FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC)

Thursday, October 25, 2018

8:31 a.m. to 1:23 p.m.

Day 2

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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C O N T E N T S

P R O C E E D I N G S

(8:31 a.m.)

Call to Order

Introduction of Committee

DR. WILSON: Good morning. First I want to remind everyone to silence your phone, if you have a phone or other devices that may make noise during the proceedings.

Do we have a press contact here? Amanda Turney is identified in our documents.

Is she here? No? Okay. So if you have any press interest and you want to reach an FDA representative for this, contact one of the FDA individuals here, and we'll link you up with her.

I'm Peter Wilson. I'm the chair of the Endocrinologic and Metabolic Drugs Advisory Committee, and I'll be chairing the meeting, and we've now been called to order. We'll start by going around the table, introduce ourselves, in case we forgot from yesterday. This is day 2, so why don't we start with the FDA? Thank you.

DR. THANH HAI: Good morning. I'm Mary

Thanh Hai, acting director, Office of Drug Evaluation II.

DR. CHONG: William Chong, acting director, Division of Metabolism and Endocrinology Products.

DR. YANOFF: Lisa Yanoff, acting deputy director, DMEP.

DR. ARCHDEACON: Hi. Patrick Archdeacon, clinical team lead, DMEP.

NIYYATI: Mahtab Niyyati, clinical reviewer, DMEP.

DR. GRUNBERGER: I'm still George Grunberger, adult endocrinologist from Michigan.

DR. NASON: Martha Nathan, biostatistician at National Institute of Allergy Infectious Diseases.

DR. KUSHNER: Fred Kushner, clinical cardiologist, clinical professor, Tulane LSU and NYU.

DR. LOW WANG: Cecilia Low Wang, endocrinologist at University of Colorado and CPC clinical research.

DR. BLAHA: Hi. Mike Blaha, cardiology,

director of clinical research, Johns Hopkins, Ciccarone Center for Prevention of Heart Disease.

DR. FRADKIN: Judy Fradkin, director of the Division of Diabetes, Endocrinology and Metabolic Diseases at NIDDK.

DR. EVERETT: Brendan Everett, cardiologist at the Brigham and Women's Hospital and Harvard Medical School in Boston.

CDR BONNER: Good morning. LaToya Bonner, DFO for EMDAC.

DR. WILSON: Peter Wilson, Emory University, endocrinology, preventive cardiology, and epidemiology.

CAPT BUDNITZ: Dan Budnitz, medical officer and epidemiologist for the medication safety program at Centers for Disease Control and Prevention.

DR. DE LEMOS: James de Lemos, cardiologist, UT Southwestern in Dallas.

DR. NEWMAN: Connie Newman, endocrinologist at New York University School of Medicine.

MR. LUMLEY: Dan Lumley, patient

representative from Kansas City.

DR. ELLENBERG: Susan Ellenberg, professor of biostatistics, University of Pennsylvania, Perelman School of Medicine.

DR. WANG: Tommy Wang, chief of cardiology at Vanderbilt University.

DR. ROBBINS: I'm David Robbins. I'm a professor of medicine and director of the Diabetes Institute at Kansas University Medical Center.

DR. ROSENBERG: Yves Rosenberg, preventive medicine, clinical trialist, Division of Cardiovascular Sciences, NHLBI.

DR. BURMAN: Good morning. Ken Burman, head of endocrinology at Medstar Washington Hospital Center and a professor of medicine at Georgetown University.

DR. WASSERMAN: Good morning. Scott Wasserman. I'm a cardiologist. I'm vice president of global development and therapeutic area head for cardiovascular, metabolic, and neuroscience at Amgen.

DR. WILSON: As a prelude, for topics such

as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair, and we look forward to a productive meeting.

Also, in the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings.

However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now I pass it over to our commander, LaToya Bonner.

Conflict of Interest Statement

CDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing,

patents and royalties, and primary employment.

