Here's my disclosures.

As everyone has said, heart failure

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care has improved significantly but morbidity and mortality remains significant. We agree with what's been said so far in terms of heart failure hospitalization and mortality being

important endpoints. However, they're not always the most practical nor the most feasible nor the most efficient in terms of assessing heart failure outcomes.

And so what we would like to talk a little bit about today is the use of surrogate or intermediate endpoints. In order for these to be useful they have to be meaningful to all stakeholders, patients, clinicians, providers and payers. They need to be biologically plausible, widely available, and least burdensome. And of course, minimally influenced by bias, and cost efficient for trial design and execution. Most importantly, they must be predictive of longer-term outcomes and corroborated by real-world findings. Two such notable endpoints are the clinical composite score and left ventricular end systolic volume, which has been mentioned a number of times.

The clinical composite score has been

around for more than 20 years, it's been used in more than 30 heart failure trials, and importantly, it looks at all conditions and each patient's individual outcome in the trial, so it looks not only at worsening but also improvements and unchanged. It has reliably predicted the improvement of outcomes in beta blockers, ACE inhibitors, in cardiac resynchronization therapy, and importantly, it has also detected disappointing results in a few antagonists and (inaudible).

Here's an example. So, we took 1,600 patients from five randomized controlled trials of CRT and looked at their six-month clinical composite score, stratified the patients based on improved, unchanged or worsened, and you can see here that worsened patients had the worst survival, unchanged patients net survival, and improved patients the best survival. Also important to note here is that although there is not a difference statistically between improved and unchanged patients in terms of survival, there is a statistically significant difference in heart failure hospitalizations

25 between all three groups.

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1 The second measure, left ventricular
2 end systolic volume, has been mentioned a
3 number of times. Some of its strengths are
4 it's a standard routine echocardiographic
5 measure of cardiac function. Dilation,
6 otherwise known as remodeling, is associated
7 with poor prognosis, and reverse remodeling, or
8 decrease in the size of the left ventricle, is
9 associated with improved prognosis. It's been
10 a powered objective in pivotal heart failure
11 trials.
12 One of those trials was the REVERSE
13 trial which looked at cardiac resynchronization
14 therapy in mild heart failure patients, New
15 York Heart Class 1 and 2. This was a preset
16 objective and we looked at patients who had a
17 reduction in their left ventricular volume of
18 more than or equal to 15 percent as compared to
19 the rest of the patients in the population, and

you can here that this reduction in left ventricular end systolic volume showed a 68 percent reduction in mortality.

Another important point about trials for us as a provider of therapies and devices and solutions to physicians and hospitals is

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the timely delivery of our therapies. With CRT, it was done based on intermediate endpoints, 453 patients followed for six months. You can see here that the trial was completed and approval granted within three years. If we would have had to do a morbidity and mortality trial it would have been 800 patients for more than 30 months. That would have delayed access to the technology by more than two years and the cost there, not only the incremental cost of the therapy and evaluation, but the cost in terms of life loss and benefit loss to the health care system while therapies are under evaluation.

And this problem continues to grow.

So if you look at, if you want to show an incremental improvement on top of, for example, cardiac resynchronization therapy and guideline directed medical therapy, to show further improvement on top of that may take as many as 3,000 patients, which is a trial that we're actually doing right now.

So in conclusion, use of surrogate or intermediate endpoints such as clinical composite score and left ventricular end

systolic volume for heart failure interventions are meaningful. They allow for accurate measure of treatment effect in an optimal timeframe. They can be corroborated by postmarket measures of long-term outcomes. They can be easily implemented and tracked. And strategic implementation may expedite access to life-saving innovations while improving lives and saving health care expenditures. Thank you very much.

DR. REDBERG: Thank you. Next we have three people who, members of the public who have signed in to speak, they will each get two minutes. And I will just remind you to please state whether or not you have financial involvement with manufacturers of any products being discussed and who funded travel to this meeting. The first person is Norm Linsky, and next will be Maria Stewart.

MR. LINSKY: Thank you. My name is Norm Linsky and I'm the executive director of Mended Hearts, the nation's largest peer to peer support organization devoted to cardiovascular disease. I have no disclosures on my own. Mended Hearts receives educational

grant support from Novartis and Abbott.

I stand today representing Mended Hearts' 20,000 members across the U.S. to urge that the patient voice is considered as part of the panel's deliberations. We ask the panel to consider that hospitalization rates alone are

not a complete reflection of the overall outcomes of heart failure treatment. While hospitalization and medical benchmark testing are vitally important, outcomes measurement should also include emotional, psychological, social and economic outcomes to insure that the treatment is resulting in improved quality of life.

Including patient-reported outcomes in overall assessment of heart failure treatment is similarly vital. This includes symptoms, functional limitations, impact on daily activities, overall wellbeing and economic impact of the patient. We appreciate the opportunity to comment and hope that while CMS measures outcomes the patient's voice is included in assessment of heart failure treatment options. This is vital and we request that the patient's voice be very

carefully considered. Thank you for the

opportunity to present these remarks on behalf of Mended Hearts.

DR. REDBERG: Thank you, Mr. Linsky. Next is Maria Stewart from Boston Scientific, and the next and last speaker is Cynthia Chauhan.

MS. STEWART: Thank you, good morning. My name is Maria Stewart and I'm the vice president for global health economics and market access for Boston Scientific Corporation, which manufactures and markets cardiac resynchronization therapy devices that may be indicated for heart failure patients. We appreciate the opportunity to provide comments here today and we applaud the steps that CMS and the FDA have taken to balance the importance of clinical trial rigor with the need for timely access to new technologies through mechanisms such as post-approval study requirements, expedited approval pathways and coverage with evidence development.

In the case of heart failure, morbidity and mortality continue to be the most consistently used primary endpoints. The time

and resources required to conduct trials of these endpoints are becoming increasing burdensome as evolving diagnostic and therapeutic options have changed the profile of heart failure treatments. Relying on completion of studies with these endpoints as requirements to determine coverage without consideration of other valid endpoints could unduly delay patients access to care.

When considering what endpoints CMS should utilize when reviewing heart failure technology, Boston Scientific recommends the following. Focus not only on the traditional RCT endpoints of morbidity and mortality but also on the following categories of endpoints: Heart failure, hospitalizations, all-cause hospitalizations, validated surrogate and functional endpoints, all of which have been discussed today. Acknowledge the importance of quality of life in patient-reported outcomes. These real-world measures are integral to

assessing new heart failure therapies and are part of ongoing efforts to improve access and quality, reduce costs, and improved patient satisfaction.

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Consider the length of follow-up carefully. The appropriate duration of clinical trials will vary depending on the type of diagnostic or therapeutic being studied. However, when considering cost effectiveness and comparing technologies, it's always critical to evaluate the lifetime cost horizon using accepted mechanisms such as market models, particularly given the longevity of some heart failure technologies.

We urge CMS to consider the effect of total costs of heart failure treatment in all settings, including ongoing monitoring and related decision-making, as well as the total costs avoided by diagnosing and treating heart failure earlier.

Finally, Boston Scientific encourages the MedCAC to acknowledge that various technologies and diagnostics under consideration will provide either clinical or economic benefits, or both, to the health care system at different points along the care pathway. To truly assess the impacts of novel technologies for heart failure, all associated outcomes at all time points must be given due

consideration. Thank you for your time and attention.

DR. REDBERG: Thank you. Next is Cynthia Chauhan, and if you could just state if you have any involvement, and who funded your travel to this meeting. Thank you.

MS. CHAUHAN: My name is Cynthia Chauhan. My travel, I'm a heart failure patient, my travel was supported by Abbott but they had no input or influence on what I am about to say to you.

I am here as a face of the heart

failure patient to give you input on what it's like for us, and I would like to start out by saying I'm very disappointed that there is no patient on the panel. I think there should be.

I have stage 3-C heart failure with preserved ejection fraction, which was diagnosed two years ago in April. There are very few treatment options for patients with heart failure with preserved ejection fractions. In fact, 50 percent of us are dead within five years of diagnosis.

I am by nature an independent active woman. During my first year after diagnosis, I

had numerous hospitalizations to try to control the aggressive symptoms of the disease, particularly pulmonary edema, which is the most frightening experience I've ever had in my life. To me, being hospitalized because of heart failure means not only stopping my active life, but also helplessly watching my loved

ones give up their priorities, sorry, to take care and deal with the heartache of my fragility and my level of function decreasing and my dependence. My loved ones and I have put other aspects of our lives on hold, passively relying on the hospital professionals to restore my level of function or at least to stop my decline. Hospitalization moves me out of my community, insults my autonomy, and weakens my personal authority, in addition to causing physical weakness and subjecting me to possible infections.

In April 2016 my physician implanted a pressure monitoring device in my pulmonary artery which monitors me on a daily basis, allowing my physician to adjust my medications and activities before I am in acute crisis. Since the implantation I have had no

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hospitalizations and am able to lead an active life. Heart failure has changed my life into having to take twice as long to do things half

as well but I am, thanks to my monitor, staying out of the hospital and being an active engaged contributing member of society. Thank you for your time and for your interest in heart failure patients, and for, just for everything you're doing, and I'm happy to answer any questions you might have.

DR. REDBERG: Thank you very much.

(Applause.)

DR. REDBERG: I would like to thank all the speakers for their comments, and also invite all of you to take seats now in the front row, and we'll have an hour for Q&A from the panel, we're running ahead an hour so we'll have this hour, and then we'll break for lunch still at noon, or slightly after noon.

And it would be probably easiest if whoever has questions just turn your tent card up, and I will recognize you in order. We'll wait to just give the panel a moment.

DR. HSICH: My name is Eileen Hsich, I'm from Cleveland Clinic and am a heart plant

transplant cardiologist. My question actually is really more for CMS. This was very interesting to me but also very hard. I spent a lot time thinking about the questions and I think we've heard some wonderful thoughts and a lot of them reiterate some of the same things that were going through my head as well, that actually really, the answers to the questions depend on the stages of disease, so early versus late.

Also, the patient population. As an example, if you had all stage C and you had women versus men, one cohort is all women and one cohort is all men, the underlying disease is very different, okay? The perception of symptoms may be different, there's some studies saying women have more symptoms, and yet survival is also different, so the patient population matters, and the therapy that we're trying has been used to determine outcomes.

So I almost wonder, how could you fit one shoe for all of this, because I can create

situations where outcomes depend on all these three factors.

DR. CHIN: Thank you for that question

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and also, it's a good point, because I think we look at this with many of our decisions and many of the studies that we look at. So I think I would suggest, and actually for the panel, I would suggest you focus on it from a standpoint of a broader, you know, sort of population view, whereas I think we know, you know, that there are age and patient characteristics, disease characteristics that would influence a particular consideration, I think just looking more broadly from a population standpoint may actually be one way to look at these questions, and I think that's the way we actually have considered it. And typically in our decisions we will approach it that way, and I think if there are really, you know, some particular variables or criteria or patient criteria or some specifics, we can make

note of that, and that's what I think I would suggest.

DR. REDBERG: Julie, then Bram, then Art.

DR. SWAIN: Julie Swain. I guess a question to everyone here. We've seen a lot of data here about 30-day endpoints, and we're

talking about generally permanently implantable devices and chronic diseases. Can anyone justify, of this group, justify a 30-day endpoint, really? Because we know things like TEEs get swallowing dysfunction, aspiration in, you know, a lot of these patients, so, you know, they're dying three months later in a ventilator. So tell me more about who thinks it should be a 30-day endpoint for any of this, realizing of course that one TAVR valve in Europe got a CE mark on 78 patients followed for 30 days, and their TAVR was approved, but tell me more about the justification for 30-day

endpoints.

DR. REDBERG: Yes, Chris.

DR. O'CONNOR: Chris O'Connor. And I think that it depends, just as Eileen said, on the disease state. If you're looking at a device in cardiogenic shock, which I think (inaudible) so that 30 days would be appropriate.

DR. SWAIN: But not for anything other than absolutely end stage when you're dying in the hospital?

DR. O'CONNOR: No.

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DR. SWAIN: Thank you.

DR. REDBERG: Thank you, excellent question. Bram?

DR. BOZKURT: And just to reemphasize, the acute shock may not be an end stage, so those issues in the young individuals who will be healthier end up at the 50 percent survival, so I wanted to make sure that we acknowledged that.

DR. B. ZUCKERMAN: First of all, I'd like to thank all the speakers for some really great presentations this morning. My comments are directed more towards Dr. Adamson and Schaber. The spectrum of heart failure is extremely complex, one size doesn't fit all, and certainly one construct that I hope the panel will work with this afternoon is that provided in the central illustration of the Schaber panel, of the Ferreira paper or, I believe it was slide 18 of Dr. Adamson's talk, where he talks about congruence of several intermediate endpoints plus a trend towards improvement in mortality and reduction in hospitalizations.

What's not clear in your talk, at least from the FDA perspective, is the requirement that these studies are designed as adaptive Bayesian studies such that there's a numerical requirement for what type of

probability needs to establish a major endpoints when we see a PMA submission and that probability is expected to increase as the trial continues in a randomized fashion for eventual CMS submission.

But be it as it may, Dr. Schaber, you talked about the use of several potential surrogates, and the first question I'd have is, do you have any data on how any of those surrogates actually stack up when you use a quantitative questionnaire such as Prentice's criteria or other criteria? It's very easy to show correlation, but quantitatively, I think that we're in a quandary here.

DR. SCHABER: That was a very long question. In terms of do we have, we've not done analyses in terms of correlation with causation, with those endpoints.

DR. B. ZUCKERMAN: Let me make the question, then, more specific. For any potential imputed surrogate, it's nice to show

correlation, but the real challenge is to use the metrics developed for showing real surrogacy, which is a different standard using use criteria, Prentice's criteria or really showing in actual clinical trials that the change in the imputed surrogate really goes in a well formalized relationship with the actual hard endpoint.

DR. SCHABER: So we have done additional outcomes analysis showing that, not with those particular criteria, but looking at independence and direction, and looking at it as not just a cut link with medium ranges, but across the spectrum of ranges, and they do seem to retain direction across the entire spectrum of those endpoints. Whether it's a five percent change, a 10 percent change or a 15 percent change, those changes are all in magnitude, but the improvement increases with the positive outcomes in terms of reduction and other observations.

DR. B. ZUCKERMAN: Thank you.

DR. REDBERG: I'll just add to that, I think it's an important question. I'm thinking

25 way back to when I was a cardiology fellow and

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1 we were looking at (inaudible) as a predictor
2 of mortality and people who had more of them
3 did worse, but then the randomized control
4 trial where you had mortality as an endpoint,
5 it showed that it actually increased mortality,
6 so the surrogate was certainly a decrease of
7 (inaudible) but the problem was that people
8 were dying. More recently the SIMPLICITY
9 trial, which was a device (inaudible)
10 intermediate outcome didn't, so I think it's a
11 question worth coming back to. Next was Art.
12 DR. SEDRAKYAN: Art Sedrakyan from
13 Weill Cornell Medicine. I do want to ask a
14 question to Dr. Pina, and then I was going to
15 also chime in about the rehospitalizations, and
16 we all know rehospitalization is important to
17 reduce and it's a good endpoint to help your
18 system with questions aside from patient policy
19 questions.

But what I would like to learn from your personal experience and others, how manipulable is this endpoint in a clinical trial setting versus real-world evaluation of the associations and reductions that we care about? I don't want to mention a device, but

it certainly created this whole change in the way we perceive a readmission, because it was possible potentially there was some bias in seeing the trial results.

And a related question to that is, what do you think about interventions that make physicians pay more attention to their patients, and as a result they get reduced hospitalizations? It's two sides of the same thing, but I would like to hear your point, and obviously others can chime in.

DR. PINA: Thank you and thank you for your question, I think it's right on the money. Certainly when we're doing a trial, we know what the endpoints are, and I do a lot of

clinical trials, and we know that one of the endpoints is reduction in hospitalizations. And sure, it's really attractive to say wait a minute, I don't want to put the patient in a hospital again, let me try this, you know, let me try the diuretic in the office, let me try to bump up this medicine or maybe double this while trying to get them down. I really think it's in the eyes of the beholder, because if I see the patient, I can maybe stop the

hospitalization. Not just for the trial, because I don't think some of those hospitalizations are good for the patient and I think the patients do better not getting hospitalized, but somebody else who sees that patient may immediately say, oh, hospital. So whoever does that assessment is as critical as the assessment itself.

Now, the other side of the coin is we know that if you follow patients closely, it

can work, and so we have established -- and that we need to use our team members to work with us. We have data, and we have large data together with the guidelines showing that if you get that patient in quickly for an appointment with whomever, and we don't even classify how that appointment should be, we can really reduce the rehospitalization rate. Whatever happens in that appointment, and in our post-discharge clinic I've got a lot of different processes that happen, you know, including the assessment of quality of life, we get a pro VMT, like little cubbyholes, we try to fill in the cubbyholes for these patients, and we have an eight percent readmission rate

from our post-discharge clinic.

The earlier the better. Physiology tells you that. So again, that continuum of care, but your question is right on the money, I hope I answered some of it.

DR. CARROLL: It's an important

question, I'm John Carroll from the University of Colorado, and socioeconomic characteristics of a patient have a major impact on rehospitalization. I do a Mitra Clip on a patient who's wealthy, who has an internist who comes to visit the home, has resources, is his own chef, has the right diet, it goes on and on, versus someone who doesn't have those resources who may be less compliant. Of course that makes it easy to have an impact on rehospitalization rates, especially if it's an observational study, and I would choose study sites that have higher socioeconomic status of their patients if it was an observation.

It brings out the importance of randomization to get rid of that factor hopefully, but I think this is a major modifier of what you asked.

DR. SEDRAKYAN: John, just to clarify,

Art Sedrakyan from Weill Cornell Medicine, do

you think the bias is figuring out the spatial context, or in a trial context measuring this rehospitalization when we're facing the bias of knowing what people get? I mean, you can just leave it as I don't know, because the question is how we get a trial design that can help with this because of the inability to blind the investigators and patients, whether the trial might be more biased.

DR. CARROLL: Well, I would respond, John Carroll responding to two points. Number one, randomization should help, but some people aren't entered into trials because they may be of a socioeconomic group that can't comply as well and so they're not included in trials that we want. Still we will be treating those patients, and so we may have some artifacts produced from not having a broad spectrum of patients.

DR. REDBERG: I think that seems to be a slightly separate point, because I think the issue on who does and doesn't get into trials is a little different than the issue of bias in a non-blinded trial, when investigators are

obviously invested in the trial, they are perhaps eager to see the treatment work, and then the point about hospitalizations, certainly I think there's a lot of subjectivity, some people admit people, some people don't, it is not a very hard endpoint.

I actually think back to, it was more than 20 years ago when I was rounding in the CCU and one of our fellows has just come back from a heart failure course that Lynne Warner Stevenson evidently taught, and he said, and we were admitting someone for what was then called (unintelligible) holiday and he said that we shouldn't be admitting people onto the unit for (unintelligible) holiday because it was like any kind of holiday, all the problems were waiting for you when you got home.

(Laughter.)

And that really, you know, it is something that we should be more aggressive when we do need to admit people, and I hope

I've taken it to heart and I work very hard now because I know people do prefer to stay home. So that was how I took your question, Art, was that there is a lot of subjectivity, and in a

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non-blinded trial when the investigator knows who's getting the treatment, there's a lot of discretion as to who you admit and who you don't admit.

I'm going to try to move on because we have a lot more questions. Next I had Dr. Segal.

DR. SEGAL: Thanks. Jodi Segal. I'm not sure if this has been addressed, and so I'm wondering whether the outcomes that have been discussed would differ depending on if we're thinking about pre-approval trials, post-approval trials, pragmatic trials, or if it's coverage with evidence development or if it's just establishing outcomes for collection in registries. Does that influence which

outcomes are collected and chosen?

DR. BOZKURT: Biykem Bozkurt, heart transplant physician at Cleveland Clinic and here representing the ACC. I think it's in line with the former statement of external generalizability. In the clinical trials if the real population that we treat is included, then it wouldn't matter whether it's pre- or post-approval or, in essence, the heart failure

practitioners wouldn't end up treating more sicker patients and a lot of comorbidities, then it matters. So if the trial represents the real population, it may not.

DR. REDBERG: Dr. Zuckerman.

DR. D. ZUCKERMAN: Thank you. I actually have three questions but I'll just do one now and then wait my turn after. This is for the PCORI speakers, both of them actually, or either one. One of the things that was striking to me was the trial design and what to study and what's important to them, but as

(inaudible) what's important to them. So I wondered if you had any thoughts about, concerns about composite scores and what burden that puts on patients to not be able to make decisions that are true to their values or there concerns.

DR. ALLEN: -- thank you for that question, this is Larry Allen from Colorado, representing PCORI. I think that composite endpoints like you mentioned have advantages and I think it depends on your perspective. So, we talk about composite endpoints like mortality and hospitalization, and there's an

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advantage of putting those together because when people die they may not be eligible any longer for a hospitalization endpoint, or it can be hard to follow forward when somebody's health status is such that they're no longer able to fill out those questionnaires. So I think from one perspective for dropout or for

skewing endpoints it can be important when you're evaluating a therapy to think about the composites together, that's logical.

The second is that, I think if you're trying to decide whether something's medically reasonable or offers overall large benefit versus not, I think considering all the benefits together and averages can be helpful to a payer like Medicare to say, you know, we put all the benefits of this together, not just survival but quality of life measures, whatever those may be that you decide are relevant, with some of the other potential risks, and put that together, that can kind of help you to say whether this is something that offers relatively large value on average, versus this doesn't seem to offer significant value relative to the costs and risks. And so I

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think when you're looking at it from that kind of global perspective to decide overall whether something is reasonable or not reasonable, I

think the composite works well.

On the flip side of that, I actually think that it's important from individual patient perspective to split them apart and offer them up to people to understand. So for instance, like I said, patients may have very different perspectives about what a gastrointestinal bleed or a stroke represent, and that could be true for lots of different kinds of endpoints.

And the other is, a lot of people have talked about the ranked endpoint and I like the concept of a ranked endpoint where you take a group of people and you say as a whole, which of these endpoints is more important than another endpoint, and I think that gives you some perspective about sort of the global value of something to decide yes or no, and whether that's reasonable from a peer or societal perspective. But I think when you go to these individual patients, ranked endpoints are extremely difficult for them to interpret and

internalize.

So I guess the answer is both, yes, it's really helpful to collect all these pieces. From some perspectives it's important to put them together and decide kind of a global summary value, but when you bring it back to patients, I think it's important to split them back apart, provide them in a way that people can then say, well, this is now covered by Medicare or this is endorsed by some agency as being reasonable, but whether I want to do this for myself, I need to go back to the kind of individual pieces.

DR. REDBERG: Dr. Berliner.

DR. BERLINER: Hold on. He had something.

DR. LAWRENCE: Bill Lawrence, PCORI. Just to add a little bit, it is sort of a tradeoff in trial design, as Dr. Allen just said. I think it's important to be able to have people understand that we have looked at limitations of the trial, but the abilities to

(inaudible) would be an important (inaudible).

DR. SEGAL: Just to add some

clarification, I don't know if PCORI has done

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this, but it occurs to me that, you know, when

you have a composite score, tiny changes that

aren't very meaningful to patients can add up,

and so if your score looks like not much is

happening, whereas one bad thing can, you know,

really affect a patient much more than all

those little tiny good things would help, and I

just wondered if PCORI or you have looked at

that at all.

DR. LAWRENCE: I would agree with you,

but I don't know (inaudible).

DR. REDBERG: There may be some of

those, but I think I've read studies where the

composite scores are generally driven by the

weakest of the endpoints, which are often

hospitalizations or, you know, unstable

revascularization, that tends to be a lot more

softer. Dr. Berliner.

DR. BERLINER: Hi, I'm Elise Berliner. I have a question about the functional outcomes. So, Dr. Allen showed that outcomes like the KCCQ, VO2, six-minute walk test were all following each other, were correlated, and I notice that in the slide that Dr. Pina showed about the outcomes, that they actually are

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tracking functional outcomes with KCCQ, but then Dr. Brawner said that exercise measures such as VO2 outperformed measure such as KCCQ.

So, can you all help us understand that? So, do you need to measure functional outcomes separately, or are they reflected in the KCCQ?

DR. PINA: Ileana Pina, clinician. In the KCCQ remember, the KCCQ is not a quality of life instrument, it's a health status instrument, of which one of its domains is functional status, and for years we've been trying to correlate Peak VO2 and the functional

status, and it's certainly not perfect. It gets close but it's not perfect. But when you look at a list of prognostic variables, the most powerful prognosis of death is Peak VO2, a well done test, and Dr. Hsich has published on this as well as we have, so that functional assessment is way better if you can get the patient on the treadmill and you can do it, and I think that in centers like ours, we do that all the time. So the effect seen by a questionnaire is an approximation, but it's certainly not perfect.

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DR. REDBERG: Dr. Stevenson.

DR. STEVENSON: I also want to thank the panelists for really thoughtful presentations. I want to go back to the hospitalization for a moment, and I think you did a really nice job of demonstrating how fast the background is changing in terms of the different ways to try to avoid hospitalization, and it answers a huge question, does any one of

them actually significantly increases the length of the workday for the person who plans it, so I think it's unlikely that they're going to admit people they don't need to. One of the things, I think they're all important, as you demonstrated; however, clearly the severity of a patient who is given IV diuretic and goes home is different than someone who has to spend five days in the hospital.

So one of my questions is, do you think we could have a hierarchy there, such that IV infusion is one thing, EV is two days, and the hospitalization is however many days it is, so you get a total of days that has some hierarchy there for severity. That's one question.

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The other question is, do you think we can interpret that on its own, or do we need to make sure that anytime we would do this, we would also compare it to total hospitalizations

to make sure that there isn't something else that's increasing as we're decreasing heart failure hospitalizations?

DR. BOZKERT: Biykem Bozkurt from Houston, representing ACC. The first question I think is, or suggestion is wonderful. I think yes, we need to layer it like that, and I will perhaps add on to say that an IV diuretic in urgent care, or even in a clinical setting, and then perhaps an overnight stay and then the length of stay, because they are different things right now, and I think we need to be able to catch that.

And then the second question, remind me again.

DR. STEVENSON: Total hospitalization.

DR. BOZKERT: Oh yes. That I think will differ for different patient populations and the device. If the device has a potential risk for bleeding, stroke, the total hospitalizations matter. HFpEF, total

hospitalizations matters, and comorbidities matter. End of life, older, perhaps a sicker population where the comorbidities are the competing diagnosis, total hospitalizations matter. So I want to give a generic yes to that, but it depends on the patient and the device.

DR. REDBERG: Thank you. Yes?

DR. SWEITZER: Nancy Sweitzer, University of Arizona. I just would add to that that there are data to suggest that as we reduce hospitalizations, hospitalizations with the shortest length of stay seem to treat a population with a higher mortality, and that we may be actually moving patients out of the hospital too early and there's a significant cost to that, so I do think we have to always look at what's happening totally as a patient.

And I can tell you at our hospital, if you're hospitalized on the hospitalist service, your length of stay is going for heart failure is going to be drastically shorter than if you're hospitalized on the cardiology service. So again, randomization is important, having

25 some control over where patients are in their

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1 care is very important, because a lot of these
2 things are driven by things other than the
3 severity of the heart problem.
4 DR. REDBERG: Thank you. And it may
5 be stating the obvious, but if a hospital has a
6 high mortality rate, we'd see a low rate of
7 hospitalizations, because dead people are not
8 getting rehospitalized.
9 I would just note the speakers, if you
10 would just say your name, that's sufficient,
11 it's just for the transcriptionist, and the
12 MedCAC panelists don't need to repeat your name
13 because I'm calling on you by name. Dr. Fisch.
14 DR. FISCH: Yes. I would like to get
15 back to the issue of the composite endpoint. I
16 guess my starting point that I would like to
17 get your comment on, that CMS should value and
18 pay for endpoints that are understandable to
19 the public and patients and not just

understandable in terms of researchers or payers making complex decisions, and so I'd like some feedback on that position.

But also for Dr. Allen, I wanted to ask, are there other examples that you can see with doing decision making with patients where

you can use something like the CDF in decision making, so that a patient's preferences can be realized?

DR. ALLEN: You know, I'm not sure that I've actually seen (inaudible) exact interpretation, but certainly when you use decision aids and option grids, you know, the different components of a score like that often are presented, and actually the one that I showed you for left ventricular assist devices, you start out with what is most important for most patients, which is survival, and then move to kind of what is quality of life and then what are some of the individual components. So to some extent, we try to do that in the way

that we design decision making, but I think that the medical decision making community has kind of moved towards that in the way that they present. So to some extent, yeah, I think that it would probably make sense. As I said before, there is some value of trying to get a global value assessment, but having the composites presented to patients also allows them to weigh the different tradeoffs and put them together as well. So to some extent, I

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think we do that, both on the patient side and from the global side.

DR. FISCH: Do you try to explain clinical trial data to individual patients when talking about the composite endpoints, as a composite endpoint?

DR. ALLEN: So I do clinical care, I do spend a lot of time in the clinic actually going through various options, and that exercise represents hopefully what we're

grappling with today, which is that, you know, it's our job to really understand the nuances of trials and to explore the different clinical courses that patients can have with the various options. But I think, one, the experience of doing that over and over and really listening to patients, but also having the help of a well-designed decision aid that has input from various stakeholders, not just patients and clinicians like me who think they know a little bit what's important, but also payers and stakeholders like Medicare, to me that all kinds of goes together. And again, I think composites do try and take the overall tradeoffs to global value, but they probably

need to be combined in different ways, presented in different ways, depending on what the situation is where they're being used.

DR. REDBERG: Yes?

MS. CHAUHAN: I heard your question a little differently. I believe very very

strongly that clinical trial results should be accessible to patients, not just presented to patients, but understandable to patients. I believe patients should be included in the development of trials from the very beginning and should be viewed as participants and not subjects, so that when you come to the end, the language has to be meaningful to patients, and we are the final authority on our decision making, I believe, and we can't do that decision making without adequately translatable information from the trials.

DR. REDBERG: Dr. Hirsch?

DR. HIRSCH: Thank you. Let me ask a methodologic question. All of us in the panel are grateful for the wonderful discussions by the presenters, but as we look at patient focused outcomes as a really realistically important endpoint for trials for devices for

chronic diseases, I have a little bit of a

worry. If I had a trial with a sample size adequate to show a series of patient focused outcomes that were positive, how much do we know about the reliability, flexibility and durability of that device?

In other words, in trials we are dealing with a very specific usually well polled, well represented cohort, where people may feel better in downtown Chicago, Boston or Philadelphia, but if I go to a central valley of California or somewhere in rural Minnesota, it may be that those outcomes might not really be present or durable, and I want to present this to Dr. Allen or one of the group. How do we know in the future when Medicare provides this as a benefit that it will be generalizable and durable? Do we need to do postmarket surveillance of patient focused outcomes, and how would that ever happen?

DR. ALLEN: Well, a couple of -- Larry Allen -- a couple of thoughts. It's a great question. The first, I just want to start of with, somebody talked about subjective endpoints and that was in reference to

patient-reported outcomes, and I actually take a little bit of an issue with that. Whether I decide to admit somebody or how long I keep them before I discharge them, or whether I give them the IV Lasix in the clinic versus sending them down to the emergency department, all of those things are somewhat subjective. Now they correlate very well with other outcomes like death, which is certainly more objective, but I would be careful to say that a patient-reported outcome is somehow subjective in the way you're defining it, and lesser, as opposed to whether somebody gets a certain therapy that I may have control of.

Now your question was actually about the durability of, I think patient-reported outcomes over time and their generalizability across patient populations.

DR. HIRSCH: Through the populations of the American Medicare public.

DR. ALLEN: Yeah, and you know, I

think some of it depends on the development and validation of the patient-reported outcome that you're looking at. So to some extent, I don't think you can group all PROs together and say

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that, you know, how they're going to perform and how well they apply to various groups. I think those people who know a lot more than I do about the development of PROs spend a lot of time looking at, you know, what is a clinically significant change to various populations, how does that correlate to other outcomes, and how durable is that over time? All of those things are part of the development process and I would say, I think you have to look at the various PROs to determine that. Other people know more than I do.

DR. HIRSCH: Do we know that we actually have the patient-reported outcomes that really have been validated in the postmarket environment, as we have for other

endpoints?.

DR. SWEITZER: Nancy Sweitzer. Speaking just for the KCCQ, which I spoke on, absolutely, it's been validated in many populations, men, women, all races across the country, in other countries. It's been translated into 80 languages at this point, I believe, and validated in many places in the world. It seems to be generalizable across

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other populations in a trial setting.

DR. HIRSCH: So that's in a trial setting, I'm aware of that.

DR. SWEITZER: And outside of trial settings, yes, absolutely.

DR. REDBERG: What I thought you were getting at, Alan, is that there's a difference between the trial populations, and Dr. Pina alluded to this in her talk, that are often enrolled in trials that got to FDA for drug and device approval, and that they're younger, they're more likely to be men, they're more

likely to be white, and they're more likely to be healthier, because so many trials have comorbidities as an exclusion. And then, therefore, they're very hard to then generalize to a Medicare population, which is what we're talking about today, because those people are older, more of them are women, they are more ethnically diverse, and they're more likely to have more comorbidities.

DR. CARROLL: John Carroll. You're really making the case for clinical registries, post-approval studies where it's a broader patient population, and you're able to get away

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from the more focused patient population in the treatment centers that are highly selected. And with a national coverage decision, it's been really a way to substantiate clinical trial results and further nuances of treatment, and to individualize risk versus benefit rather than giving the global average in a trial.

DR. REDBERG: I agree. I will just say that the issue with registries is that there's no more control groups, so we have to assume that we've reached superiority compared to control, and then we're going to look at other populations. Briefly, Dr. Pina?

DR. PINA: Briefly, yes. Dr. Hirsch, you're absolutely correct. It can be done on the outside, but the way that we have been using it for years is to categorize the patient, so you've got an ejection fraction, you have a Peak VO2, and now you have a health status, and it gives you in your mind where that patient sits and how aggressive do you want to be. So it's not just did they respond to the treatment, but where are they at this point when I'm starting to take care of them.

DR. REDBERG: Dr. Salive.

DR. SALIVE: You almost stole my question, but you gave me a great intro. I was going to ask about generalizability as well and

I think, but from a slightly different point of view, which is, heart failure patients really have a lot of comorbid conditions, as you mentioned, and it's really almost universal and quite common, you know. In spite of that, I think some of the presenters have said that heart failure is dominant and we should only worry about that, but I tend to disagree except when it's very advanced, that's when it needs to be. But there can be dominance from cognitive impairment, dementia, and I think some of these conditions have drug interactions and drug contraindications that become prominent. And so I think, you know, this raises a lot of questions, I think for that evidence development with, you know, broader inclusion criteria for trials that we can, you know, try to encourage that. I think FDA has done some work on that, to their credit.

It also raises questions, I think, on the outcomes which we're getting at, and I heard some commenters say that only disease

specific quality of life is important, I disagree with that, and I want to know about generic quality of life measures such as SF-12, EuroQol, because I think it's heavily validated in some settings, but needs a little bit of work in the elderly. Generic quality of life, I think can address safety, it's very broad, it can help with quality determinations which some people are interested in.

And so my question is, could generic quality of life be useful for communicating the risks and benefits to patients, and so I guess my question is for PCORI, or anyone.

DR. SWEITZER: Nancy Sweitzer, I'm not PCORI, but I was the quality of life presenter. We actually did a study comparing five generic quality of life questionnaires to KCCQ in a large patient population, and while all of the generic quality of life measures picked up the change that KCCQ did, the KCCQ did so much more sensitively and with much larger confidence intervals, sorry, much smaller confidence

intervals, and this was across a very large
population that included many elderly patients,
many with a great number of comorbidities, and

this has been shown for KCCQ in multiple
settings. So I think we are fortunate to have
an incredibly well validated tool that's highly
sensitive to changes in our patients.
With a mild heart failure where
there's a severe comorbidity that's much more
dominant, that may not be true for that
individual patient, but in large populations of
heart failure, KCCQ is as sensitive or more so
than any more generalized quality of life tool
that's been looked at. So, I think that we are
just in a very fortunate position, particularly
with this survey.
DR. REDBERG: Dr. Stevenson. On this
point?
SPEAKER: Just that sensitivity is not
the only issue.
DR. STEVENSON: I just wanted to take

that one more level because I think it's really important. Certainly I think it's a well validated tool in terms of heart failure, but when we looked, Eldon Lewis actually studied this in about 750 non-trial patients, only about half of the ambulatory patients said that heart failure was the major factor in their

qualify of life. So from the trial standpoint it's very useful, but when we go to the patient and say your quality of life is going to improve this often, we need to recognize that there quality of life may not have been limited by their heart failure.

So I wonder if every time we're going to use that, that we also have a promise or some other modern technological way of getting at this, so we can at least determine whether it's really heart failure quality of life, because that's going to be very important for our patients.

DR. REDBERG: Exactly. I have a patient, they're not limited by their angina but by the fact that they have arthritis in their hip and they can't look at these outcomes to improve their functional status.

I want to let Dr. Yancy ask a question, and I also just want to note that we have about 20 more minutes for the questions to the speakers and then we're going to break for lunch. We have another hour for discussion amongst ourselves, so if any of you have questions that you think are more for ourselves

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and not for the speakers, maybe you can wait, because I certainly want everyone to be able to -- it's great that everyone has questions, but I'm watching the time. Dr. Yancy.

DR. YANCY: Thank you, Dr. Redberg. I have questions for Dr. Sweitzer and Dr. Allen. Our task today is largely to look at outcomes, their absence will influence mortality, or absence the documentation of mortality, and it

means that quality of life once again becomes very important in this discussion. I support the theme that's just been mentioned over the last minute that the patient-reported outcomes measurement information system is a validated tool particularly in the field of cancer.

But I'm uniquely interested in a statement that was made in presenting the American Heart Association's position that the quality of life tool should be a separate assessment and not incorporated in a composite, and that would seem to lessen its influence because it would be, oh, we're not going to treat it as generously as a standalone, as opposed to being part of a composite. But both you and Larry can talk about the construct of

the composite that improves quality of life which I think is reasonable. I'd like you to tell me why you think it should be separate, and Larry, if you can comment on that as well.

DR. SWEITZER: Nancy Sweitzer. Thank you, Clyde. I think this gets to Dr. Redberg's point that when you have a composite and it's driven by the softest endpoint, that tends to cause a lot of consternation, and the quality of life is often considered the softest endpoint. I think that we all feel that this is incredibly valuable and I think it would fine as, you know, Dr. Allen pointed out, if you want to talk about the overall impact of a therapy on a patient, and quality of life can be taken into that overall impact and used as a composite, but I do think it's going to be important at the end of the day to separate the quality of life outcomes out from other harder outcomes. Just because, just to be fair, regulatory bodies want to do that, you know.

I think we could probably make a case for quality of life being an important part of this, but I think that the reality of the opinions of those bodies is that it's likely to

dampen the enthusiasm for approval if an endpoint is seen as driven by that.