The agenda involves discussion of the "Guidance for Industry: Diabetes Mellitus, Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" and the cardiovascular risk assessment of drugs and biologics for the treatment of type 2 diabetes mellitus.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Scott Wasserman is participating in this meeting as a non-voting industry representative,

acting on behalf of regulated industry. Dr. Wasserman's role at this meeting is to represent industry in general and not any particular company. Dr. Wasserman is employed by Amgen.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussion. Thank you.

DR. WILSON: Next, we're going to hear from Dr. William Chong from the FDA, with his introductory remarks.

FDA Introductory Remarks - William Chong

DR. CHONG: Thank you, Dr. Wilson.

So welcome to our second day. I hope everyone had a good night's sleep and was able to think about all the interesting perspectives, opinions, questions and answers we heard yesterday.

I think it's worth taking a few minutes to reorient ourselves to the guidance and what we're here to talk about today. As we discussed yesterday, 10 years ago, there was a concern. There was concern that diabetic drugs increased cardiovascular risk, ultimately leading to the publication of this guidance. And over the last 10 years, we've generated a lot of data, as we've heard yesterday, and learned a lot.

The question now before us is do we still have that same concern, and as we go into our discussion topics and our question, I think that's something that we should keep in the forefront as we think about what is the appropriate way to move forward. And as a reminder, our authority to require these trials in the postmarketing setting is based upon a safety concern.

For these glucose lowering drugs, if we have

a concern, we can require these trials, but over the last 10 year, we've been requiring the trials of all diabetic products because of an overall potential concern that was discussed 10 years ago. So with that in mind, I think it's worth going through the discussion topics and the question. As we hear from our public speakers, I believe we will have some time for additional clarifying questions to the FDA. And then as you move into the discussion, it's worth keeping all those things in mind.

As I mentioned, today we'll be going through our public comments, so the open public hearing will follow, and then we'll get to the meat of the matter and get to your discussion. And we'll look forward to hearing all of your thoughts and recommendations as we finish the day. So for the first discussion topic, again, we want to hear your opinions on the impact of the recommendations of the guidance on the assessment of cardiovascular risk for drugs indicated to improve glycemic control in patients with type 2 diabetes.

For the second discussion topic, we're looking to hear your opinions on the recommendations described in the guidance, specifically the establishment of an adjudication committee, inclusion of patients at high risk; the specific goalposts, as they are described; the inclusion of 1.8 prior to approval and 1.3 afterwards. We also want to hear from you on whether cardiovascular safety findings from certain members, or a single member, or however many should or should not be applied to all members of a drug class.

The last question is going to be a voting question. And as I mentioned, the guidance provided recommendations on excluding unacceptable cardiovascular risk for all new therapies. And as I said, this was based on a potential concern that was discussed in 2008.

So moving forward, the question we are posing to you is, should an unacceptable increase in cardiovascular risk be excluded for all new drugs to improve glycemic control in patients with

type 2 diabetes regardless of the presence or absence of a signal of risk in the development program? And when we get to your vote and your answers, we'll really be looking to hear the discussion part of it.

If you vote yes, we are interested in what changes you would recommend as well as the reasons behind those recommendations, and what you think would be appropriate, and at what time in the development program it should be conducted pre-approval and post-approval. If you vote no, we want to hear in your discussion what might constitute a signal of risk that would warrant additional data collection, whether it be a cardiovascular outcomes trial or other forms of cardiovascular risk assessment.

So I am looking forward to hearing all of your thoughts, and I'm looking forward to hearing from the open public hearing speakers as well, and I'm looking forward to a productive meeting today. Thank you again for all of your service, and we appreciate your input.

Open Public Hearing

DR. WILSON: Thank you. Now we're moving to the open public hearing session, and we have introductory remarks that I'll voice now.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with industry.