DR. YANCY: So, Dr. Redberg, as Dr. Allen comes to the microphone, I think part of the focus that needs to go on in this discussion is to recognize the importance of quality of life parameters and not allow the thought process to prevail that it's of lesser importance. And that means, as Dr. Stevenson pointed out, there are more sophisticated instruments that can allow us to get much for specificity, and as Dr. Allen has already pointed out, hospitalization is an incredibly subjective endpoint.

DR. REDBERG: I think that we have heard that consistently, and certainly I think my mission as a doctor is to help my patients feel better and/or live longer.

DR. ALLEN: I mean, again, I think I wouldn't call it a softer endpoint, what I would say is that quality of life questionnaires or health status measures, they happen and everybody here can answer them, and they are typically a continuous variable, and

so consequently these processes can be worked

with so the small changes can be picked up, and (inaudible) it's often more rare and it's a yes or no, so the power to pick up the difference is less, so to some extent I think that, you know, when you combine these endpoints, some of them end up dominating over others, not because of which is more important, but because of the nature of the endpoint.

The other comparison I would make as people are moving forward here, and this gets into a discussion of general health outcome measures like EuroQol or SF-12 or 36 versus a disease-specific measure, it's a little bit like the argument that FDA and others, and Dr. Zuckerman will probably have a lot more to say on this, is between kind of an all cause deaths versus CV deaths, or all cause hospitalization versus heart failure hospitalization, and I think it depends

somewhat on your perspective. If you're trying to determine what's valuable to Medicare and patients, at the end of the day, if you prevent one kind of death but you increase another, that's not really a value. But over and over, when we try and design efficient trials that

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are able to look at differences, we have greater power to see important differences that are affected directly by the therapy and remove some of the noise in some of the other events.

So to some extent, when I think about KCCQ versus measuring a more general type measure, the general measures do have advantages, it's actually what's most important to patients, but I may have to design a larger study in order to show the difference in that, which may be fine, except that we also heard the argument stated earlier that requiring less sensitive endpoints that require bigger studies carried on for longer periods of time not only requires more costs on society or whoever is

running those trials, but it also leads to delay of approval of therapies that actually could be meaningful to patients.

So you know, everything's a tradeoff, which I think I said earlier, and I think you all have to decide that, you know, if you're thinking about quality of life measures, which one you want to use, and that depends a little bit on how important it is that you made a difference to the patient overall.

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DR. REDBERG: Dr. Zuckerman, did you want to comment on that?

DR. D. ZUCKERMAN: Well, about the KCCQ, it is a composite, it is a composite of functional and quality of life, and there's actually not that much that is quality of life. It asks are you happy, it asks are you depressed, it asks are you able to do things you want to do, which is functional or psychological, so it is a bit of a problem in

terms of knowing whether it should be used.
But I was struck in, I think Dr. Sweitzer's
Power Point, that she talked about the placebo
effect and I think that's really important, not
just for quality of life in the sense of how
happy we think we are, but functionally, that
you need a control group and a well controlled
study, and you need to look at what's happening
over time and whether the person feels like
they're functioning is better now because they
were in the hospital having a procedure, and
compared to that they're doing really well.
So, I think there's a real problem with some of
the data when we won't have a control group, we
don't have percent of compared to what, and not

just compared to other people but compared to,
you know, how good I feel either
psychologically or functionally.
DR. REDBERG: Dr. Sedrakyan.
DR. SEDRAKYAN: I just wanted to
comment on the evolution of these specific

measures. About 20 years ago on the SCAI SF-36, that was the only instrument available, '99 was the first time we tried to involve patients, sent this questionnaire out, because it was a popular way to measure quality of life, and no one was measuring cardiac valve populations. And I brought these study results to Ollie Feinstein at Yale, who was running the program, and asked why do you need all these questions, why don't you just ask patients a physician questionnaire, one question, compared to before surgery, do you feel better today? That's trust your patient, they probably know best, you don't have to ask so many questions. But his point was -- my answer was that I can't measure that, I can't run my domestic regression, my old regressions would fail. I need more questions, I need a continuous endpoint so --

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DR. REDBERG: Okay.

DR. SEDRAKYAN: But my point I'm trying to make is there a physician questionnaires and self-regulated health questionnaires.

DR. REDBERG: Dr. Kobylarz.

DR. KOBYLARZ: Fred Kobylarz. My question is, there's a short, there's a long version. We kind of discussed, you know, the domains. We talked a little bit about some of the limitations and my initial question was had it been cross-validated in specific populations, and I think you answered that.

But I guess, someone mentioned the whole cognitive impairment issue and it seems to be kind of under appreciated. How is that being addressed in a self-administered survey? And are there, you know, any informant-based surveys that are out there?

DR. SWEITZER: Nancy Sweitzer. Obviously when cognitive impairment is significant, these surveys don't work. You know, if you ask compared to two weeks ago and you can't remember two weeks ago, you cannot do it. I don't know of any surveys for heart

failure that can be used in the cognitively impaired population.

DR. PINA: What happens to the patient, it's not that cognitive impairment isn't present, so we have actually been giving a clock-drawing test to the patients at the same time that we give them the KCCQ, because we're looking at two separate things. Cognitive impairment is really tough to get your hands around when you think of, can you draw me a clock, you know, can you tell me what you had for breakfast this morning, maybe some of us can't remember, but that's the kind of questions that we would have to integrate into a format, and I think we need badly something like that, and it may have to be the caregiver that answers the questions if a patient can't.

DR. KOBYLARZ: I was referring to the more, you know, advanced cognitively impaired people. It's the MCI folks, the early dementia, that nobody asks that, you know,

how's the memory, and you go on to administer the survey. But you know, are they truthfully, you know, answering the questions, and how valid is the information.

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DR. REDBERG: Ms. Renbaum.

MS. RENBAUM: Thank you, Dr. Redberg. My question really comes from the fact that we talked about the patient's journey at the beginning, and patients who start out as stable and ambulatory before a hospitalization, but they continue to decompensate as they go along but without any signs or symptoms of that. So it seems that if we measure, if we're able to measure how quickly they're decompensating before that admission, then it may help us to measure after, but I'm not sure I heard it, how is that measured today?

DR. ADAMSON: Phil Adamson from Abbott. I hear your question, and the data set that has been built over years has come from

implantable monitoring technologies, both standard delivery devices that provide diagnostics like CRP devices and ICDs that have led to the evolution of implantable devices for monitoring pulmonary artery pressures. And in trials in which pulmonary artery pressures get measured, those pressures changed long before patients develop symptoms. And if they go unchecked or untreated, they lead eventually to

the development of symptoms, but that symptom development is late in the progression of events and then hospitalization.

So currently, implantable monitoring systems are the way we are able to gain insight to provide the provider and the patient information about their transition from an ambulatory and mainly stable to pre-congestion or pre-symptomatic congestion.

DR. REDBERG: Is there any data linking pre-congestion to survival?

DR. ADAMSON: The only data would be

to look at -- yeah, actually there is. There's a recent article that, a retrospective evaluation of the (unintelligible) experience some years ago, published in Circ Heart Failure by Dr. Giles and his colleagues, including Dr. Stevenson, and essentially for every one- to two-millimeter of mercury reduction in pulmonary artery pressures over time, there's a long-term benefit in terms of survival, and survival is directly impacted by elevation in those records from baseline to six months as well. So what that study demonstrated is similar to what we see with systemic

hypertension trials, five-millimeter mercury reduction in systemic blood pressure led to a 41 percent reduction in long-term risk of stroke, and if had a blood pressure cuff on the pulmonary artery we'd see similar type behavior of pulmonary artery pressures by actively lowering them and keeping them from going into

that presymptomatic congestion phase.

DR. REDBERG: Thank you. Dr. Swain.

DR. SWAIN: I just wanted to talk a little bit more about the placebo effect. The problem we have in virtually all these trials is it's impossible to blind them because if you have a blinded patient but you don't have a blinded treating physician, I'm convinced that the patient will end up knowing the results. We've had several studies over the years that have told us all about this, the knee arthroscopy, the migraine treatment with needles, to the PMR, percutaneous myocardial revascularization, holes in the heart with a laser and you know, in the PMR study the treatment group was 41 percent of the patients, and in the placebo group, 41 percent of the patients, and I urge you all to read snapshot

literature from Harvard that the placebo effect is proportional to ritual, how much you do to a patient, and is very long lasting. After many

years at the FDA I couldn't interpret it. I looked at them but it did not involve my regulatory recommendation because I had absolutely no way to figure out what any of these patient-reported outcomes means. And for those who were receiving the red placebo caps, the big red pills, the placebo pills used for patients that you wanted to cut down, amazing results with that.

So I don't like to call them soft outcomes because the most important thing is how the patient feels, but I don't know how to measure it in an unblinded trial.

DR. REDBERG: I think that's a really important point, and we know that's even more powerful for procedures and devices that it is for drugs. And you're right, I mean, it's important that people feel better, but if they feel better from a placebo, why have the harm of an invasive procedure or an intervention.

DR. CARROLL: John Carroll. You've made an excellent point and that's why you have

to have different domains of outcomes. So if you're changing some anatomy, some physiological area, you have to show that the device does that, and then does it correlate with patient-reported outcomes. Things like migraine are difficult because there's no objective effect with migraine, it's totally subjective, but most of what we talk about, there are objective measures.

DR. SWAIN: Not always, and Ileana's point about who gives the test. In CDC registries it's the treating physicians that mark down, you know, you're doing better, aren't you? And so the patients are doing better, but it's a huge problem of how we measure it.

DR. REDBERG: And it's definitely not blinded. I mean, I took your point to mean that it has to actually be double blinded, you know, with a sham procedure, because we know that even for the neurosurgical procedures like Parkinson's, there was a sham surgical

procedure and those people who got a sham hole in their skull did as well, they improved.

DR. SWAIN: Oh, and we have PET scan

evidence that giving a placebo or doing a placebo changes the brain just like something that would be beneficial, like a narcotic, so it is physiological. When you say it's in the patient's head, it actually is neurologically in the patient's head and there is a physiological anatomical reason that placebos work.

DR. HIRSCH: I think it's very important for the panel to come back to this after lunch. We really need to get to this, because as we expedite approvals with 21st century cures that come with little evidence, we have opportunity costs of what we know and we don't know, so what do we provide the patients, so we need to come back to that.

DR. REDBERG: Dr. Berliner, you get the last question before lunch.

DR. BERLINER: My question is only of Dr. Sweitzer, who I heard mention clinically significant. First of all, I'm wondering for all of the intermediate outcomes, things like exercise tests, do we have a clinical significance, do we know what that is?

And also, just back to my question

before about some of these things that are far away discordant but not quite, like KCCQ, if we wanted to have like a core outcomes measure set that was measured in all studies but not being depicted as undue burden, what would that core measures set look like?

DR. SWEITZER: That's a perfect segue, I was just commenting to Larry about this. When we started using the KCCQ we had the Minnesota Living With Heart Failure Questionnaire, and we had been told that a five-point difference was clinically significant, and so we were asking the

question, what should it be for the KCCQ? And that hard point has been derived from a group of us called, it was called the quality outcomes group, where we said five sounds good. And then we sat there and we did six-minute walk, we did CMP and we did repeated testing in a group of our own patients in the clinic, and that's how we came up with five.

When we did HF ACTION, it was a two-point difference that became statistically significant, but we had 2,331 patients.

For peak VO2, if you look at the

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literature, about a 15 percent increment is what we consider clinically significant from baseline; in other words, the patient's own improvement. When you compare these group to group, you're comparing apples and oranges, so I like to look at the patient's own improvement, and 15 percent, Clint, wouldn't you say, I think is what's recognized in the literature as being functionally significant,

that it takes you to another level of your function in your daily life.

For the six-minute walk, I think that's still out, unless anybody has -- 54, we said 54, 55.

DR. REDBERG: Thank you. Well, we clearly are going to have a rousing discussion after lunch as well, but right now we get to take an hour, so we'll come back at 1:10 and have panel discussions. Thank you all.

(Recess.)

DR. REDBERG: Thank you. We're going to start our afternoon discussion, and so I welcome back the panel. And just to remind you, we have an hour now for discussion among the panel, and we can talk about any of the

things we have been talking about, but in particular we will be voting after the hour of discussion, so if there are any unresolved questions, including about any of the voting

questions, now is a good time for us to talk about it.

It seems like some of the issues we talked about were composite outcomes, primary endpoints, secondary endpoints, surrogate mortality, quality of life in a broad sense or disease-specific quality of life. I'm just throwing out a few of sort of the major threads of our earlier discussions.

DR. STEVENSON: I would like to review this, I had one question this morning, and it is, what is your hope of what we will come up with? Because it's not going to be this one measure is going to work no matter what your therapy is and no matter who your patients are, that's not going to happen. So without that, what is it that you are reaching for in your answers to these questions?

DR. REDBERG: And are you directing that to Joe, or to me?

DR. STEVENSON: To anyone who can help

us.

DR. HIRSCH: Joe, that would be helpful to all of us.

DR. CHIN: So, I think just looking at the endpoints in general in the context of the population that we looked at and the studies that we reviewed for a potential decision, so I think it was sort of mentioned earlier, it may be specific populations, but I think overall is what we're trying to look at from that standpoint, so if there are some characteristics or factors that need to be mentioned specifically, I think that would be helpful, but in general I think you can say what an average benefit is.

DR. SWAIN: I guess I have sort of a follow-up to that. The voting questions say standalone. I was a bit confused originally with standalones, because there's a footnote about mortality. So when you're talking about standalone, do you mean standalone with mortality, which is not the definition of standalone. This is Swain speaking. So you know, because if you say standalone without

consideration of mortality in the primary, you

might just want to ask if anybody in the panel would agree with any of that, and then maybe the questions ought to relate to as a composite with mortality, all those questions you have.

DR. CHIN: So, I think we accept mortality and that's the one we actually will favor in many instances. I think it's really what, if it's not studied, what else could be an endpoint, a primary endpoint that would be important.

DR. SWAIN: Instead of?

DR. CHIN: Yes.

DR. REDBERG: That's a big issue because from a planning point of view, as I think we saw, there's a big difference in time and expense when planning for mortality than there is for planning for any of the other endpoints.

DR. SWAIN: We're confused. You're

asking this question about truly standalone, and mortality is not in the primary endpoint?

DR. CHIN: Yes.

DR. CRUZ-FLORES: The other question, I'm sorry, in a similar vein, are we considering research like a broad category,

that is to say, are we considering all types of studies? Because I think what the panel or the speakers describe is an endpoint like quality of life and function, and perhaps hospitalization might be better than mortality in this case, but then biomarkers were mentioned, but those may not matter to patients, so biomarkers and some intermediate endpoints may be better suited for a place to study for those, so is the question broad enough to include all phases, or just Phase III?

DR. CHIN: I think it's a broad approach including all phases, because as I think was mentioned this morning, as we see

really new technologies or new developments earlier in the product development cycle, I think we're seeing earlier studies.

DR. REDBERG: Right, although generally Medicare is only talking about approved studies, so it wouldn't be early phase.

SPEAKER: So, same question. So what, we're talking about approval for beneficiaries, we're not advising the FDA today.

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DR. CHIN: No, we're not advising the FDA.

SPEAKER: So we're not concerned with Phase III, there has to be approval.

DR. CHIN: Well, I think there's some instances where, you know, depending on what type of study has been done for their marketing approval, it might not actually be a phase study, so there could be some of the initial studies that we see actually, that are earlier

phased studies than we typically do.

(Inaudible colloquy among panelists.)

DR. REDBERG: Right, I thought Medicare criteria were reasonable and necessary, and so that's what we would look at, which to me is the more fully developed.

DR. HIRSCH: One more thing, I mean, back to the setup for this, it's not just phases. I mean, that's the classic regulatory, sort of FDA approval environment. This also includes probational studies, other types of data, correct?

DR. CHIN: Yes.

DR. HIRSCH: And we talked about broader evidentiary categories, right,

everybody?

DR. CHIN: I would ask Dr. Zuckerman from the FDA to explain a little bit more about the situation we sometimes encounter.

DR. B. ZUCKERMAN: Sure. It's a challenging one, and we certainly appreciate

everyone's efforts here, and that's why I would go back to the Ferreira article, the central illustration, or put Dr. Adamson's slide on the board, because the reality is that although one size doesn't fit all, many cardiovascular devices will be coming through the expedited access pathway. As part of the 21st century Cures legislation, Congress has mandated that the benefit-risk assessment of device technology will proceed in a way such that we can optimize patient access.

And certainly I would encourage people to look at the FDA website regarding the expedited access pathway and look at the Ferreira article, but the bottom line is that for many Class 3.b heart failure devices, the FDA trial paradigm is to assess the following in terms of effectiveness. There are three intermediate endpoints that must be separately

met in different categories to avoid some of

the problems with composites that were talked about this morning.

In addition, the trial is designed as an adaptive Bayesian trial such that we would have a certain predictive probability regarding mortality and hospitalizations. Now it's not the traditional predictive probability that you would assess in a 3,000 patient heart failure drug trial, but it is enough to potentially present in FDA approval with the hope that the randomized trial continues to show a more precise reduction in heart failure hospitalizations and mortality.

At this point the data would be presented to CMS, so we're trying to develop a unified system for that particular device technology, which I would put as Class 3.b, but I would emphasize that one size doesn't fit all. Certainly people are well aware of the LVAD technology and that really requires, I believe, a different trial design, but the panel is here to question that, as well as what Dr. Adamson referred to this morning as the early diagnostic monitoring systems.

Certainly both FDA and CMS are interested in being able to properly assess diagnostic devices that hopefully prevent this continuous spiral from Class II to III to IV with early warnings, and this has been a very controversial area of device development and assessment. Joe, does that help you?

DR. CHIN: Yes, thank you.

DR. REDBERG: I'm going to make a comment and then I'm going to start getting everyone involved.

SPEAKER: I just had one, I didn't understand the last thing you said, the Class II to III to IV, I didn't understand what you were saying.

DR. B. ZUCKERMAN: Okay. With better invasive monitoring of heart failure, there's the hope that we can stabilize patients so that there's not this inexorable progression of heart failure disease that really confronts the country, it's really a public health dilemma

right now.

SPEAKER: Thank you.

DR. REDBERG: So, we can talk more about it, but there's certainly a lot of

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tension, I think, between wanting to get effective therapies to patients soon and not wanting to have ineffective therapies or harmful therapies. And it's particularly a tension, I think, for devices and particularly implanted ones, because I don't think FDA, I don't know of any devices that get pulled off the market when we find out that they actually didn't work or they're harmful, and I don't think right now postmarketing, while we talked about it, I don't think it's robust at all. And so that means essentially, we're putting untested or minimally tested and possibly unsafe devices in patients that are now permanently implanted. I mean, that's essentially what this early phase is, and then

we find out, or we don't, that they're harmful, and then we have lots of patients that have harmful devices implanted. That seems like a problem.

DR. B. ZUCKERMAN: Dr. Redberg, if I may respond to your statement?

DR. REDBERG: Sure, Dr. Zuckerman.

DR. B. ZUCKERMAN: Certainly Dr. Redberg's comments are extremely important,

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but I would advise you that we're here to be reasonable, because we have a very important public health mission to try to grapple with. I believe what Dr. Redberg is speaking to is that technically no PMA-approved device has ever been pulled off the market by FDA. That doesn't mean that the rigor of postmarket surveillance has not increased within the last five to ten years.

For anyone in the interventional cardiology arena, I think at last week's ACC meeting, you're probably aware of the safety

communication that went out with the Abbott bioabsorbable stent. I think many of us are aware of the postmarket surveillance that's been done with our CMS colleagues in both the TAVR and LVAD arena, so I would be the first to agree with Dr. Redberg that postmarket surveillance at this point in time is not perfect, it was a key area that Dr. Califf, our recent commissioner was working on. But I would also encourage all of us to look at the recent JAMA editorial written by Drs. Califf and Shuren where we talk about the nest initiative and the significant changes

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that we do believe will occur with postmarket surveillance in the next five years. So while nothing is perfect, I think we have a lot of tools to work with and to have this panel dive into. Thank you.

DR. CHIN: Thank you, Bram. So I think that's where the context is of really

looking at the specific endpoints that we see for our determinations of reasonable and necessary devices and services.

DR. REDBERG: Thanks. Dr. Zuckerman, then Swain, then Segal.

DR. D. ZUCKERMAN: Thank you. So, I wanted to bring up the article that we were given to look at by Desai, et al,because it purported to show the effectiveness and the importance of hospitalization as a standalone measure, and yet three-quarters of the patients disappeared before the 12-month follow-up data, and almost half of them were gone, or never entered into the six-month data. So I was concerned about that.

I mean, there were other shortcomings of the study that the authors pointed out themselves, and also that, in the accompanying

article by Harlan, had pointed out. So in addition to the problems of using billing data, and you don't have very much information about

the patients, you know very little about what's actually going on with them, but in addition to those big issues, the fact that they started out with 1,900 patients but only 1,100 were studied at the six-month point, which was the first point, and then you lost more than half of those, so it's about 500 at the 12-month, and I just wasn't sure how you could do much. And then there's of course no control group because the patients are their own control group, I guess. I don't know how you can draw any conclusions when you've lost three-quarters of the patients and you don't know why, and you can't know why because it's billing data.

DR. REDBERG: So you're raising concerns about the current status of our postmarketing efforts.

DR. D. ZUCKERMAN: Right, and I wanted to know if I was missing something because, I mean, I didn't see anything about --

DR. B. ZUCKERMAN: Dr. Zuckerman, I'd like to correct one thing that Dr. Redberg just

said. That's an interesting article to discuss, because of the methodological problems we heard in the article. However, I'm sure everyone doesn't have time right now to pull the CardioMEMS summary of safety and effectiveness, which is on the FDA website, but that is not the postmarket study for the FDA, for all the reasons that you just pointed out. And certainly we can go into what the specifics of a postmarket requirement would be, but it's really important to underline that this is an interesting article but is not FDA postmarket surveillance.

DR. D. ZUCKERMAN: But is the FDA postmarket study a peer-reviewed published article?

DR. B. ZUCKERMAN: Excuse me?

DR. D. ZUCKERMAN: Is the FDA postmarket study a peer-reviewed published article?

DR. B. ZUCKERMAN: No. It's an ongoing PAS study right now.

DR. REDBERG: Right, so the data, then, is not available to clinicians.

DR. B. ZUCKERMAN: The data is being

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monitored right now. If the company wants to make the data available at any forum, that's their ability to do so.

DR. REDBERG: So it's in the company but it's not available to clinicians; is that correct.

DR. B. ZUCKERMAN: That is correct.

DR. REDBERG: I mean I, last year or so we had the INTERMACS meeting to review the postmarketing LVAD INTERMACS data and we had a discussion, and that's held, I believe, by the University of Alabama, and we had specific questions -- Medicare, like if I was reviewing the data beforehand and I had specific questions, then we were told we could not address them, because we could only address what was going to be released by University of Alabama. A lot of the questions by the panel

on that date were not able to be answered because it was a very limited set of data that Medicare was given as part of this postmarket study.

And then what really struck me was about six months after our MedCAC meeting, the Cleveland Clinic, I think in conjunction with

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University of Pennsylvania, published a study on their problems with LVAD pump thrombosis that was a fatal error, and none of that had been discovered in the postmarketing INTERMACS registry that we had discussed six months prior. So that's what gives me concern about our current postmarketing.

I did certainly read Dr. Califf's and Dr. Shuren's article and am very glad to hear about it, but I haven't seen that postmarketing improvement yet, and therefore as I said, as devices get implanted, I'd like to have the effectiveness and the postmarketing in place

first.

DR. D. ZUCKERMAN: I just wanted to add that with Dr. Califf gone and with the newly nominated commissioner having a very different view of regulatory science, we don't know what's going to happen next.

DR. CHIN: Just a comment. I'd like to refocus that, I think that one article was background material and we didn't really want to focus on any particular device, so I think, just keeping it in the broader sense.

DR. HIRSCH: So I'd like to say,

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again, to get us to move along, it sounds like, again, we're not here to discuss particularly the postmarketing surveillance or what it will be in the future, we're not here to discuss new regulatory supervisors, we're here to actually look at the bulk of the data we know that's available, not one article provided, right?

DR. REDBERG: I think that's true, but the argument for moving up premarket is that

postmarket will be better.

But anyway, I want to go on with Dr. Segal, Dr. Swain, and then Dr. Hsich.

DR. SEGAL: So, would you just clarify? The trials that you're talking about for coverage decisions, that would include the premarket trials from FDA, plus others? Where do those others come from?

DR. CHIN: So we in our usual review, we will actually review whatever has been published, we do an extensive literature search in sort of the public databases. So they can include all types of studies, you know, the initial studies, postmarket, premarket.

DR. SEGAL: But you wouldn't go to industry and request trials for coverage

decisions, or do you?

DR. CHIN: Not in our specific reviews. I think in our decisions, you know, coverage with evidence development decisions,

that's a framework for studies, so we don't typically ask for particular manufacturer studies.

DR. REDBERG: Dr. Swain.

DR. SWAIN: Yeah. Before I ask about reverse remodeling, just one comment is that as Dr. Zuckerman said, you don't have any access to any, CMS does not have access to this postmarket data, and we have seen and it's been presented, I presented it at a public panel once, one company who had a failed study just changed the endpoint and published it as a successful study in the New England Journal, and nobody else knew except that we had a public panel to say that. So it's a huge issue.

But what I wanted to ask about is this exercising testing and the bunch of parameters for reverse remodeling, anything you want, systolic volume, whatever, is we really need the MCID, minimally clinically important

difference, and we need a validated one which needs data, and we just don't have that in virtually any of these.

And when you look at the exercise testing as predicting mortality or heart failure, hospitalizations, we saw several slides where you guys look at the C statistics, the area under the receiver operator characteristic curve, so the ROC on these are like .6 and .7. You know, .5 is a coin flip, 1.0 is absolutely predictive, all of these are less than halfway there. So to say that they could be a standalone when none of them have a ROC, a C-stat over, .76 I think is the best one we saw, is difficult.

DR. REDBERG: Dr. Hsich.

DR. HSICH: Lynne had something first.

DR. STEVENSON: This is Lynne Stevenson. I think it's very important when we talk about these surrogates to define which are really a surrogate, because the patients could care less about their end systolic volume or their NT-proBNP. On the other hand, peak VO2 correlates very nicely with patients level of

function and their quality of life, so I think

the peak VO2 is a self-validated measure of what you could do. That has meaning whether it correlates with anything else or not, whereas end systolic volume and NT-proBNP don't have any particular direct relationship, the patients don't care what that number is.

DR. REDBERG: I think even for the VO2 we saw a .7, to Julie's point.

DR. STEVENSON: Well --

DR. REDBERG: I agree with you, I mean, I certainly --

DR. STEVENSON: But exercise capacity itself is a, has face validity. If you can do more, then there's something that's better, so I think we need to distinguish. We can argue about whether to use it, but we have to distinguish that as we distinguish the quality of life measures, on something that has no face validity on its own to patient function.

DR. REDBERG: And I would just, I think we have to separate quality of life measures to, because the patient-reported outcomes, I think, are different than surrogate and intermediate outcomes. We've talked about all of those.

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DR. HSICH: So Rita, I want to ask really of the group, so our task at hand is to answer from a population standpoint what endpoints and duration. And one of the things that, you know, that is hard for me as a heart failure transplant specialist, is that, to come up with one endpoint, right, because I can create scenarios for which one endpoint applies to only one group, okay?

When I think about all the wonderful talks we had, we all agree that quality of life matters, all these things matter, hospitalizations, everyone agrees with that. So my question to the group is, you know, Dr. Carroll actually talked about six domains

for devices and survival was one. The other was evidence to even support the biological effects or plausibility of this even being useful. And then complications, improved health, functional assessment, and the last one was freedom from hospitalization.

Would it be so hard ball, instead of looking for one endpoint, that we all, you know, that all six of these are met in not one study, whatever, however they want to get

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there, but we need the information to make the best decision. So you know, I was thinking about defibrillators, if we went back in time, with only mortality, but you could also make an argument that it does save someone's life and when they get saved, their quality of life, Lynne and I may differ, I could be emotionally distressed over being shot, and traumatized for life, and she could be grateful that she was brought back. So I think that the six domains

that were mentioned are very worthy and necessary for people to be able to make the most informed decision about whether or not this has incremental benefits beyond what we already have.

So is that a crazy -- you know, I realize it also is cost, right, if you have to actually meet all six. How do people feel about that?

DR. REDBERG: Any comments, or any questions? Bram?

DR. B. ZUCKERMAN: Actually, I think it's a very good approach and is similar to the more inclusive approach that the FDA has taken again, where you have to meet A and B and C

and D independently. You avoid the potential problem of the composite endpoint where one endpoint can drive the whole thing.

Number two, from a practical point of view, you just asked is it too costly, and the answer is no for the intermediate and/or

surrogate endpoints that have been discussed, because most of them are continuous endpoints, so the sample sizes are pretty reasonable. So I would really encourage the panel to think along the physiological reasoning that you have just challenged us with.

DR. REDBERG: Dr. Fisch.

DR. FISCH: So, my comments have to do with remarks that were made about paying attention to secular trends as it relates to the endpoint of heart failure hospitalizations, and so I was thinking about what we see in cancer medicine, I'm a cancer specialist, and so one of the endpoints that we see in chemotherapy is hospitalization or ER visits related to febrile neutropenia due to chemotherapy. And you know, back in the day that's not really a biasable endpoint, if your patient got fever and neutropenia that's where

they all went, so at a certain time that was

perfectly fine. But more recently there's changes in care delivery, so I've talked to practices that do both, you know, we just don't send patients to the hospital anymore, we've extended our office hours, they come in at midnight on Christmas with a fever and we'll take care of them in the office. And they may spend, you know, four to eight hours of medical time, it will be a medicalized experience but it won't be an emergency visit, it will be an event. And then they compete with other practices in terms of being a really great place to enroll patients on your trial, and you toxicity rates are going to be really low because of the way we've operationalized care delivery.

So maybe that's not really doable for an individual practitioner in heart failure if you're going to disrupt your day, and it would be quite a grind to do that more than now and again, but if you redesign your care delivery, you could change what's really happening in terms of the events without changing what's happening in terms of the actual experience of

care for patients, right? They will have medicalized time.

DR. REDBERG: Right. It sounds a little bit like we were talking about before lunch, the subjective endpoint of hospitalization, that sometimes people would or wouldn't get hospitalized, and it doesn't have anything to do with their condition, but more of who they were seeing and what the incentives are.

DR. FISCH: Right, it's at the level of the individual doctor deciding whether or not you go here or there, or what's really the trigger, but then it's the care delivery subjectivity. If you have access to a way of doing it outside the hospital where you got to round with the patient three times in a day and they can adjust a bunch of things, and it's really like a day camp instead of an overnight camp and, you know, that's different.

DR. REDBERG: Okay. Dr. Segal, did

you have a quick one?

DR. SEGAL: No.

DR. REDBERG: Okay. Dr. Sedrakyan.

DR. SEDRAKYAN: I think, I just wanted

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to comment, I think we talked about a lot of correlations here, we talked about statistical correlation of intermediate endpoints with a, say standalone endpoint like mortality, it's the findings that we're talking about, but we're not talking about influencing that surrogate endpoint, does it lead to improvement in a standalone endpoint. We haven't seen any evidence except in one situation in fact, for the left ventricular systolic pressure, when change of that intermediate endpoint led to improvement in the standalone endpoint.

All the rest were associations. This is correlated with mortality, but none of them were about changing that endpoint leads to reduction in mortality. So, an example that

was presented to us, the clinical composite score in fact, it has shown that improvement has no value over unchanged, so that was one example that we have seen. And the second example was really about a 15 percent reduction in end systolic volume that seemed to be correlating with mortality. For any other surrogate endpoint, we haven't seen that kind of data. Unless people can come forward and

tell us that there is such evidence, I think we should consider that that evidence does not exist currently.

DR. REDBERG: Thank you. Dr. Berliner, do you have a comment or a question?

DR. BERLINER: I just wanted to -- the day started with Daniel Canos talking about some of the efforts of the European Society of Cardiology and ICHOM to come up with standardized data sets, and I looked up the systematic review that Dr. Allen and his

colleagues did that informed their work, and so I just wanted to read some of it.

Improvements in functional class and quality of life were reported, but missing data complicated interpretation. Adverse events were experienced by the majority of patients but estimates for bleeding, stroke, heart failure, arrythmia and rehospitalization varied greatly, so that could partially be due to the subjective nature and partially due to different definitions. And they concluded that it highlights the critical need for high quality patient-centered data collected with

standard definitions.

And I would just like to go back to that ideas of having fixed domains. Can we come up with one outcome measure in each domain that would be measured standardly in all studies?

DR. HSICH: You can't do it with all

six because one of them is complications, which is actually based on whatever device. But I think as you're pointing out, perhaps we can decide about what kind of, when we talk about functional assessment, are we going to do six-minute walk versus peak oxygen consumption, if that's what you're asking.

And also, when you do that, it gets a little more complicated, because not every hospital has the capacity to do peak oxygen consumption, so already then, when you try to make it mainstream, you're changing things, the dynamics.

DR. REDBERG: Right, and not every patient is able to do VO2 just because of the apparatus. But what I heard from, I think it was Dr. Brawner when he talked about six-minute walk, I heard and certainly it's my

observation, there's some subjectivity to that, because some patients are more motivated to walk faster or slower, and some of the people

performing the assessments are more motivated to get their patients to walk faster or slower so, you know. And again, I think that was an ROC of .6 and a VO2 of .7, and I just know when I was reading echos full time, I would read echos on patients who had VF of 20 and could, you know, run to the echo lab, and I had a VF of 45 and they could barely get out of bed. And that's why I just -- and I suspect VO2 is good but it's not great.

I mean, if we have a .7, and I think that's probably, it seems like an intermediate endpoint that we've talked about, but how good is that? And we also had talked a lot about patient-centered outcomes. I thought that's where you were going, actually, with your comment of patients don't feel their LVSDSD but they do feel their functional status or their quality of life when you ask them, you know, with the, you know, the Euro quality of life score.

And then we also talked about

disease-specific Kansas City Cardiomyopathy Score, and maybe we should go back to that discussion because I felt like, you know, people were making the point, well, if your heart failure is great but the rest of you wasn't so good, was that really great for patients, or should it be a more holistic, kind of a whole person quality of life measure.

And then we were getting into how complicated is it, the SF-36 is obviously 36 questions, now there are shorter ones, because there is time in doing the questionnaire too. And I think it actually decreases data collection. In most of the registries I've seen, my observation is that it's the quality of life data that gets least filled out, for example in TVT, I think it's got the lowest data accuracy and data completeness, even though we're saying patient-reported outcomes is what's so important, so maybe we can have some more discussion on those. Art.

DR. SEDRAKYAN: Thank you for

commenting on that question, because I wanted to talk more about that single question of health transition or self-rated health that we

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ignored over time because it wasn't even giving us the scale that was so measurable, easy to measure and gets continuous endpoints that we can put into our regressions, and the methodology 20 years ago were also not well developed with this multinomial sort of assessments. The single question is harder to use as an outcome, and also publish as a paper, let's be honest, than scales and sophisticated questionnaires that we're administering.

So I think this is really important for us to go back to the basics and think about, are there those questions so meaningful for recovery that we're not taking into account and we're addicted to these scales and scores for psychometric properties and validation based on some other unvalidated instruments and anchors, while the PCORI path that we heard

today are meaningful questions from the patient perspective, but then we don't know what to do with them, whether patients are changing their decision or they would change their decision to get surgery. How do we even incorporate that into outcome assessment for a device, the change of mind sort of endpoints?

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So I think this quality of life and patient-reported outcome measures, I think we need to rethink what matters and how long the questionnaire should be, because also, the longer it gets, the more bias gets used because patients get tired and they start simply filling out things, so I'm not sure we're getting what we're trying to measure because they get tired and annoyed, while a few questions, they would give us a pretty good answer.

DR. HIRSCH: It's not our job today, I don't think, to talk about the difficulties of

creating a survey instrument and, you know, the differential effects and how we approach it, that's a methodologic thing. I think I'm hearing you say that you believe they're important outcomes.

DR. SEDRAKYAN: Certainly, but I think as a MedCAC panel member, we should comment on the developments that are needed in this field as well, because we've got a lot of certainly the smartest clinicians in the country here, and manufacturers who are developing this questionnaire for a reason. Any innovator that

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comes up with a new device wants to find an outcome that they can measure, and then they have to do a lot of marketing, I am not being cynical here, but to make it as an important endpoint. So I think we need to be careful in advising the stakeholders on what's the best way to measure as well the quality of life.

DR. HIRSCH: I think I've heard the panel say that we like a single set of short

questions that are operationally effective across trials. I also thought I heard our experts say that the Kansas City questionnaire being used in heart failure might serve that role.

DR. REDBERG: For a disease specific.

DR. HIRSCH: For disease specific.

DR. REDBERG: But then we were talking about a more general one.

DR. SEDRAKYAN: Can I comment? This disease-specific questionnaire's development was tied up to the fact that we couldn't get the effects in a general quality of life measure. So it's almost like target vessel revascularization versus MI, so I think there's the history to that as well, how we came up

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with so many disease-specific measures. I'm not criticizing, they're great, but we need to take into account why they exist.

DR. REDBERG: It's like target vessel

revascularization, I know that's clinically meaningful. But, Marcel, Dr. Salive.

DR. SALIVE: Yeah, I guess this is a little bit along with what Art was saying, but we have questions on surrogate and intermediate endpoints, and I won't go as far as what he said, but I wanted to just put a point on biomarkers, there's a whole thing on biomarkers, and no one presented to anything to us on validating biomarkers as an intermediate endpoint today, that I saw. It's on this chart that Bram Zuckerman pointed to as one of the three things, but you know, I'm not personally aware of BMT evidence so again, I'm not going to vote for that because I haven't heard anything.

DR. REDBERG: I think that's an accurate summary. Dr. Zuckerman, and then Dr. Segal.

DR. D. ZUCKERMAN: I just want to emphasize, I don't think we should be thinking

of quality of life or even functional improvement as surrogate markers, I think they're real. You know, they're as important, I mean, they're different than survival, but they're extremely important, they're essential. The problem is finding a way to measure them that's not just valid and not just reliable, but is in a study where there's a control group, and you have a sense that you know what you're measuring.

I think that the Kansas City questionnaire is apparently reliable and valid, but it includes a few questions that would probably be better off in a separate depression inventory, and I think either the Beck or the Hamilton inventory is only ten questions, so you could have a separate depression scale and then you could have a functional scale maybe using the Kansas City questions, and then you would have two different valid reliable scales that measure two different things, and I think they are two different things.

But you know, my main point is just that these are really important outcomes and if

we could get a better handle on them, I think

they're something we should care about as much as anything else, but the problem is finding that way to do it.

DR. REDBERG: Right, and I think for depression you have the PQ-2, which is just a two-question screen, that is as valid, from what I've read. I'm not the expert on it. Jodi, did you want to comment?

DR. SEGAL: Yeah. I feel like I'm still trying to wrap my head around what we're doing but, are we supposed to just assume that the outcomes that are important to patients and clinicians are the same thing, are the same outcomes that are important to CMS? Because that doesn't feel believable to me. That's a Jodi type question.

DR. REDBERG: Joe?