For example, this financial information may include industry's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any financial relationships. If you choose not to

address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking, however.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect -- final words -- therefore, please speak only when recognized by the chair, and thank you for your cooperation.

I will let you know in advance, we have what looks like on the list, 8 speakers, 7 or 8; it keeps getting revised. I apologize. There will between 3 and 20 minutes, the times that they've requested, so there will be varying durations.

Why don't we start with speaker number 1?

If you would come to the podium, please remember to introduce yourself and any affiliations or sponsorship, et cetera. Thank you.

MS. CARRACHER: Good morning, and thank you to the chairperson, committee, and FDA for the opportunity to speak on a critical issue for people with diabetes. My name is Anne Carracher, and this is Martin Kurian. We're speaking as representatives of Close Concerns, a healthcare information company that aims to improve patient outcomes and making everyone smarter about diabetes and obesity. Inevitably and increasingly, this also involves research and writing on cardiovascular disease. We attend nearly 40 scientific meetings per year on diabetes. For disclosure, multiple for-profit and nonprofit organizations in diabetes and obesity subscribe to our fee-based newsletter called Closer Look.

There's no denying that CVOTs has improved our understanding of diabetes therapies, but 10 years after the guidance was put in place, what can we learn about trial design from 26 completed and

ongoing CVOTs? For one, we ask whether endpoints might be reconsidered. For example, evidence from SGLT2 CVOTs supports benefit on heart failure and renal outcomes, two areas of high unmet need, and this evidence has given rise to other dedicated outcome studies, including 4 in heart failure and 3 CKD. There's also evidence for renal benefit with GLP-1 agonists.

As Dr. Sabatine suggested yesterday, is it time to reassess the outcomes we care about and the way we evaluate them? Based on the available data, there might be reason to believe that more adoptable outcome trial design can yield more useful information for patients and providers. How can the field get to the most important safety and efficacy data faster while retaining quality and still keeping the data relevant to heterogeneous populations of today?

MR. KURIAN: The design and conduct of CVOTS could also warrant further discussion in several areas. Trial setup, patient enrollment and data monitoring are all resource, personnel, and time

intensive. As detailed yesterday, trials can be streamlined for efficacy while maintaining randomization. The ongoing development of remote monitoring and mobile health technologies can enable simplified patient contact procedures. Similarly, pragmatic designs with fewer sites and less intensive data monitoring on events of lower interest can all significantly reduce the cost of demonstrating CV safety. Like many, we'd love to see trials reflect the heterogeneous population of diabetes patients. We are hopeful more can be done toward that end.

A step further, we believe that the rise of real-world data programs and the emergence of so-called big data technologies over the past few years should be taken into consideration. With the CVD-REAL program, for example, AstraZeneca has built a database of over 600,000 patients to assess the real-world safety and efficacy of SGLT2 inhibitors.

Could there also be a role for registries to reinforce or simplify safety? For example, the

Center for Devices and Radiological Health has set up NEST, a standardized real-world data collection system for medical technology with the goal of ensuring patient safety and also measuring outcomes. Additionally, companies are starting to use data from completed trials to run virtual studies in specific populations.

Could there be a role for this type of modeling and machine learning? This question in particular has elicited strong and divergent opinions.

MS. CARRACHER: Finally, in an era where two classes of diabetes drugs have demonstrated the ability to reduce cardiovascular events, the continued use of placebo-controlled, or rather standard-of-care controlled CVOTS, should be reconsidered. Recently, Dr. Steven Nissen said at Keystone 2018 that the diabetes field is rapidly approaching the end of the placebo-controlled era. He explained how Novartis' has heart failure drug, Entresto, was required by FDA to demonstrate benefit against ace inhibitors rather than placebo.

Well, GLP-1's and SGLT2's unfortunately have not become the standard of care for the vast majority of patients. The field should strive to save, lengthen, and improve as many lives as possible, including in long-term RCTs. What would that do to trial requirements overall?