DR. CHIN: Well, I think that's true, I think it is similar, so we do, really do try

to take a patient-centered approach to our considerations and reviews, so I think there is a lot of synergy with that.

DR. REDBERG: What's leading to your concerns?

DR. SEGAL: So, this is kind of along

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the same lines. One of the things that we're supposed to distinguish between in the questions is whether consider general hospitalizations as an endpoint, versus heart failure hospitalizations. And one of the things we've debated about is whether quality of life should be measured with a disease-specific approach versus a general approach, and that actually I haven't even figured out in my head, so I'm just going to talk out loud what's going through my head.

So on the one hand I'm thinking about what Lynne had said about the importance of, you can improve someone's heart failure and yet you may not impact their quality of life

because maybe that wasn't driving their quality, so they, it matters a lot to them whether or not they improve. But we're talking about devices and medications that are going to be reimbursed to treat a disease, and if I use a drug like Viagra that was initially meant for angina, if I was now to constantly start ordering it for angina instead of for its other purpose, that doesn't make sense to me.

So I am wondering, does it really make

sense to use general hospitalizations, general quality of life when the devices and medicines are to treat a specific disease even though the person has more other issues, and I can't figure that out in my head, because I think that it really should be disease specific if the device and the medications are supposed to be treating it.

But I do fear one thing, what happens if the device and medication harms, and do we

need to monitor for that, and that's where I'm kind of torn. I don't know if anyone else has a better way of looking at it, but I think it matters.

DR. REDBERG: Right, and I think that's an important point. I mean, both the disease specific, and then there's the question, well, their heart failure got better but they felt worse, but was it because of the treatment for their heart failure they felt worse, or were they already feeling worse because of something else. And also, we haven't had a very robust discussion of harms, but you know, to have a net benefit, you have to also consider what are the harms of whatever

is also leading to the benefit. Dr. Stevenson.

DR. STEVENSON: I think these two questions are very parallel if we could think about them at the same time, as Eileen did. So there's heart failure hospitalization, that's what we hope to decrease, so let's say we

decrease those. I want to make sure that nothing else has increased at the same time, so I want you to measure total hospitalizations and make sure they didn't go up. And similarly, when we look at heart failure quality of life, that's what I really want to make better, but I also want to measure with the promise overall, general quality of life, to make sure that certainly it hasn't gotten worse, but is there some trend that it's better. So I think one is really where we're putting our money in terms of the endpoint, but you need to check it in a broader context to make sure you're not having some unexpected effect, or a lack of effect on the overall person.

DR. REDBERG: So then, it seems to me you're saying it should be total hospitalizations --

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DR. STEVENSON: No, I'm saying you

measure total hospitalizations.

DR. REDBERG: What if heart failure mortality goes down but total mortality goes up?

DR. STEVENSON: Well then, I don't think I want to use that.

DR. REDBERG: Well then, you are saying use total mortality.

DR. STEVENSON: No, I'm sorry, I'm not talking -- mortality is a hard endpoint with different issues. Certainly we wouldn't want, we would look at total mortality as well as CV, but I'm saying for hospitalizations and for quality of life, we're targeting the disease-specific ones, but at the same time we just want to monitor the overall quality and overall hospitalizations to make sure there isn't a signal in a different direction.

DR. REDBERG: Although I still, it seems as if you're saying but if there was a signal in a different direction for hospitalizations, then you wouldn't be interested in it.

DR. STEVENSON: Well, we would need to

look at it very carefully because that would be a difficult decision, okay? I think none of us can anticipate all the possible results we could get, but if they went in the same direction for instance, you would be much more comfortable taking the heart failure hospitalizations than if they went in a different direction.

DR. REDBERG: Dr. Yancy.

DR. SEDRAKYAN: It seems like a powering question rather than anything else, because you're powering it specifically to make sure the trends are towards better, even though you're underpowered.

DR. YANCY: So I'd like to go back to kind of a basic premise of taking care of these patients. There really are only two goals, we want our patients to feel better and we'd like to change the natural history of their disease, some would call it the life course, those are the only two goals that matter here. And we're

saying, can we be confident that a new technology helps a patient absent data on mortality per se?

We can certainly incorporate mortality

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and totality of hospitalizations and the safety dynamic, but what we really want to know is that there's concordance of, whether it's quality of life, functional capacity or some other metric that we're talking about, but the one important consideration that I think is necessary to emphasize is that not all heart failure is the same, and not every group of patients experiences heart failure in the same way. Heart failure with preserved ejection fraction is a very different animal than heart failure with reduced ejection fraction. We shouldn't conflate those representations of heart failure.

So it is more awkward, more painful for us to think that way but it's necessary,

because we have to be able to ensure that what we're recommending for one core of the patients doesn't disadvantage another, even if the disadvantage is nuisance because it's of no benefit or no harm. So we should be very specific about what kind of heart failure we're dealing with.

I personally take exception to the idea that we can't use biomarkers in some

dynamic where we're talking about surrogacy. There's quite a bit of data. No, there's never been a patient who comes in and cares about their BMP, but there's not a patient that comes in that feels well that has a BMP that's ten times normal, and so there is information to be had there. But for HFpEF, I have much less confidence that the BMP is predictive, so that's one example where there's a digression of a potential surrogate that we have to consider.

So this is really a more complex

conversation when we're talking about heart failure. We really should be very careful.

DR. REDBERG: Thank you. Dr. Fisch and then Dr. Salive.

DR. FISCH: I was thinking about the issue of comorbidities and the statement, we're trying to make people feel better and change the natural history of their disease. I totally agree with that, but it shifts depending on which disease you think you're trying to modify, right? So you know, one man's junk med is another man's disease-modifying agent. And I was sort of

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imagining that reference to junk meds as imagining a patient showing up in the hospital who is dehydrated, hasn't moved their bowels and has an exasperation of their bipolar disorder, and the heart failure we succeeded at. So it becomes really complicated. All these patients have multi morbidities and that

really confounds what we're up to here.

DR. YANCY: Well, wouldn't that be the advantage of having a general quality of life measure to go alone with the disease-specific quality of life measure, because then those things would necessarily have to track in the same direction in order for us to have the right confidence about the intervention.

DR. REDBERG: Marcel?

DR. SALIVE: So in terms of, I think, a difference between heart failure and hospitalizations and all cause hospitalizations, I think there is certainly a big issue of misclassification also that, you know, so I know a lot of the trials do this very well, but it doesn't mean that it will always be done well. So I think, I agree with the comment that you know, you want to be

specific and look at heart failure hospitalizations, and it's certainly, I think it's a very important and meaningful outcome,

but yes, I wouldn't want to miss that it is really just shifting.

And also, the last commenter's point applies in the hospital as well. What exactly caused the hospitalization, you know, sometimes it's hard to tell.

SPEAKER: You need the patient's outcome.

DR. SALIVE: Yeah, yeah, because if you have heart failure outcomes then, you know, how exactly to classify it is very important.

DR. REDBERG: And actually, can you comment, why were you concerned that there was a disconnect between what patients want and what CMS wants? That was your question earlier and I wasn't sure I followed.

DR. SEGAL: I don't know, I guess maybe I'm not entirely sure how CMS makes coverage decisions about devices, being more from the drug world. Maybe I just don't know. I don't know, is there, you know, is your coverage including bundled payments for all of

the outcomes that happen in those first 30 days or in the first six months, or just, I feel like there's so much beyond just talking about what specific outcomes we're talking about in the trials that are largely done by industry for FDA.

DR. YANCY: So Rita, if you don't mind, I can add to this.

DR. REDBERG: Sure.

DR. YANCY: I've never had a patient come in and give me any conversation about their 30-day hospitalization rates, not a single time. But that is important in our global health care system and we are sensitive to that. And there's nothing physiologic about 30 days. So patients simply want to feel better, and if that means coming in the hospital at whatever time point it is, then they want that to happen.

So I think there are some different, I won't say disconnects, but there are nuances here that we have to respect.

DR. REDBERG: Thanks, Clyde.

DR. CHIN: Just to, I guess the prior comment, so typically our considerations in our

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national coverage determinations are focused on fee for service, the fee for service system still, so typically it does not include alternative payment mechanisms or models.

DR. REDBERG: Bundled payments being one of those. Dr. Zuckerman, Diana?

DR. D. ZUCKERMAN: Sure. Yeah, I just wanted to say about the hospitalizations, I mean, I think we can all agree that patients don't want to be hospitalized and that's a good outcome measure to look at, but again, what we've said is there's so many things that influence it, it's not just the subjectivity of whether the physician decides it's a good idea, it's the decision. I mean, I personally know several patients who were told you have to go back in the hospital for another procedure and they said I want to die at home, and sometimes

they don't die at home. But you know, that's what they're told and they would rather die at home.

So you've got patient choices that are made, you have physician choices, and you have what you've talked about, which I would call a quality of care alternative. You know, I think

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that's a wonderful thing if they don't have to go into the hospital and their doctors will take care of them in some other way, and even if the motivation sometimes is less than pure, I don't care, you know, if the patient is going to benefit in that way.

So again, how do we measure hospitalization as an outcome, which I think we all think is important, and deal with the fact that there are so many reasons for it that have nothing to do with how well the patient is doing. That's a question. I don't know the answer.

DR. REDBERG: Dr. Swain, did you want to comment?

DR. SWAIN: Yes. I think the original discussion about the FDA trials, I guess for CMS it's necessary but not sufficient, and then you need more data, which I think we've determined that you have a hard time getting the correct data, or the real data, and we're depending on kind of surrogates. But when we look at the FDA's expedited review that's been quoted on several sets of the slides, you know, you have a BMP type agent which, the question

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is whether that would stand alone. Then you have a functional, and we've discussed some of the limitations, especially since mostly it's six-minute walk, it's like pulling teeth to get people to do cardiopulmonary exercise testing. And then you have a QoL or patient-reported outcome and again, the problem is you're generally testing an invasive new great device versus a very often optimal medical therapy

which the patient views as nothing new, and so that's an automatic win on QoL. I can tell you from placebo effect, it's an automatic win.

And the important thing is that, in all these composites, is that you show a trend. The definition of trend is certainly different. One of the FDA statisticians said, you know, his definition is P less than .15, so you've now got Bayesian models looking at mortality, and that helps, but the basic problem that you come up with is you have the three independent endpoints that have to be approved that perhaps all have different issues about being a real surrogate versus QoL, which is an automatic win.

So I think it's a hugely difficult

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problem for CMS to take an expedited approved device and then say is it reasonable and necessary, making that jump is almost, I think almost impossible, because you can't get real

data. You need the actual postmarket study data that's somewhat controlled, not TVT registries because they're not audited, it's a huge problem with TVT registries or any of the popular registries, so --

DR. REDBERG: What are you thinking of?

DR. B. ZUCKERMAN: You've got the FDA paradigm almost a hundred percent correct, except for one thing. Step one is presentation of the data to FDA through the EAP pathway with three, or whatever, concordant intermediate endpoints in a Bayesian predictive model for mortality and heart failure reduction.

But for presentation to CMS there's a part two, which is continuation of the randomized trial to show with more conventional statistical testing that reduction in heart failure, hospitalizations and mortalities, similar to what you are suggesting. So there's no real attempt to change the evidentiary level

that CMS has seen for Class 3.b devices for the last ten years. In fact, compared to what was done in the CRT era, as mentioned on one slide, this is actually an increase in rigor for the reasons that you mentioned, but it will take a total commitment of the investigator and industry community to make this seamless process work.

DR. SWAIN: But an increase in rigor from what used to be done, it's kind of like saying I'm the tallest member of my family. That may well be true but, you know, an increase in rigor from previously, which is not rigorous at all, to something now that is better than that, you know, I think we ought to aim for a whole lot better than that.

DR. REDBERG: Right. I think we're getting back to sort of whether postmarketing actually occurs, whether the data gets released and is publicly available to clinicians as well as the patients, and whether coverage changes on the basis of postmarketing, you know, the registry.

And I don't know what you're alluding

to, but in the ICD registry we've gotten a lot

of data collected, mostly in hospital, but coverage hasn't changed based on all of that data, we're not -- if you want to make postmarketing work, it has to be an iterative process, I believe, where we're continuing to look, and I mean, I think some TVT has been used to expand some indications for TAVR. I haven't seen otherwise a lot of data on how it's guided or changed coverage.

And Julie, I wasn't sure, you had another comment, but you had alluded to problems with the TVT registry in your last comment, I didn't know if you wanted to --

DR. SWAIN: Well, single arm registries that aren't monitored, it's a problem gathering data, and I can't give you exact examples, but I can tell you I just question some of the data that goes into the TVT registry, how much gets done. And if you

don't audit, if you don't have the threat of auditing in a significant proportion, then it's a problem with data.

DR. B. ZUCKERMAN: Okay. So perhaps Drs. Chin or Canos would like to comment on this specific item, because we haven't gone

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into the postmarket phase of this device development process, but mention has been made to the TVT registry as an appropriate model, and while it's recognized that all the problems initially that Drs. Redberg and Swain pointed out have been acknowledged in the TVT, to the betterment of all parties, CMS has been very carefully monitoring data quality in that registry, including the KCCQ acquisition development, and to the betterment of everyone, it's improved substantially. Do you want to comment, Joe, or Dan?

DR. CHIN: Sure, and I think that's -- we have, we've been working closely with that registry to really try to improve the data that

we actually are seeing, so I think with really the postmarket studies and what type of studies we can actually require, I think that's a different question than perhaps what we're actually trying to look at today because I mean, obviously there are situations of what type of studies CMS would like to see, and what type of studies that we can require, and also with the changes in the pre and postmarket.

So I think if we can assume like an

ideal, you know, state with the approval process, I think looking at what type of, you know, really them coming to us, to CMS for a decision, really what type of outcomes by themselves, then it would be, I think with all the concerns that were raised, I think that's given, and perhaps not something to address today.

DR. REDBERG: Joe, can you comment on how complete the quality of life data is in

TVT?

DR. CHIN: I think we've looked at it. I don't have the number offhand, but I believe since we've actually looked at it, it's actually gotten much better.

DR. REDBERG: Is it like Julie being tall?

DR. B. ZUCKERMAN: Dr. Carroll may be able to comment, but it's been a significant prime directive of all parties involved over the last two years, and that data can be made available.

DR. REDBERG: But not right now.

DR. B. ZUCKERMAN: I haven't memorized it, I'm sorry, but perhaps Dr. Carroll if he's

still here, could comment.

DR. SWAIN: This is Swain. But as Dr. Pina pointed out, if who collects the QoL is me as the surgeon saying your heart operation went great, you feel great, don't you, versus someone more independent, and

that's a huge issue too. You may get a lot of data but again, it's hard to tell what it means.

DR. REDBERG: Yes, go ahead, John.

DR. CARROLL: So, there's some false impressions being given. Number one, I think we know -- John Carroll -- the STS data, and it's audited, the same independent organization does audit TVT registry, number one. Number two, I don't sit with my patients and say this is how to fill out your KCCQ, it's done independently without anyone present to prompt the patients, so it's really quite independent. Thirdly, the data completeness is really in the 90 percentile range when you look at in hospital and 30-day, and that's as far as STS goes.

We are in addition getting one-year data, and the KCCQ completeness has gone from

30 to 75 percent at one year, because we've had

500 sites opening up, doing something that's never been asked before in all routine clinical care, to gather this type of data. So it's really improving rapidly, and I just wanted to clear up those matters.

DR. REDBERG: Glad to hear that it is improving. I would say that it would be easier for all of us if it was publicly available, and we wouldn't be having this discussion because then we'd all be able to look at it.

DR. CARROLL: It's --

DR. REDBERG: I go on the TVT website and I can't look at any data there.

DR. CARROLL: Well, every year there's a publication giving an update on all these things.

DR. REDBERG: That's a very select, that's not publicly available.

DR. D. ZUCKERMAN: I just wanted to add, I mean, in addition to what you had said, in one of, I think the first presentation we had from Dr. Pina, she said, what makes me happy and what is it that makes my patient happy? It makes my patient happy when I tell

my patient, you know, the procedure went really well and look at all these good things that are happening. So it isn't necessarily any kind of effort to have an impact on the outcome of a study, that's just the nature of the interaction, it seems to me, between the doctor and the patient, that when the patient seems to be doing well and the doctor is telling the patient they're doing well, then everybody feels good.

DR. REDBERG: Dr. Segal.

DR. SEGAL: I would like someone to talk more about the blinding question that was started a little bit before lunch, and whether the trials need to be blinded, since that's one of our questions. And these trials really aren't, they don't have sham controls, right? Well, you kind of could, put a catheter in and leave it there. I don't have anything to say on the topic.

DR. REDBERG: I would say, I mean when

I reviewed with a colleague the data on premarket approval for the high risk devices, only 10 percent were blinded and I don't think, it seems like, it's a big issue in device

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trials. Because as Dr. Swain can tell you, or Dr. Sedrakyan, any of our surgeons, you know, when we do procedures or implantations, you do the procedure and people have a lot invested in it and they tend to feel better.

DR. SEDRAKYAN: Absolutely. I wanted to add to this, and there's a disconnect that we also have seen here about six-month outcomes for quality of life assessment. If we know that there's such a strong placebo effect after surgery or after intervention with a device, how can we even live with six-month quality of life measurements? Because again, a six-month quality of life measurement can be strongly still affected by that initial strong effect of the intervention. It's documented that there's

early strong effect after surgery of improvement, right? So I think we do have to have much longer follow-up for endpoints that are prone to these placebo effects. So that's one point I wanted to make.

The second point I wanted to make, and maybe Lynne, Dr. Stevenson can answer this, because you were commenting, I believe on the CardioMEMS discussion of the panel, and you

commented about something which was a package deal, physician plus technology evaluation, and in the context of it's not possible, really, need to separate from each other when we have this monitoring technology kicking in and there's this placebo effect with it, but it's really not possible to separate it from monitoring because technology is transformational and changes the way we handle the care.

How do we even handle, say this is placebo effect? Again, this is another side

now, from the more than six-month quality of life measurement to the fact that there's some transformational technologies that would change the way physicians would care for patients, and it's irreversible if it gets adopted. So essentially there might be an improvement, because we pay more attention, and physicians take advantage of these placebo effects, because that might be a good thing sometimes too. I mean, if that's what it takes for us to have the placebo effect, maybe if it's not expensive and breaks our banks, maybe it's a good thing.

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DR. REDBERG: I just want to remind everyone, we are going to be voting in the next few minutes, so we should just focus in particular if there's issues related to the voting questions that you want to resolve. Dr. Stevenson.

DR. STEVENSON: I just wanted to

answer the blinding question, a couple of things. Number one, if you have something where to do a sham procedure is really high risk, obviously we're not going to blind, and those are the procedures in which I agree totally, we wouldn't want six-month outcomes, because you want time to get over the stresses and the potential side effects as well as the surgery, so you'd want a longer time interval.

I do think that by in large we should aim to blind in most cases. However, if the intervention itself is actually a strategy that involves patient empowerment, which we all know is going to be increasingly important, there's no way to blind a study where the patient is involved in his own care, and tell him you're going to be making decisions on data that may be completely fabricated, you can't really do

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that. So if you're testing the strategy that includes the patient's empowerment, I don't think it's possible to blind, but I think other

than that and the high risk, I think we want to blind everything else.

DR. REDBERG: Thank you. Although I would say, as I said earlier, even in high risk, I think it's, and I gave the example of neurosurgery and I think Julie gave some other ones, but those are high risk procedures, but to me the danger of not blinding in a high risk procedure is that you're assuming that a high risk procedure has benefit that it doesn't, and then you have really an ineffective high risk procedure that's no better than a sham procedure. So, you know -- and I think that has been, sort of gone through ethics approval and people agree, it's better to do a sham high risk procedure than to make a false conclusion.

DR. STEVENSON: Well, I think it depends on the procedure. We're not putting in any VADs that don't pump.

DR. REDBERG: Clyde.

DR. YANCY: We haven't made much comment about the issue of mitral insufficiency

and subsequent repair. The way the question is worded needs clarification. The question is worded as if we're dealing with degenerative mitral valve disease, because it says heart failure secondary to mitral regurgitation, for which there's an evidence database that informs what we should do, and guidelines as well. I think the greater conundrum or the greater question is functional MR where the MR is secondary, but it would matter how I vote depending on what the intent of the question is.

If we're talking about degenerative MR or functional MR, that might be too specific, but if you can help with that.

DR. REDBERG: I think that's an important question for Joe.

DR. CHIN: So, I think it's been degenerative and that's what we have typically focused on.

DR. YANCY: Because the trials that are being done now, just to take this one step

further, are focusing on functional MR, because there's already an FDA-approved indication to intervene on degenerative disease.

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DR. CHIN: Right, so I think as we've been seeing these types of devices being approved, and that would be actually a consideration for what we actually have available right now, I think have been the degenerative ones.

DR. B. ZUCKERMAN: Okay. So Joe, you are correct, the FDA-approved device is for degenerative, but as Dr. Yancy is indicating, there's a whole slew of EAP devices coming down for functional MR with associated significant heart failure. So could this question be divided into two parts here where one, you ask for the degenerative MR cases, and for the other for functional MR with significant heart failure, something like that? I think that's what Dr. Yancy is suggesting.

DR. REDBERG: Thanks, Dr. Zuckerman

and Dr. Yancy.

DR. CHIN: Sure, I think that's an option that's up to the panel.

DR. REDBERG: Okay. Dr. Berliner, I think you had your card up for a while.

DR. BERLINER: No, I just wanted to ask a question. Are 3.C and 4.C, it says

composite standalone; is that composite or standalone?

DR. CHIN: That does seem like a typographical error.

DR. REDBERG: I think it means whether the standalone endpoint could be a composite, or the standalone should be a primary health outcome. That's how I interpreted it.

DR. STEVENSON: Dr. Redberg, as a point of procedure, as we go through each question, can we just clarify a little bit, because some of the questions there's something kind of vague about, and rather than answer all

the questions now, if we could go through each one question one at a time and then clarify before we vote, would be helpful.

DR. REDBERG: We'll do that. I'm gong to -- Dr. Segal, did you have a question?

DR. SEGAL: No.

DR. REDBERG: Okay. So Maria is going to give out the clickers and we will start voting, and I'm happy to clarify. We did go over some of these on the call last week, but I don't think everyone could be on that call.

DR. CHIN: Also, I'd like to mention

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that when you vote, actually there's an opportunity to explain, so I think if there are specific points you want to make about how you interpreted it or how you voted, there is an opportunity for that.

DR. REDBERG: While Maria is giving out the clickers, I am going to start to read the first question. And just to remind you, the voting scale is written there on your form,

so if you have low confidence, you would vote a one; if you have high confidence, you would vote a five, and you can vote any integer in between.

So the first question is, how confident are you that the following are standalone meaningful primary health outcomes in research studies of heart failure treatment technologies? And I'll read them individually. A, heart failure hospitalization. Then we'll vote on heart failure hospitalization or heart failure hospitalization equivalent events like outpatient intravenous therapy for heart failure. Or C, total hospitalizations. So obviously we will take A, B and C separately, so you can now vote on 1.A.

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DR. STEVENSON: So we are to assume that we would have no mortality data; is that right?

DR. REDBERG: Right, and these

questions are standalone, so you're saying you would accept this in lieu of mortality, this would be a standalone, you would not have mortality.

DR. STEVENSON: Well, I think we'd want to clarify that this is assuming safety and no reason for concern about mortality, I mean, so that there's no adverse trend.

DR. REDBERG: How would you get that data without collecting it, how would you assume safety?

SPEAKER: Do you have any clicker instructions just so we make sure we're doing it right? Press one button once?

DR. REDBERG: Yeah, and it will be posted up there.

DR. YANCY: What was the response to Dr. Stevenson's question?

DR. REDBERG: My understanding, it stands alone, you're voting on this as an endpoint by itself, so you cannot assume you

would have other data.

SPEAKER: Well, you'll know who's dead.

DR. CHIN: Also, I think we are looking at, these functional devices are in the postmarket, so I think there is an assurance of function and safety in that situation.

DR. SWAIN: This is Swain. Is it helpful -- so, are we considering this along with mortality or not? It says standalone, Rita has one explanation. You're saying we can assume that mortality is being measured, so it's not a standalone.

DR. CHIN: No, I didn't say -- I guess we can assume that it's being measured now. I think I was just trying to respond to Dr. Swain's comment or question earlier about the scenarios, so I think in terms of whether there is initial, you know, evidence on safety and effectiveness, and I think that is what we would actually see with a postmarketing approval.

DR. SWAIN: But being safe and effective doesn't mean that nobody dies from

it.

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DR. HIRSCH: Joe, isn't the assumption that if a drug or device here had a clearcut mortality benefit, we wouldn't be really voting on the hospitalization, so now this would be a new device or drug brought to CMS with a, let me put this in a hypothetical, a neutral mortality benefit within the hospitalization setting.

DR. REDBERG: Alan, we would not know the mortality.

DR. HIRSCH: So no assumption.

DR. REDBERG: Right. No assumption. You're saying would you accept data short of the mortality benefit, and this is the question.

DR. SWAIN: Standalone.

DR. CHIN: Instead of, right. So in that situation where we're actually seeing this, if you can sort of imagine the scenario

that we're being asked to review these new technologies.

DR. STEVENSON: But if a lot of people died, then they wouldn't get hospitalized for a lot of the reasons that we're talking about, so we're assuming that there's no reason to be

concerned that there's a competing outcome between death and hospitalization, we'll just assume that?

DR. REDBERG: No. You could have a low hospitalization because a lot of people died.

DR. STEVENSON: But I would know that those people died. If I know that they got hospitalized, I would know if they died.

DR. CHIN: I think that's a factor in how you actually vote, and you can have an option to say, you know, I voted in that manner.

SPEAKER: So this is nearly nonsensical, because you would need to at least

have a safety awareness, you wouldn't necessarily need mortality as a sufficiently validated endpoint but you would have to have some safety awareness.

DR. REDBERG: What is safety awareness, how would you define that?

DR. YANCY: Whether it's in a clinical trial, a basic trial, observational data, there would have to be something that reassures that there's not a signal of harm.

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DR. REDBERG: But what would that be?

DR. YANCY: The things that I just identified, some predicate data set that indicates that there is not a signal of harm. It may not be a definite advantage on mortality, but says that it's not a signal of harm.

DR. CANOS: Daniel Canos, Coverage and Analysis Group. So, I completely agree with the assessment of the question. So it's asking

as far as a meaningful primary health outcome, not in an imaginary world where we're blind to whether there's mortality or not, so if a sponsor has come in with a study that's primarily driven by heart failure hospitalization as a meaningful health outcome primary, there could be secondary analysis to look at mortality, look at harms, so we're not trying to create this contrived environment. You know, we're seeing studies where heart failure hospitalizations are the drivers of the study, we look at mortality as other endpoints and do that as another consideration so, you know, capturing harms as secondary endpoints. But if they were to come in with the study, and

again, there are plenty of study designs you're seeing with secondary endpoints and tertiary endpoints that capture these assurances, but if heart failure hospitalization was the primary driver of the study, for example size and, you know, for the meaningful health outcome, that's

how the question should be viewed.

DR. REDBERG: So Daniel, is it fair to say you're talking about a study that would be powered on hospitalization, you might collect mortality, but it would not be sufficient to make any conclusions?

DR. CANOS: Exactly, your scientific conclusions are based on that primary driver of hospitalizations.

SPEAKER: Is that a secondary analysis, not a primary analysis?

DR. CANOS: Yeah. I wouldn't -- the mortality data could be captured as part of a secondary, you know, sort of as a secondary analysis as a composite or otherwise, but when you view heart failure hospitalization as a primary driver for the study, sample size and to the hypothesis being tested, was the nature of the question.

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DR. SWAIN: This is Swain. So, you

might want to vote again, since we've already cast our votes.

DR. REDBERG: We haven't voted yet.

DR. SWAIN: This is totally different than what I thought. So it's more like the FDA thing where you have a primary and then you have a trend, and so you would have mortality. So it's, I view it as a composite of mortality even though that's not powered, and your answer of one of these?

DR. REDBERG: No. It's a primary endpoint that's powered on hospitalizations.

DR. SWAIN: But you have all the mortality data, is what he's saying.

DR. CANOS: There's a discussion part about the composites as a sub.

DR. REDBERG: Right. But the voting question, Julie, to be clear, is it would be a primary endpoint of heart failure hospitalization, that's it.

DR. SWAIN: But you would have all of the mortality data.

DR. REDBERG: You might have that, it would not be powered for that, and you might

not have sufficient power to make any conclusions.

DR. STEVENSON: For the purpose of argument, could we say that we're voting on a trial in which the mortality is equal in both arms, but there's a significant difference in hospitalizations?

DR. REDBERG: I don't think we can.

DR. STEVENSON: That's what the question is.

DR. SEDRAKYAN: But can we say mortality data is available? That's pretty easy, right? We can say mortality --

DR. REDBERG: I think you can say mortality data is available, but you can't say that it would give you any meaningful information because it wasn't powered for mortality.

DR. SEDRAKYAN: We don't know what the results are, agreed.

DR. REDBERG: There may be a signal

one way or another.

DR. HSICH: I'm concerned that composite endpoints that are driven by one feature are not the solution either.

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DR. REDBERG: I want to stick to the voting question.

DR. DESVIGNE-NICKENS: So Rita, is it that for heart failure, the assumption is that the mortality is sufficiently stable that heart failure is the signal? I mean, that's saying where we are?

DR. REDBERG: No, there's no assumption on mortality. The question is, can a primary endpoint be heart failure hospitalization as a standalone. That's the question. Mortality data may be collected but it will not be what you're voting on, and you will likely not be powered because it's not going to be powered for mortality. You will have a signal one way or the other.

So, let's start the vote, because we are now -- did you have a question?

SPEAKER: We've already done 1.A, right?

DR. REDBERG: No, seven of nine. Two more people need to vote.

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

DR. REDBERG: Okay, the vote for 1.A

was 2.44. Maria, do you want to finish the B and C now and then talk, or talk after each one?

MS. ELLIS: We need everyone to state their votes.

DR. REDBERG: Okay, for each one. So we'll go down the line, and everyone can say their vote, and one sentence on why you voted.

DR. HIRSCH: I voted three. My level of confidence is intermediate because there are physician and patient outcomes (inaudible).

DR. CRUZ-FLORES: Cruz, three as well,

similar reasons.

DR. FISCH: Fisch, two. It will be similar reasons, with a different number.

DR. KOBYLARZ: Kobylarz, four. I think hospitalization would be a good primary endpoint.

DR. SALIVE: Salive. I gave it a three. There is definitely problems that were alluded to, but there's also I think geographic differences in hospitalization that can play an effect, and also international ones where this has been seen in the global device studies, that there may be differences by country.

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DR. SEDRAKYAN: Art Sedrakyan. I voted three, with the assumption that mortality data is available. I know it's not powered, but at least it's available for weighing benefits and harms even if it's a trend, so that gives me a little more reassurance with that assumption. We agreed it's manipulable,

it's open to physician influence, patient influence, but I'm also still unconvinced about this role of new technology transforming our health care and how more effects are possible through that placebo effect and whether it's a good thing or bad thing, and how we can take advantage of that. So I think I would like to, I'm comfortable with a three.

DR. SEGAL: This is Segal, two. I think it's a patient-relevant outcome but I think it's too hard to standardize the trials based on what was discussed.

DR. SWAIN: One, because it said standalone and it does not guarantee that mortality data is available.

DR. D. ZUCKERMAN: Zuckerman. I said one not just because of the mortality issue, which is important, but for all the other

reasons we talked about, subjectivity and patient choices and geography now, and I'm even wondering does this count people going to

nursing homes, are they hospitalized or not hospitalized, so there's just so many other things that can happen to people.

DR. HSICH: Eileen Hsich. I said three because we're including the whole population and it's only a standalone for patients with low mortality risk, and then hospitalization matters a lot; and then people who are going to die, and then hospitalization matters a lot. So that really takes a chunk of patients, but for the people in the middle, it does not apply.

DR. STEVENSON: Lynne Stevenson. First of all, you have to have mortality so it's not a competing outcome. I voted four for the first one, four for the second, assuming there's a hierarch so that you get more points for having --

DR. REDBERG: We're only doing the first one now, Lynne. We're going to come back. You can only vote one at a time. We'll come back to you for that.

DR. STEVENSON: Okay. I'm assuming we know mortality, because otherwise it makes no sense.

DR. REDBERG: Okay, thank you.

MS. RENBAUM: Adi Renbaum. I voted a three for mainly reasons that have already been stated.

DR. BERLINER: Elise Berliner. I voted a two, I think it's really really important, but in conjunction with other things.

DR. DESVIGNE-NICKENS: I was really conflicted on this but I think in a low mortality, assuming that it's a low mortality cohort the hospitalization would be important. I voted a three.

DR. YANCY: I voted five, and I voted five because we have to respect the natural history of a hospitalization. One year after hospitalization, the risk of death is 25 percent, that's been consistent in all the trials. A therapy that lowers the risk of

hospitalization with a neutral impact on mortality would be very important.

DR. B. ZUCKERMAN: Bram Zuckerman, I

voted four. I think even with all the problematic issues mentioned, it's still an extremely important endpoint.

DR. REDBERG: Okay. Now that you're all experts in voting, I we're going to vote on part B of the same question. So it's how confident are you that the following are standalone, meaningful primary health outcomes in research studies of heart failure treatment technologies, but now you're voting on heart failure hospitalization or a hospitalization equivalent, like an outpatient intravenous therapy study.

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

DR. REDBERG: Okay, so this was a 2.78.

DR. HIRSCH: To keep the discussion

going, Hirsch, I gave it again a three. It's actually better when combined in inpatient-outpatient settings, but I actually respect the other voting as well. Three.

DR. CRUZ-FLORES: Cruz, four. This response added, or captures a few more patients than just hospitalizations.

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DR. FISCH: Fisch, three, upgraded from before where it was two, because it's a little bit less possible within the specifications of this one.

DR. KOBYLARZ: Kobylarz, four. I'm being consistent with A, I think a good primary endpoint would be preventing hospitalizations by whatever means.

DR. SALIVE: Salive, three. I think it has the same issues as A.

DR. SEDRAKYAN: I'm also consistently three, Art Sedrakyan. In fact, I really think that hospitalizations should be categorical, it

should be number of days, and as Dr. Stevenson commented on, counting these as one day or something, we need to come up with a good measure and in addition to a categorical endpoint, we should have something more meaningful, amount of time being hospitalized.

DR. SEGAL: Segal, three. I think it's better than the first in that it's an indicator that the patient needed some intensification.

DR. SWAIN: Swain, one again, because of the mortality issue with the question as

written, but also I think it's somewhat worse than hospitalizations. If it were with mortality, I would call it a two or three, but it can be gained, we've seen that in the famous study done, and more importantly, the people evaluating a patient in an unblinded trial will try to keep them out of the hospital by giving outpatient therapy, so it's unintentionally biased.

DR. D. ZUCKERMAN: Zuckerman, I voted one. I do think that maybe some of these other measures would be better than hospitalizations perhaps, for a variety of reasons that hospitalization is so disliked by patients, among other things, but we didn't really talk about these other options.

DR. HSICH: Eileen Hsich. Three, for the same reason as the last vote.

DR. STEVENSON: Lynne Stevenson, four, again assuming a hierarchy across the IV outpatient to the inpatient.

MS. RENBAUM: Adi Renbaum, four. I think it's an improvement over the last measure.

DR. BERLINER: Elise Berliner, two. I

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think it's very important but not as a standalone.

DR. DESVIGNE-NICKENS: I voted a three, and while I think it also is perhaps

more, it could be more powerful than just plain hospitalizations, but it really lacks external validity, you know, I think it lacks external validity. There are some questions, you know, what happens in hospitalizations, I don't know you will these other visits mean.

DR. YANCY: I voted three. We should recognize that there's no evidence base to support outpatient clinic for anything, including diuretics, and it's probably a signal of harm.

DR. B. ZUCKERMAN: Bram Zuckerman, I voted four. There are problematic issues but it still remains an important endpoint.

DR. REDBERG: Okay. Thank you all. And now the last is the same beginning of the question but you're voting on total hospitalizations, same scale.

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

DR. REDBERG: Could everyone just vote

again? You may have voted before the clickers were activated. One more.

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

DR. REDBERG: And this was a mean of 2.11, which is low or low intermediate confidence. So, we have a discussion question, and only for part B, because the discussion question is only for health outcomes that had a greater than 2.5, so greater than an intermediate confidence level. And so for part B, which was hospitalization or hospitalization equivalent -- oh, I'm sorry, I'm getting ahead. Go down the line.

DR. HIRSCH: I'll make this short. I downgraded this to a two. It's a complicated question. We really had to talk about the noise of a positive or negative signal, but in the spirit of a heart failure outcome for a heart failure patient, I downgraded to two.

DR. CRUZ-FLORES: Cruz, two. I thought total hospitalizations may not reflect just heart failure, but other patients.

DR. FISCH: Fisch, four. I thought

25 total hospitalizations was a little bit of an

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1 upgrade because it's more robust to the patient
2 experience.
3 DR. KOBYLARZ: Kobylarz, three. I
4 thought that there are, you know, other reasons
5 for hospitalizations, and I think focusing on
6 heart failure would be more of the primary
7 endpoint that should be considered.
8 DR. SALIVE: Salive, two. I think the
9 reasons were mentioned.
10 DR. SEDRAKYAN: Sedrakyan, two as
11 well. It introduces more noise, it can go both
12 ways. It's important to measure that because a
13 reduction in heart failure hospitalizations
14 might lead to some other hospitalization
15 increase and then it's a problem, but we need
16 to probably measure this if we're measuring the
17 other two, but at the same time it introduces a
18 lot of noise for other reasons for
19 hospitalization such as surgery.

DR. SEGAL: And Segal, two. I think it's noisy as a primary outcome.

DR. SWAIN: Swain, one, same reasons of noise.

DR. D. ZUCKERMAN: Diana Zuckerman, one, same reasons, but also I hadn't mentioned

before, you know, sometimes people are hospitalized because they don't have anybody to take care of them.

DR. HSICH: Eileen Hsich. I wrote this as a three, I have a problem with this as a primary endpoint as a standalone without heart failure hospitalizations. Even if you reduce it total, you're reimbursing for heart failure and if it's not affecting heart failure hospitalizations, what issues get credited to whatever disease you are affecting.

DR. STEVENSON: Interesting. I gave this a five. I would have incredibly high confidence if you achieved this, because most heart failure patients are hospitalized for

heart failure. I just think it would be foolish to power your trial because I don't think you would get there. It's a high bar, though, I would be very confident if I got there.

MS. RENBAUM: Adi Renbaum, three.

DR. BERLINER: Elise Berliner, two, for all the same reasons.

DR. DESVIGNE-NICKENS: I voted two. I had some initial confusion about total

hospitalizations, whether that was total heart failure hospitalizations, but if it's just a general, I gave it a two.

DR. YANCY: I suppose I'm going to be a minority today and I'm going with a five, because you have to recognize that if there is a strategy that is targeting heart failure, you have to be aware of changes in renal function, you have to be aware of falls, you have to be aware of syncope, you have to be aware of

mental confusion, you have to be aware of complications from a procedure or drug. I would agree that this is a very high bar, I'd be very confident if I saw this. And as well, nobody would collect total hospitalizations without also concomitantly collecting heart failure hospitalizations.