We look forward to the rest of the day's discussion, and thank you again for the opportunity to raise several questions toward the end of improving lives further for patients in the system.

DR. WILSON: Thank you very much. Next we'll hear from speaker number 2. Please come to the podium, introduce yourself and any organization you represent.

MR. GOUGH: Mr. Chairman and committee members, my name is Stephen Gough, and I am the global chief medical officer for Novo Nordisk. On behalf of the company, I am grateful for the opportunity to provide our perspectives on the evaluation of cardiovascular risk, of new antidiabetic therapies to treat people with type 2 diabetes. Here are my disclosures.

Novo Nordisk is a global healthcare company with 95 years of pioneering, innovation, and leadership in diabetes care. We have R&D centers in the U.S., Denmark, India, the UK, and China, and conduct clinical research in 56 countries. Our ambition is to discover and develop better biological medicines to make them accessible to people with diabetes all over the world.

Novo Nordisk has developed five new diabetes medicines that have been approved by the FDA in the last four years. Our medicines are available in over 170 countries worldwide, and we currently supply around half of the world's insulin.

In recent years, Novo Nordisk has conducted seven large comprehensive clinical trial programs, as can be seen on this slide, on both novel insulins on GLP-1 receptor agonists. As part of this program, underlined with the 2008 FDA guidance on the evaluation of cardiovascular risk, we have also conducted and completed both pre-approval and post-approval cardiovascular safety studies.

The ongoing oral semaglutide program

includes PIONEER 6, a pre-approval CVOT in over 3,000 people. Looking at completed CVOTS within these programs, I would like to briefly discuss LEADER and SUSTAIN 6 with specific focus on trial design and execution.

As a reminder, LEADER and SUSTAIN 6 was designed to evaluate cardiovascular risk for liraglutide and semaglutide, respectively. And here you see the Kaplan-Meier plots for events over time for both. The LEADER trial, shown on the left, was a CVOT designed and conducted to determine the effect and long-term safety of liraglutide versus placebo, both used in addition to standards of care for diabetes and cardiovascular disease. Not only did the LEADER trial demonstrate cardiovascular safety, but also that liraglutide was superior to placebo with respect to the primary endpoint, which was time to first adjudicated 3-component major adverse cardiovascular event or MACE.

The trial randomized 9,340 patients with a median observation period of 3.8 years. In

addition to the assessment of cardiovascular outcomes, LEADER importantly also included prespecified endpoints for glycemic control, diabetic nephropathy, and patient-reported outcomes. SUSTAIN 6, shown on the right, was a dedicated CVOT, which established the cardiovascular safety of semaglutide. It was a two-year trial including 3,297 randomized patients with type 2 diabetes at high cardiovascular risk.

Again, the primary endpoint was timed from randomization to first occurrence of an adjudicated 3-component composite MACE. SUSTAIN 6 also demonstrated a statistically significant 26 percent reduction in MACE with semaglutide. In addition, it had as a secondary objective to serve as a long-term safety and efficacy trial in the semaglutide development program and included secondary endpoints of time to first microvascular event.

Both LEADER and SUSTAIN 6 were designed to ensure not just that the trials were adequately powered for the primary endpoint, but also so that

meaningful, unambiguous interpretation of the data could be made. The design therefore included prespecification of the components of MACE in accordance with the 2008 guidelines. In addition, in the LEADER trial, which was larger and of longer duration, not only was MACE prespecified but so, too, was both noninferiority and superiority with statistical hierarchical testing.

With respect to conduct of the randomized blinded-controlled trial, it was governed by a steering committee and an independent data monitoring committee. Moreover, prospective event adjudication was performed by an independent blinded external committee. Based upon the design, conduct, and ability to derive meaningful interpretation of the results, Novo Nordisk recommends that this level of scientific rigor should be maintained in future guidelines for the demonstration of safety and efficacy in outcome trials.