DR. B. ZUCKERMAN: Bram Zuckerman, three, problems with noise.

DR. REDBERG: Thank you. Now we can have that discussion just for the B, which again was hospitalization or hospitalization equivalent events like outpatient IV therapy. What would the appropriate length of follow-up post-heart failure intervention be for this

outcome? Alan, did you want to throw out a number?

DR. HIRSCH: Well, we can start the discussion, we haven't spent much time on it. So for nonacute, LVAD, you know, shock patients, I think for many of us in cardiology

a one-year period is fairly standard. Getting to six months allows a short-term benefit, noise, and a loss of an expensive device or drug, and frankly I'd advocate for longer, relevant period of time of two to five years, although again, I realize the response is not the greatest, but one year is my usual number.

DR. REDBERG: So one year. Yes, Dr. Fisch.

DR. FISCH: Michael Fisch. I think it depends on the condition and the expected trajectory of the illness, as well as the trajectory of adverse events and the magnitude of, or rate of adverse events, there's a lot of things that go into it. But I'd say generally speaking, taking the whole pool of things, one year seems reasonable to me.

DR. REDBERG: Does anyone -- Julie.

DR. SWAIN: I agree with one year for

the sickest patients, but if you get down to

NYHA II, I think longer than that, at least two years. FDA has a problem ever mandating anything longer than two years, I think that's still the case, but for the minimally symptomatic that's going to have a permanent device for a chronic disease, it's got to be longer than one year, and maybe longer than two years for some.

DR. REDBERG: Dr. Zuckerman.

DR. D. ZUCKERMAN: Yeah. I guess I would just ask, this is really a question, are people thinking in terms of separately measuring inpatients and outpatients, you know, as separate scores, or just combining all procedures, all so-called equivalent events?

DR. REDBERG: It would be all heart failure hospitalization equivalent events plus heart failure hospitalizations.

DR. D. ZUCKERMAN: Plus outpatients, I mean including outpatients, so one score.

DR. SEDRAKYAN: Can I comment on competing risk issues here because of high risk of mortality, just making sure that is taken into account in a time frame that is being

measured. If it's pretty high mortality risk within a year, then we just need to comment about that, and we need to take into account the high chance of dying.

One more comment. I'm not sure Dr. Stevenson's votes are being counted, because she said she voted five.

DR. REDBERG: Art, just the panel's votes get put up there, not the nonvoting members.

DR. SALIVE: I agree with one year but I wanted to make this short comment, that I think for the coverage decision you can do a year follow-up on this outcome, but you would want, as was said, I think lifetime actually follow-up for safety problems for some kind of novel device.

DR. REDBERG: Certainly for an implanted device that is in for a lifetime, a lifetime seems reasonable.

There was a mention of composite, and

that is actually what we're supposed to be discussing now, is the merits of composite outcomes which included the combination of mortality, heart failure hospitalization or

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heart failure equivalent events. So it's kind of what we were just talking about. What would you think of the merits of that composite outcome? Dr. Stevenson.

DR. STEVENSON: That's what you would be measuring, whatever you call it, that's essentially what you're going to be measuring.

DR. REDBERG: Right, that's what you would be measuring, is the composite outcome. It would seem to me, you know, the issue would then be whether mortality was up but hospitalizations were down, so then the overall composite would be, look favorable, but the actual --

DR. STEVENSON: But safety wouldn't.

DR. REDBERG: Right.

DR. STEVENSON: And just for the record, there's very few heart failure interventions that we've thought about using in which quality and hospitalizations go in the right direction and people die. Usually we don't have to make those sorts of decisions.

DR. REDBERG: Dr. Desvigne-Nickens, did you want to comment on composite outcomes? Your card is up.

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DR. DESVIGNE-NICKENS: No, I don't, I think I am in concordance with what other people have said.

DR. HSICH: So, I guess I've always viewed hospitalization as an event, and for an event when you're doing research, you count the number of events, you have to have the clinical significance between groups, so it's tied to events. And you know, it goes back to Dr. Allen's comment about what stage of the disease, if it's New York Class II versus IV, so I kind of, I understand picking a time point

for quality of life because you have to decide if when you're going to do it, I understand it for functional capacity, but I don't understand it for hospitalization where you have to have an event.

DR. REDBERG: Dr. Swain.

DR. SALIVE: Well, I think, though, you can have multiple hospitalizations, and people pointed that out, you could have four, and so then your time to event is not an analysis you can easily do with that. And you know, I agree also that this is a composite for censoring purposes also, you know, they're not

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at risk once they die.

DR. REDBERG: Right.

DR. HSICH: But we're creating one population of heart failure patients that range from well to sick, and so that's where it gets very complex.

DR. REDBERG: So I think I've heard we

need to note the severity of heart failure we're talking about, that would certainly affect the length of time of follow-up and how we look at it, and also that we're interested in a more continuous variable, not a time to event, because Dr. Stevenson suggested days of hospitalization, I think we've heard interest in how many hospitalizations, and that would give a richer data source. Dr. Swain.

DR. SWAIN: Yeah, and I agree with Dr. Stevenson that we've got to get some sort of hierarchy figured out because you've got mortality, ones that have mortality, you may have heart failure hospitalization, which I think is still defined as a calendar day, calendar night, come in at ten p.m., go out at eight a.m., that's hospitalization, and the amount of invasiveness of the out-of-hospital

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intervention, and so somehow one has to figure out a hierarchical approach to this.

DR. REDBERG: Dr. Zuckerman.

DR. D. ZUCKERMAN: Yeah. I agree with that hierarchical approach, and I also, I mean, I don't know if this is part of the question, but you know, to the extent that you can statistically control for other variables that you know of, that might be relevant in terms of affecting why a person is hospitalized or not, I think that would be helpful.

DR. REDBERG: Okay. That was excellent. We're going to go on to the second voting question, and it's a little different than what we've just been talking about, because it's looking at different, sort of what you were interested in, different types of heart failure. And the question is, how confident are you that surrogate and intermediate endpoints are predictive of standalone meaningful primary health outcomes? And I'm sorry, let me rephrase that.

How confident are you that surrogate and intermediate endpoints such as reduction in mitral regurgitation, cardiac remodeling,

ejection fraction or biomarkers are predictive of standalone meaningful health outcomes in research studies of heart failure treatment technologies for heart failure with preserved ejection fraction? And again, the voting scale is the same. So the voting question is whether you think you have confidence in surrogate and intermediate outcomes for technologies for heart failure with preserved ejection fraction.

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

SPEAKER: I would suggest that for the endpoints listed, I don't have any confidence for heart failure with preserved ejection fraction that any of these would work.

SPEAKER: Ditto.

DR. REDBERG: We need two more people to vote. Okay, this was a 1.56, and Alan, do you want to discuss your vote?

DR. HIRSCH: Hirsch, one. There just hasn't been anything presented that would give me confidence that these are relevant.

DR. CRUZ-FLORES: Cruz, two, same reasons.

DR. FISCH: Fisch, one, similar

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reasons.

DR. KOBYLARZ: Kobylarz, three.

DR. SALIVE: Salive, one.

DR. SEDRAKYAN: Sedrakyan, two. We have never seen evidence about change in surrogate endpoints leading to change in standalone endpoints that would decide it for me, not the correlation. There might be a lot of correlation of vitamin deficiencies associated with birth defects, but not all birth defects can be prevented by giving vitamins to people, just like an immunological example that we know about.

DR. SEGAL: It's Segal, two. We didn't hear very much about the preserved ejection fraction group.

DR. SWAIN: Swain, one for most of these, except the amount of MR; for functional

MR that would be a zero, but you don't allow zeroes.

DR. D. ZUCKERMAN: Diana Zuckerman, one, for the reasons everyone else has said.

DR. HSICH: Eileen Hsich, one.

DR. STEVENSON: Stevenson, two.

MS. RENBAUM: Adi Renbaum, two.

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DR. BERLINER: Elise Berliner, one.

DR. DESVIGNE-NICKENS: Patrice Nickens, one.

DR. YANCY: Clyde Yancy, one.

DR. B. ZUCKERMAN: Zuckerman, two.

DR. REDBERG: Okay. We're going to vote now on mitral regurgitation and as you recall, Dr. Yancy suggested we split this into degenerative and functional, and so we're going to do that, so the first one, we're voting on degenerative mitral regurgitation. So the same, starting out about the surrogate and intermediate endpoints, but now do you think

that they are meaningful primary health outcomes in clinical research studies for heart failure secondary to degenerative mitral regurgitation?

DR. STEVENSON: Can I just clarify the question? So you're saying, is a reduction in mitral regurgitation a good indication of how patients will do who were supposed to have complete treatment of their mitral regurgitation but still have mitral regurgitation, is that right? So we're saying people who were ineffectively treated for

mitral regurgitation.

DR. REDBERG: The question is as a treatment for degenerative mitral regurgitation, do you consider reduction in mitral regurgitation a meaningful standalone primary health outcome?

DR. STEVENSON: Well, this kind of gets back to does the therapy actually do what it's supposed to, which is kind of, sort of a

tetrology.

DR. SWAIN: Swain. Let me ask, when you say reduction, I guess there's a problem, because four to a three is incomplete, you know, the AHA guidelines say mitral insufficiency is the disease, but I guess if we could not talk about reduction, just measuring amount of MR.

DR. REDBERG: So the question is written, just assume a reduction in mitral regurgitation, it wasn't quantitated.

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

DR. REDBERG: Okay, and that score was 1.78. Dr. Hirsch.

DR. HIRSCH: Hirsch, one, and Swain

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zero. If this is the holy grail of cardiovascular medicine and heart failure, we don't have evidence to correlate, then you're right, it would be a reduction, but you would

want it to be abolished.

DR. CRUZ-FLORES: Cruz, two.

DR. FISCH: Fisch, one.

DR. KOBYLARZ: Kobylarz, two.

DR. SALIVE: Salive, two.

DR. SEDRAKYAN: Sedrakyan, two.

DR. SEGAL: Segal, four. I think I didn't understand the question that well.

DR. SWAIN: Swain et Hirsch, one.

DR. D. ZUCKERMAN: Diana Zuckerman, one.

DR. HSICH: Eileen Hsich, two.

DR. STEVENSON: One.

MS. RENBAUM: Renbaum, two.

DR. BERLINER: Berliner, one.

DR. DESVIGNE-NICKENS: One.

DR. YANCY: I guess I'm not only a minority but an outlier now, but the basis upon which the technologies were approved to address degenerative disease, that they were able to reduce MR, able to affect reverse remodeling,

able to lower the biochemical signal, so I'm going to be an outlier and give it a three.

DR. B. ZUCKERMAN: Zuckerman, three, for the same reasons.

DR. REDBERG: Okay. The next is, remember we split mitral regurgitation, so now we're going to vote on functional mitral regurgitation, the exact same question but functional; we just voted on degenerative. You can vote.

DR. YANCY: Rita, would it help to define functional MR for those members of the panel that aren't quite aware of the significance of that nomenclature?

DR. REDBERG: Do you want to go ahead and do that, Clyde?

DR. YANCY: It's easiest enough to do.

DR. REDBERG: Sure.

DR. YANCY: But in the setting of heart failure when the muscle is weak and dilated, the process of the muscle becoming weak and dilated makes the mitral valve less efficient, it fails to close correctly and that leads to residual mitral insufficiency which

25 may be important. So the question on the table

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1 is whether or not addressing that kind of MR,
2 which is less because the valve is problematic
3 and more because the heart is misshapen and
4 enlarged, leads to reasonable outcomes in heart
5 failure, so that's why it's called functional.
6 So it's a very different etiology than what we
7 just addressed, which is where the valve itself
8 was a primary disorder, as Dr. Swain just
9 alluded to.
10 (The panel voted and votes were
11 recorded by staff.)
12 DR. REDBERG: We need three more
13 people to vote. Okay, that's a mean of 1.67.
14 Alan?
15 DR. HIRSCH: Hirsch, two.
16 DR. CRUZ-FLORES: Cruz, one.
17 DR. FISCH: Fisch, one.
18 DR. KOBYLARZ: Kobylarz, three.
19 DR. SALIVE: Salive, one.

DR. SEDRAKYAN: Sedrakyan, two.

DR. SEGAL: It's Segal, three.

DR. SWAIN: Swain, one, unlike degenerative which, that is the disease.

DR. D. ZUCKERMAN: Diana Zuckerman, one.

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DR. HSICH: Eileen Hsich, one.

DR. STEVENSON: Lynne Stevenson, three, because it's a good thing to do, but I'm a little worried because we're not measuring when you do something else if it hurts the heart somewhere else.

MS. RENBAUM: Adi Renbaum, four, based on the explanation I just heard.

DR. BERLINER: Berliner, one.

DR. DESVIGNE-NICKENS: Patrice Nickens, one.

DR. YANCY: Yancy, two. We really need to have an evidence base instead of in principle, this is a reasonable thing to do.

DR. B. ZUCKERMAN: Zuckerman, three.

DR. REDBERG: And now the C, because we split B into two, so C is the same stem, but the heart failure is now heart failure with reduced ejection fraction, so it should be D.

DR. SEGAL: Can you clarify, can it be any one of those markers? If I like one but I don't like the other two, how do I vote?

DR. REDBERG: Any of them.

DR. SEGAL: Any of them, so I vote my highest, okay.

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

DR. REDBERG: Could everyone please vote? We need one more person. Okay, 2.33. Alan.

DR. HIRSCH: You know, we studied surrogates --

DR. REDBERG: You didn't state your vote.

DR. HIRSCH: Oh, I'm sorry, three. So

with that, I'd have a higher level of confidence if we had a series of endpoints, but three.

DR. CRUZ-FLORES: Cruz, two.

DR. FISCH: Fisch, three, certainly an upgrade.

DR. KOBYLARZ: Kobylarz, three.

DR. SALIVE: Salive, two.

DR. SEDRAKYAN: Sedrakyan, two, but I'd like to change to three. I was undecided over time, so I'd like to change.

DR. SEGAL: It's Segal, four. I think cardiac remodeling sounds good to me.

DR. SWAIN: Swain, one, only because MR is in that; otherwise, it could be a three

if you didn't have MR in it.

DR. D. ZUCKERMAN: Diana Zuckerman, one, because I just didn't feel like we talked very much about this.

DR. HSICH: Eileen Hsich, three. I think it's a little nebulous as a question

because ejection fraction for a normal remodeling can go from dilated to normal, so how much I value it is dependent on what our goals are, and what, you know, and I wouldn't, going back to Lynne's comments, not all of those were things that I valued.

DR. STEVENSON: I think three, if it were huge, in fact maybe a four, and it would be quite low if it was some sort of structural girdling that decreases the LV size, I wouldn't have much confidence.

MS. RENBAUM: Renbaum, three.

DR. BERLINER: Berliner, one.

DR. DESVIGNE-NICKENS: Patrice Nickens, three.

DR. YANCY: Yancy, a four. Every effective therapy for reduced ejection fraction heart failure either affects reverse remodeling or has a biomarker signal, so we can't ignore

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that.

DR. B. ZUCKERMAN: Zuckerman, four. I think the physiology would be shown here as important.

DR. REDBERG: Okay. So all of the, A, B, C and D were all less than intermediate confidence, so we're going to move to question three, which is on quality of life measures. And this question is, how confident are you that quality of life measures, and the examples here are the Kansas City Cardiomyopathy and Minnesota Living With Heart Failure, A, are adequate measures which reflect the patient's experience? And please go ahead and vote.

DR. D. ZUCKERMAN: I have one question because several people, speakers and others, have noted that the Kansas City Questionnaire isn't really a quality of life measure, so we're just, I wasn't really sure what to do with this question. And also, almost all the data we talked about today was the Kansas City data and not the Minnesota data.

DR. REDBERG: That is all true, but I think for voting, you can consider that any quality of life questionnaire, so the SF-36, or

any, EuroQol, any of them that we did not talk about in detail, but any of those, because they're all quality of life.

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

DR. REDBERG: Okay, this was a 3.78. Alan.

DR. HIRSCH: So I'm going to go first, and isn't it interesting that in 2017 compared to maybe 20 years ago, that during the presentations the patients reported outcomes that were so robust, but they're not perfect, and we're still waiting for them to be validated, so I put down a four, I'm impressed with their foundation.

DR. CRUZ-FLORES: Cruz, four, it's to reflect what patients want.

DR. FISCH: Fisch, four. I interpreted it as patient-reported outcomes instead of quality of life, and it's a matter of semantics, but four for similar reasons.

DR. KOBYLARZ: Kobylarz, and I gave it a four. I think it's the most sensitive and specific, you know, measure for heart failure.

DR. SALIVE: Salive. I gave it a

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five. I think it's here to stay.

DR. SEDRAKYAN: Sedrakyan, four. It's certainly important, we just need to decide what and how.

DR. SEGAL: Segal, five. I was impressed by the KCCQ discussion.

DR. SWAIN: Swain, two, because of the placebo effect in invasive studies.

DR. D. ZUCKERMAN: Diana Zuckerman, I gave it a two. I probably would have given it higher if it was only the Kansas City, but the Minnesota I wasn't so sure of, and also, I mean perhaps a whole other issue of placebo effect and control group.

DR. HSICH: Eileen Hsich. I gave it a five. I think the patient's perspective is

important, and it also assumes the patient's still alive.

DR. STEVENSON: I'm between a four and a five, I guess I'll give it a five.

DR. RENBAUM: Renbaum, five.

DR. BERLINER: Berliner, four.

DR. DESVIGNE-NICKENS: Patrice Nickens, four.

DR. YANCY: Yancy, four. I think we

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can do better than the KCCQ, and we should aim for that. The promised measures I think are quite important.

DR. B. ZUCKERMAN: Zuckerman, three. I think it's still difficult to tease out a possible placebo effect.

DR. REDBERG: Okay. And now we're going to vote the part B, so it's the same stem, but now you're voting on should it be included as the standalone meaningful primary health outcomes in research studies. So again, this would be the primary outcome of the study

would be powered on the quality of life measure.

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

DR. REDBERG: Okay, and this was a 2.89. Dr. Hirsch.

DR. HIRSCH: Hirsch, four, but I found the question to be, again, to be a little confusing, because could be included is different from should be, and could be implies other variables, because as a primary outcome alone where a placebo effect is found, and we've all talked about that, so you have to

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co-directionally maintain physiologic, patient-reported, and ideally relevant health outcomes at the end of the day, so four.

DR. CRUZ-FLORES: Cruz, four, similar reasons.

DR. FISCH: Fisch, three. I sort of started at a five at the concept of PROs and

the patient's voice, but downgraded for bias, placebo issues, practical realities of interpreting missing data, responsiveness of the measures to change under certain circumstances, so practical issues, down to three.

DR. KOBYLARZ: Kobylarz. I gave it a two because I think there are other measures that can be captured in other tools.

DR. SALIVE: Salive, four. I think it's useful in some selected settings quite profoundly. And sure, it has some limitations, but I think it can be used and should be used more in trials.

DR. SEDRAKYAN: Sedrakyan, this is two as opposed to the other one being four because this is standalone and powered for that. And we know there's bias, we talked about that, and

in fact comments on previous questions apply to this one more, this is where bias kicks in as an outcome measure, so it's definitely a two.

DR. SEGAL: It's Segal, three, maybe not in a pre-post study or an uncontrolled study, and so if we're going to have a trial, a controlled trial, I would like it.

DR. SWAIN: Swain, one if it weren't a blinded, four if it were a blinded trial like drugs.

DR. D. ZUCKERMAN: Diana Zuckerman. Yeah, I made it a three, I guess in the same thing that you just said, that it has to be placebo controlled as much as possible; to me that's different from standalone. I think it's important enough to stand alone, but it has to be controlled.

DR. HSICH: Three, for the same reasons.

DR. STEVENSON: Three, because it has to be in a favorable context.

MS. RENBAUM: Four.

DR. BERLINER: Berliner, three. I think there should be other things not standalone, but if did just have to pick one, I

think having the patient-centered outcomes would be the primary one and the best we can do.

DR. DESVIGNE-NICKENS: Patrice Nickens. I gave it a one. I think I was very concerned about bias as a standalone. Perhaps there are ways to protect against that and I do think that patient-reported outcomes are extremely important, I just think it's a bias that outweighs the benefit.

DR. YANCY: Yancy. So I go with a three, taking the Hirsch interpretation of the question, one, if it's truly a standalone.

DR. B. ZUCKERMAN: Zuckerman, three, for the problematic issues already mentioned.

DR. REDBERG: Okay. So we're up to part C, and Joe just reminded me that during the call last week when we discussed the questions, we did agree to strike the standalone, so I will read, it's the same stem, and should be included as a meaningful primary health primary health outcome in research

studies. So again, it's the same quality of life measures, should they be included as a composite meaningful primary health outcome in

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research studies, and you can vote.

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

DR. REDBERG: Okay, and the mean was 3.33. Dr. Hirsch.

DR. HIRSCH: Let's make it simple. I gave it a three, and I think the question is still rather undefined, composite as a quality of life composite, or composite with the other things that go along with it, and therefore I gave it a three.

DR. CRUZ-FLORES: Four. I took it as composite with other events.

DR. FISCH: Fisch, two, also tortured about what composite means in this situation.

DR. KOBYLARZ: Kobylarz, four.

DR. SALIVE: Salive, five. I wasn't that confused, I guess I didn't understand the

question at all, but I think it can be used as an endpoint in studies, yes.

DR. SEDRAKYAN: Sedrakyan, four. I would like to see that composite measure is that hospitalization, MR plus quality of life, how do you combine the three? I would like to see that measured.

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DR. SEGAL: Segal, five.

DR. SWAIN: Swain, two. I don't know how to combine them, and placebo effect.

DR. D. ZUCKERMAN: Diana Zuckerman. I took a one because I think it should be a standalone looking at quality of life, and I don't think it should be combined with other things that just muddy the water, and then you still have to deal with placebo effect.

DR. HSICH: I said a four, this is Eileen Hsich, because I think it matters from the perspective of the patient that we need other endpoints, and so I share your concern of

how do you combine them, but I think I would want the data for them, and so for the fact that I want them to be added to what is collected, I wrote it as a four.

DR. STEVENSON: Yeah, I'm a five on this. I can accept some ambiguity but I'm interested in the context.

MS. RENBAUM: Renbaum, I gave it a four for the reasons Eileen just mentioned.

DR. BERLINER: Berliner, I gave it a four, also for the same reasons, I don't know how you would combine it as a composite, but it

also goes to the idea that I think it should be, which is to measure a bunch of different things, and quality of life is a very important part of it.

DR. DESVIGNE-NICKENS: Patrice Nickens. I did give this a five, I'm not sure if I understood, but this is so important to include, but I do agree that it's measuring something different than some functional

measure or difference, but I think that we should consider ways of including as a part of primary considerations patient input.

DR. YANCY: There's no volume, but I voted a five.

DR. B. ZUCKERMAN: Zuckerman, four.

DR. REDBERG: So now, the last question is the exact same question we just did, except now we're going to be looking at functional assessments instead of quality of life measures. So how confident are you that functional assessments like the six-minute walk test or VO2max, A, are adequate measures which reflect the patient experience? You can vote.

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

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DR. REDBERG: So, this is 3.22. Dr. Hirsch.

DR. HIRSCH: I couldn't help, with humor, it's not the ventilator threshold, and

actually I gave it a four, because working with six-minute and VO2 leads to effects that are quite reasonable, they do correlate well, and I want to remind you, we never get tests with .9, most of our tests are moderately correlative, and we still do the tests.

DR. CRUZ-FLORES: Cruz, three.

DR. FISCH: Fisch, three, and I sort of took it to mean that this is something generally useful, maybe not necessarily adequate to reflect the patient experience per se, so I gave it a three, and I was wavering between a three and a four.

DR. KOBYLARZ: Kobylarz, three.

DR. SALIVE: Salive, five. I think the six-minute walk is kind of like real life although kind of not, and the stats are good, I agree.

DR. SEDRAKYAN: Sedrakyan. I put three, because it says patient experience and only six-minute walk test reflects that, the

other ones are not patient experience necessarily, that's why I'm voting three.

DR. SEGAL: Segal, four.

DR. SWAIN: Swain, three for six-minute walk, four for VO2, but I'm waiting for the Fitbit, you know, a week's activity measured by a Fitbit.

DR. D. ZUCKERMAN: Diana Zuckerman, one. I did a one because my experience with looking at six-minute walk is that it isn't really reflective of how the patient lives, it's reflective of their motivation to do the walk and the test. And the other two, I really wasn't sure of either.

DR. HSICH: So I rated it pretty high, I rated it a five. I think that especially for peak oxygen consumption, we have evidence even in normal patients that it predicts outcomes and how they do, so I felt that this was very good.

DR. STEVENSON: I rated it a four. I would rate the six-minute walk slightly lower than the objective other two measurements. And I would emphasize that that's for functional

25 capacity. The patient experience, you could

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1 have a therapy that makes them nauseous half
2 the day and disturbs their sleep and they could
3 still exercise, so this does not fully reflect
4 the patient experience, but it's good for
5 functional capacity.
6 MS. RENBAUM: Renbaum, four.
7 DR. BERLINER: Berliner, three.
8 DR. DESVIGNE-NICKENS: Nickens, four.
9 DR. YANCY: Yancy, a three. I would
10 agree that these measures are not quite as
11 precise and don't necessarily track how the
12 patient does.
13 DR. B. ZUCKERMAN: Zuckerman, four,
14 even with the above, it's an important
15 endpoint.
16 DR. REDBERG: Okay. And now we're
17 going to vote the same stem but the question,
18 and we have modified it in response to the
19 feedback from the earlier question to take out

included, so I will read it. Should be, that the functional assessment should be the standalone meaningful primary health outcomes in research studies.

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

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DR. REDBERG: Okay, so this was a 2.44. Dr. Hirsch?

DR. HIRSCH: I could have put it on either two or four. I put it on two because I'm trying to wear my CMS hat, not my FDA hat. If I'm looking for, you know, a drug or device effect, I think these are very reliable outcomes and I would give them a four or five. But I'm thinking from a beneficiary point of view, where if this was all we were offering the patient, the patient would shrug. It might even be a minus one, but I gave it a two.

DR. CRUZ-FLORES: Cruz, three.

DR. FISCH: Fisch, one, take a useful measure, but really overreach in what we're

trying to do in the standalone realm.

DR. KOBYLARZ: Kobylarz, three. I think a lot of it depends on the population.

DR. SALIVE: Salive, four.

DR. SEDRAKYAN: Sedrakyan, two, and again, same logic. Anything that is standalone, needs to change that standalone measure should also correlate, lead to change in the main endpoints that we talked about, mortality, hospitalization. So by themselves

they cannot be, unless there's evidence that change in this score leads to change in the overall, so it's two.

DR. SEGAL: Segal, three.

DR. SWAIN: Swain, three.

DR. D. ZUCKERMAN: Zuckerman, one. I just think it isn't very meaningful compared to a lot of other things.

DR. HSICH: Eileen Hsich, two.

DR. STEVENSON: Lynne Stevenson,

three. It depends what you're testing. If you were testing some sort of exercise training I would make it a five. If you're testing some sort of drug that's supposed to improve cardiac function then I would probably leave it at a three.

MS. RENBAUM: Renbaum, three.

DR. BERLINER: Berliner, one.

DR. DESVIGNE-NICKENS: Patrice Nickens, two.

DR. YANCY: Yancy, a one. I would remind everybody that the predicate for this was a CRT where it was approved for about a 25-meter improvement in the six-minute walk as the only outcome, so we should keep that in

mind.

DR. B. ZUCKERMAN: Zuckerman, three. Just for the record, CRT first approval was based on the MERIT trial, where all three endpoints were positive.

DR. REDBERG: Okay. And for the last

part of this question, it is the same stem, and now it's should be included as a composite meaningful primary health outcome in research studies. Let's see if everyone can vote.

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

DR. REDBERG: Okay, so we have a 2.89. Dr. Hirsch.

DR. HIRSCH: Interesting. Composite to me is a beautiful thing, it's the triple crown where everything's going to align in the right direction, so this to me is a four. I want function, I want patient-reported outcomes, I want hospitalization survival, and I ranked it up.

DR. CRUZ-FLORES: Cruz, four. I think that these outcomes in combination with, for example quality of life, would give it more meaning.

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DR. FISCH: Fisch, two. And again, if

you consider composite as one amongst other things that you should look at to make useful interpretation of research, then I would upgrade it substantially, I think that's really a great use of that test. But I keep imagining it as literally being combined with other things and scored where you have to interpret the whole composite at once in a confusing way that doesn't make sense, and I couldn't explain it to my grandmother, so that made it a two to me.

DR. KOBYLARZ: Kobylarz, three.

DR. SALIVE: Salive, two.

DR. SEDRAKYAN: Sedrakyan. I put four and I again, took out the standalone part and I looked it as a composite similar to quality of like, so in that context I agree.

DR. SEGAL: This is Segal, three, and I almost went four.

DR. SWAIN: Swain, three, and again, I agree that it depends on what you're looking at on those studies, so it could be a two, could be a four, but three looks reasonable.

DR. D. ZUCKERMAN: Diana Zuckerman. I

did a one just because, again, I didn't think it's all that meaningful and I'm not sure that combining it with a lot of other things makes it more meaningful, but since we didn't say what we'd combine it with, I really have no idea, but that means I'm not very confident.

DR. HSICH: Eileen Hsich, I made it a four. I didn't make it a five because not everybody can start with walking, and I thought of myself. I wish that I could dunk basketballs; yet, if you make me taller, I probably still can't do it. So, you know, some of my patients who can't walk because of arthritis, but probably still want to participate in studies, and that is kind of why I downgraded it from a five to a four.

DR. STEVENSON: Four. I think it's very important, but not standalone.

MS. RENBAUM: Renbaum, four.

DR. BERLINER: Berliner. I voted one because I'm still wondering if these tests are

overlapping with something like the KCCQ, and the KCCQ seems more patient centered, so are you double counting if you take a vote on the outcome. So if I had to pick, based on what I

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heard, I would pick the KCCQ.

DR. DESVIGNE-NICKENS: Patrice Nickens, two.

DR. YANCY: Yancy, four. I think this is very important because if we're talking about a new endpoint for which we would reimburse a new technology, having something like a functional assessment and a quality of life tool that are going the same direction would be very reassuring. And so I think because it's part of a composite, it is at least a four if not more.

DR. B. ZUCKERMAN: Zuckerman, four.

DR. REDBERG: I think we've had a really rich discussion. We've finished the voting questions and as you can see, there are

several more questions for discussion and I'm just going to highlight, because I think we have covered a lot of what's in there already, but we can have a little more discussion if there's some specifics.

We talked about how long follow-up should be for the surrogate outcomes but we didn't talking about it for patient-reported measurements, and we had said kind of one year

or longer depending on the severity of heart failure. Would you think the same for patient-reported measurements, or does anyone think it should be longer or shorter?

DR. SEDRAKYAN: Can I comment? Like an example in joint replacements when FDA in fact requires qualified measurements at six months, two years, five years, ten years, it goes way longer time period. I mean, I'm not saying whether it's possible in the real world or not, but certainly recognizing this issue of subjective and possible bias related to placebo

effect, I really think we need to think about longer term qualified measures to have a good picture and separate the effect of, as much as we can, placebo effect from sustained quality of life benefits.

DR. SALIVE: Salive. I would just say, you need kind of a natural history study then, or a cohort study to work in parallel with that, because I think interpreting such data from just people who got implanted with X is, you know, difficult. So I would, you know, I think, and I agree that longer term, such a study of heart failure patients would be very

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interesting to examine.

DR. REDBERG: But you're saying it's important to have a control group or some comparison group, and of course that's an issue, I think, with a lot of our registries, is it's already assumed, in my opinion, that there's been a randomized control trial that

showed a benefit over alternatives, and now we're just looking at more detail.

DR. SALIVE: But I think even in terms of communicating this to the patients, you know, interpreting those results is very challenging if you don't know kind of the A group, of some sort of cohort that's followed over time, you know, even with the vagaries of technology changing over time.

DR. REDBERG: And that does kind of lead us into, another question was how best to capture patient preferences, and we again, have had some discussion, but if anyone has more suggestions on that.

DR. HIRSCH: Well, one thing I heard earlier was that a randomized trial well done with fantastic nursing support and you know, usually downtown settings with not diverse

populations cannot reflect the full real world of what America is and will be. So the idea of spanning these real world settings, which is

difficult because we don't reimburse for it, so we're working as fast as we possibly can, and it would seem to be important for a longer-term study, at least from my perspective. Medicare beneficiaries deserve that confidence regardless of their background when they're not included in the trial.

DR. REDBERG: Dr. Swain.

DR. SWAIN: Yeah. I think the longer term is so essential. Now that we know the TAVR data at seven years and the degeneration that, you know, partial repair of a valve, does this really work, things of that sort. We've just got to go over the two years, and even over the standard five years.

DR. REDBERG: Dr. Zuckerman.

DR. D. ZUCKERMAN: Yeah, I'll just agree with that.

DR. REDBERG: And then that leads us into how to best consider the impact of adverse events associated with heart failure technologies while balancing potential for

improvement. Dr. Swain?

DR. SWAIN: Well, again, when we look at these composites that are all weighted the same, we see devices that say they're better than surgery because that's been totally drive by amount of blood transfusions, or prolonged ventilation defined as 25 hours on a ventilator, counts the same as deaths. So I think that one has to have a qualitative judgment and somehow hierarchically look at these, because it's a huge problem in these trials when they least, least, AE drives it completely.

DR. REDBERG: Any other comments on the impact of adverse events or how to collect that data?

DR. STEVENSON: I just want to get back to Larry Allen's work, because I think it's really important that we capture the individual serious adverse events which have different implications for patients, like stroke isn't the same as bleeding, isn't the

same as an infection, so I think when we have high tech high resource interventions, we need to capture each one of those and talk

individually to patients about it, even though from the standpoint of a device efficacy you might lump some of those together.

DR. HSICH: I echo that. I mean, that's incredibly important, especially when we're talking about very risky devices, and they are willing to take some risks and not others.

DR. REDBERG: Dr. Fisch? Thank you.

DR. FISCH: So, I think that including patient-reported outcomes in adverse event reporting would be useful. In cancer land we have this PRO-CTCAE as sort of a newer measure, where adverse events have previously been described by the clinicians. And being able to measure the patient's data over time at a distance, so they don't have to be face to face at the time of the clinic visit through

digital engagement, would also be useful and might allow us to get very early data and also be able to measure late effects of some of these devices that are in for a long time.

DR. REDBERG: Great. And now, Dr. Segal?

DR. SEGAL: And just to comment about

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the preferences, the question as phrased here sounds like it's patient preferences about treatments but it's probably patient preferences about outcomes and how they value different outcomes, I would think, right? Or, I guess it could be either, but that's how I would interpret it.

DR. REDBERG: I think their feelings about treatment are determined by their feelings about the outcomes.

And that could bring us to the last discussion point before we conclude, which is how to balance the short-term benefits and

harms, it says with treatments that may decrease length of life.

DR. HIRSCH: So I'm going to charge into this one. Often we measure as physicians the benefit and harm and then we sit in a room and we try to calculate that benefit-harm ratio, you know, a thrombotic event, a bleeding event. What is that event benefit or harm at three months, or out to five years. And the recent methodology is asking people to stand or gamble, you know, how much harm or risk are you willing to take for one potential benefit, and

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that's different at different time points. And those measurements of stand or gamble are done randomly, not within the clinical trial. But the participants, not the subjects in the clinical trials, are poised actually to tell us, not us judging, that relative risk and benefit.

It would be different probably at the study's start, full of hope, you know, at the

time of the event with the stroke, and when the stroke recovers five years later. That's an area of research that we've barely even begun, but very important.

DR. REDBERG: Dr. Zuckerman.

DR. D. ZUCKERMAN: Yeah. I guess I would just add that my experience is that patients are, you know, they live on hope, and they want to think things are going to work out, and maybe as patients get older and sicker, that changes. But just generally, they're very optimistic that if something has a ten percent chance they'll be that ten percent chance of helping, of being helped, and if there's a ten percent chance of dying, it won't be them. So it's hard to balance that for

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patients, because, you know, it's their lives and they're not going to go into this in this logical statistical way. And we just have to do the best we can to provide that information,

but how it's received is different.

DR. REDBERG: Dr. Berliner, and you will have the last comment.

DR. BERLINER: So I mean, I think the way that the kind of decision is, that PCORI talked about, is the way to help patients make individual decisions about risks and benefits.

Another project that we're working on at AHRQ is building off of our FORCE TJR orthopedic registry, where we're funding the development of an app where patients put in their characteristics, that builds built up the data in the app, the app will tell them what their most likely outcomes are, both risks and benefits, and I think those are the kinds of tools, individualized to individual patients that will really help patients make decisions.

DR. REDBERG: Thank you. Clyde, the last word.

DR. YANCY: I think this is easier in clinical practice that it is in trials, because

when you're dealing with people that have advanced disease and are symptomatic at rest, they simply want to feel better, and nothing else gets into the equation. We deal with this on a regular basis. In a trial where there's a signal of harm, we're not comfortable with it going forward, but in practice we deal with this all the time.

DR. REDBERG: Well, thank you. I want to thank all of the panel and the speakers. Oh, Dr. Cruz, sorry.

DR. CRUZ-FLORES: Sorry, I thought you said I had the last comment.

DR. REDBERG: Yes.

DR. CRUZ-FLORES: I think something that may be worth thinking and including in the design of the studies is something that's been somewhat but not completely studied, which is the framing of the decisions of all these patients. That is to say, it's not the same to say you have a 90 percent chance of dying, as saying you have a 10 percent chance of surviving. And so when people, and it was studied by (unintelligible) in terms of how it

is framed, and people become risk averse or

risk taker depending on how those options are presented to them, but I'm not sure that has been totally studied.

DR. REDBERG: It's a very interesting field, and you know, I've listened to kind of their talk recently and I think people are, and patients and doctors are not the most rational, you know, we would make a different decision on the same data depending on how it's framed, and maybe we'll be another MedCAC.

But for now, I think this was really a very interesting and innovative and creative topic and discussion. I really appreciate all of the speakers, the panel. I will say, I got here before six this morning and Maria had all the sign-up sheets out, all the badges out, so I just want to say, you make all this run, and thank you so much, and to Dr. Chin and Dr. Canos. And thank you to the MedCAC panel.

I think everybody really contributed to an incredibly, like I said, it was informative. I learned a lot, we talked about a lot of tough issues. Thank you so much, and I will let Dr. Chin make the concluding.

DR. CHIN: Thank you, Rita. So, I

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would also like to thank the panel, our invited speakers and our guests that helped us out today, I think it's been very very interesting. We've gotten a tremendous amount of information to help us. I think we're very appreciative to have such a renowned panel with us today, with so many subject matter experts on heart failure.

And I'd also like to particularly thank Dr. Redberg for not only chairing this meeting, also the past number of meetings that we've had, and she has been great to work with. Thank you.

MS. ELLIS: I would just like to let everyone know that all the changes that were

discussed during the meeting, they will be reflected on the questions that will be posted to our coverage website, just to let you know, okay?

And for the panel members who are on the shuttle, the shuttle is here and waiting for you.

(The meeting adjourned at 3:55 p.m.)

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