Turning now to patient retention, the FDA published its perspective on the prevention and

treatment of missing data in clinical trials in 2012. It stated that in almost 30 years of review experience, the issue of missing data in clinical trials has been a major concern because of its potential impact on the inferences that can be drawn from a study.

It went on to state, this analysis and interpretation of a study poses a major challenge, and the conclusions become more tenuous as the extent of missingness increases. Clearly the best approach to missing data is prevention, which is also a major consideration for Novo Nordisk in all its trials.

As you can see from the right side of this slide, the completer rates were high in both LEADER and SUSTAIN 6 with vital status also available in over 99 percent of all study subjects. Achieving a high rate of retention for both trials was driven by supported, engaged, and motivated patients. Appropriate selection of centers with dedicated investigators, nurses, study coordinators, and a high level of engagement from Novo Nordisk

employees were also important.

Specifically, we focused on some key areas, including the provision of clear diabetes education and trial related information throughout the trial. We established a forum for the sharing of best practices and also set up patient support groups of patients and their caregivers.

Future discussions surrounding the design, execution, analysis, and interpretation of all trials need to take into consideration the importance of missing data and its avoidance. This should include, for example, not just large outcome trials, but also those planned to generate real-world data in local and broader populations.

For future revisions to the guidance, Novo Nordisk believes there are three scenarios that should be considered. The first scenario is if there is no suspicion of a cardiovascular safety risk based on nonclinical and phase 2 and phase 3 randomized clinical trials, cardiovascular safety should be handled in the same way as is done for all other safety signals, including cancer; that

is, based on rigorous collection of high-quality data in randomized phase 2 and phase 3 clinical trial programs.

The second scenario would be if there is a safety signal, then a well executed randomized controlled clinical outcomes trial with high rates of retention should be required in either the pre-approval or post-approval setting.

The third scenario would be demonstrating cardiovascular efficacy, and Novo Nordisk believes future revisions to the guidance should provide further information on how to establish cardiovascular efficacy. We would also advocate this event adjudication of events beyond the primary outcome should only be required if a specific safety area is identified.

Finally, it would also be helpful for the guidance to include additional information on the level of evidence required for clinically relevant confirmatory secondary endpoints to be allowed into labeling. These could include, for example, chronic kidney disease, patient-reported outcomes,

and heart failure. We believe that clinically important results should be translated into product labels for the benefits of patients based on scientific rigorous trial design and robust conduct.

To conclude, Novo Nordisk is committed to reduce the burden of diabetes and its complications by focusing on the development of more effective and safe therapies with benefits beyond A1C such as benefits on complications, including cardiovascular disease.

To this end and accepting some of the challenges now being faced in long-term outcome trials, we would like to see guidance to reflect the need for robust and rigorous trial design of all outcome trials, including cardiovascular outcomes trials. However, we support the view that the need for outcomes trials should be based upon the detection of a safety signal during the preclinical and phase 2/phase 3 program and should be handled in a similar manner for all safety signals.

We would welcome clear guidance on the level of evidence required to demonstrate safety and efficacy in order that once achieved, this can be translated into a product label. Thank you again for providing Novo Nordisk with the opportunity to speak to this important discussion.

DR. WILSON: Thank you very much. We're now hear from speaker number 3. Please approach the podium, introduce yourself, and any organization you represent.

DR. SRINIVASAN: Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivasan. I'm a physician with a master of public health from Johns Hopkins University. I'm a senior fellow of the National Center for Health Research, which analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

Thirty million Americans have type 2

diabetes and 56 percent of this population takes oral medication to try to keep it under control. As everyone here knows, there have been controversies in the past about the safety and effectiveness of some diabetes medication, and that's why it is so important to specifically evaluate the cardiovascular risks of new drugs. Evaluation of medication in high-risk populations is extremely important to provide physicians and patients with vital data to help them make informed treatment decisions.

Yesterday, Dr. Ratner suggested that funds around these cardiovascular outcome trials can be better allocated elsewhere. That reminded us that the exact same suggestion was made by many experts when the NIH decided to study the effects of hormone replacement therapy for postmenopausal women more than two decades ago.

The experts all said, we know hormone therapy helps women feel young and healthy, so the funding that would be used to study what we already know would do more good elsewhere. But much to

everyone's shock, the Women's Health Initiative study found the hormone therapy has serious risks that outweighed the benefits for postmenopausal women. The study was stopped early, prescriptions reduced dramatically, and the research has been credited with saving thousands of women's lives. That's why clinical trials and other types of solid scientific research are so important.

We discussed these research issues yesterday with Dr. Rita Redberg, who is a nationally respected cardiologist as well as the editor for JAMA Internal Medicine. She stated that it isn't a good idea to rely on previous studies, especially ones that are several years old because the treatment of diabetes and cardiovascular disease have changed so much and will continue to change in the years to come. She pointed out that the cardiovascular disease is the leading cause of death in patients with diabetes.

As is true for the women's hormones study, requiring solid evidence instead of relying on what we think we already know could save thousands of

lives. While past studies did not demonstrate a substantial increase in cardiovascular events, we cannot conclude that these drugs would not show increased risk under different conditions nor can these studies be extrapolated to new drugs even if they are on the same class.

The results of clinical trials can be greatly affected by the type of trial, the type of patients, other dietary and treatment issues, and the endpoints studied. It is also very important to note that the previous cardiovascular outcome trials found a statistically significant increased risk of hospitalization due to heart failure. This risk was identified in part because of the high-risk population studied.

I would like to emphasize again that there is much we still need to learn about cardiovascular risks associated with this class of drugs. The 2008 guidelines allow for approval of drugs with high increase in the relative risk for cardiovascular events. Drugs could potentially increase risk by as much as 80 percent and still be

approved.

Diabetes itself is associated with micro and macrovascular risk factors. If the FDA would approve drugs that exacerbate these consequences, patients would be more likely to be seriously ill and to die. Changing the premarket requirements for the potentially high risk of up to 80 percent increased risk to get approval, to instead make cardiovascular outcome trials no longer, mandatory can lead to potentially dangerous consequences.

I hope you will agree that it will be impossible to justify recommending doing away with clinical trials in order to save drug companies the cost of clinical trials. In summary, the current guidance holds the industry accountable and responsible in establishing possible cardiovascular risk associated with their medications, medications that will provide enormous profits for those companies due to a large number of patients with diabetes.

We urge the committee to keep and preferably strengthen the guidance for industry in the

evaluation of cardiovascular risks in new antidiabetic drugs rather than doing away with the requirement to test for these dangerous outcomes. Thank you.

DR. WILSON: Thank you very much. Now I'll hear from speaker number 4. Please introduce yourself and any organization you represent.

MS. FITTS: Good morning. We are all here to improve the lives of people with diabetes. My name is Emily Fitts, and I am speaking on behalf of the diaTribe Foundation, a 501(c)(3) nonprofit organization founded on that exact mission. We aim to help people with diabetes live happier, healthier, and more hopeful live and to advocate for action.

Although over one 1.5 million people have visited diatribe.org in the past 12 months and nearly 200,000 people receive our weekly newsletter, it goes without saying that the diaTribe Foundation does not represent all people with diabetes. As many of you emphasized yesterday, this is a very heterogeneous population,

and we are honored to have the opportunity to elevate the voice of people with diabetes nationally.

By way of disclosure, there are multiple for-profit and nonprofit organizations that donate to our foundation, including several that have taken on CVOTs. The diaTribe Foundation fully supported my travel to this meeting, and our full disclosures can be found on our website.

We at the diaTribe Foundation want to express great appreciation for FDA's commitment to incorporate patient input, representation, and participation. Thank you for prioritizing this important issue and for bringing together this extraordinary group to examine our collective efforts to improve the lives of people with diabetes.

Over the past 10 years, we have learned a great deal from CVOTs that we probably would not have learned otherwise. In particular, these trials and subsequent findings have been crucial in raising awareness of cardiovascular risk in people

with diabetes and in significantly improving safety data beyond cardiovascular events.

It was not until I experienced watching the live readouts of the LEADER trial during ADA scientific sessions in New Orleans, on my 6th day on the job in 2016, that I began to understand the connections between diabetes and cardiovascular disease. In fact, when my grandmother, who has had relatively well controlled type 2 diabetes for over two decades, had a minor heart attack last fall, none of my family members nor her doctors in the hospital attributed the event to her diabetes.

Our current culture does not promote a focus on heart disease stemming from diabetes, but the FDA has the opportunity to dramatically reduce CV risk, and as a result of the 2008 guidance, the bar is now much higher for diabetes therapies.

The mandate was undoubtedly very well intentioned. Those who developed it clearly had people with diabetes in mind. The full execution on such an ambitious, wide-reaching initiative, however, was bound to have some unintended

consequences. Most concerningly as a population, people with diabetes are not doing substantially better 10 years later, particularly in terms of access to these effective new therapies. Only 4 percent of people with type 2 diabetes take GLP-1 agonists and only 7 percent take SLGT2 inhibitors, according to a study published in Diabetes Care last year.

One reason that outcomes haven't changed, despite this new knowledge of cardiovascular and renal benefits, is that still only a small minority of people with type 2 diabetes are taking these medications. Reducing costs associated with conducting CVOTs could allow more money to be allocated to improving access, which would increase the number of people who are able to benefit from significant therapy improvements prompted by the FDA's mission to quote, "make medical products more effective, safer, and more affordable."

We understand the FDA does not have direct authority to determine pricing or reimbursement decisions, but the agency's unparalleled commitment

to prioritizing both innovation and access have substantial influence on other stakeholders. FDA plays a major role in impacting the 11 percent of people with diabetes who are lucky enough to take GLP-1 and SGLT2 medications, but there is more work to do to increase this number.

This is a multidisciplinary problem that requires a multi-stakeholder approach in order to achieve the results that the field is striving for. As Dr. John Buse wisely commented during the 2017 Keystone meeting, I think it is immoral that as a society, we mandate a certain set of trials be done from a regulatory perspective and then not require that insurance companies cover these drugs if they're shown to reduce mortality. We're not talking about reducing toenail fungus; we're talking about reducing mortality.

We look forward to working with the FDA as it continues to discuss factors that could help enable greater success and wellbeing in the health of people with diabetes. Thank you.

DR. WILSON: Thank you very much. Next,

we'll hear from speaker number 5. Please introduce yourself and any organization you represent.

DR. BJORK: Thank you for the opportunity to speak today. My name is Elizabeth Bjork. I head up cardiovascular, renal, and metabolism development at AstraZeneca. I'm also an endocrinologist by training and associate professor in medicine, and I spent 15 years taking care of patients with diabetes before joining industry.

Today, I will discuss the FDA's guidance for evaluating cardiovascular risk in patients with type 2 diabetes; ways to make CVOTs broader and more relevant to patients needs, looking at both endpoints and patient populations; as well as alternatives to do traditional CVOTs for evaluation of cardiovascular safety and efficacy more efficiently.

The FDA guidance mandating cardiovascular safety studies for all antidiabetic drugs was established in 2008 after post-approval meta-analysis suggested that the drug rosiglitazone was associated with harmful cardiovascular effects.

Since then, the data on cardiovascular outcomes with rosiglitazone have been reevaluated, and FDA has determined that rosiglitazone is not associated with any statistically significant increase in cardiovascular risk.

Results have been published for 9 CVOTs antidiabetic drugs that were initiated following the FDA guidance, and you can see them here on the right side. It is important to note that there have not been any signal of increased cardiovascular risk in the phase 3 program for any of these antidiabetic drugs, and none of the CVOTs showed an increased risk in MACE. In fact, 4 out of the 9 studies showed a cardiovascular benefit compared with placebo.

So taken together, this suggests that there's little basis for assuming that antidiabetic drugs as a rule increase cardiovascular risk. Post-approval studies to establish cardiovascular safely to therefore only be required when there is a signal of cardiovascular risk in the preclinical or clinical development program for the drug or in

any other drugs of the same class.

There are numerous antidiabetic drugs available, and most patients with type 2 diabetes in the United States are receiving treatment. But despite this, many patients still have inadequate glycemic control and increased risk of micro and macrovascular complications. In addition to cardiovascular disease, type 2 diabetes is closely linked to other metabolic diseases and conditions such as chronic kidney disease, heart failure, and fatty liver disease, and these diseases and conditions all have overlapping pathogenic mechanisms.

So a need remains for antidiabetic therapies that not only improve glycemic control and manage HbA1C but also help prevent and treat these comorbidities. But despite this and the fact that cardiovascular disease and diabetes are the number one and two threats to the U.S. population, fewer and fewer large pharmaceutical companies are developing drugs to treat type 2 diabetes and cardiovascular disease.

In the past decade, some major pharmaceutical companies, including Bristol-Myers Squibb and GlaxoSmithKline, have elected to divest or downsize their cardiovascular or diabetes divisions. It's become increasingly challenging to develop drugs for diabetes, both in terms of scientific complexity and cost. To develop better antidiabetic drugs that address the unmet needs these patients have, barriers to innovation need to be reduced and drug developers need to be encouraged to return to this field.

Antidiabetic therapies can have effects that impact not just glycemic control and Hb1C, but the range of other comorbidities such as chronic kidney disease, heart failure, fatty liver disease, and NASH. In CVOTs, for assessing the CV safety of antidiabetics, the recommended primary endpoint is MACE, and that has been used in the study today, including the 9 trials I previously showed you.

But MACE is not always the most important preventable complication in patients with type 2 diabetes and other comorbidities, and a

one-size-fits-all approach to selecting endpoints risk overlooking cardiovascular and other benefits that may be more relevant to a patient population.

So when evaluating either cardiovascular safety or cardiovascular benefits, tailoring the cardiovascular endpoints and composites to the need of a patient population, and most importantly to the mechanism of action of the drug, could better capture treatment goals and better characterize the relevant cardiovascular effects of a drug.

The fact that many antidiabetics have effects that impact the range of cardiovascular and metabolic diseases also suggest that perhaps we should rethink our approach to selecting study populations in CVOTs, whether evaluating cardiovascular safety or benefit.

Instead of selecting the patients, the study population based on the type 2 diabetes indication of a drug, selecting the study population based on the mechanism of action of a drug could allow us to evaluate the safety and benefit of that drug in a broad population that is more likely to benefit

from the drug's effects.

For example, antidiabetic therapies that ameliorate fibrosis or fat accumulation in the liver could provide benefit to patients who have NASH or fatty liver disease even if they don't have type 2 diabetes, and these patients can be included in trials alongside patients with diabetes.

We want our study populations to be as representative as possible of the patients who may later be treated with a drug in clinical practice. Looking at the study populations or the SGLT2 inhibitor, CVOT -- and that's what you have on the right-hand side -- even the study with the broadest population, our declared study, it's only representative of approximately 40 percent of the U.S. patient population with type 2 diabetes. We really need to reconsider our approaches to selecting study populations.

In summary, to evaluate the benefit-risk profile of a new antidiabetic drug, optimally, we need to both broaden the study population and consider a broader selection of endpoints and

composites.

Returning to the question at hand, when a similar cardiovascular risk cannot be ruled out based on the phase 3 program for antidiabetic therapy conducting a CVOT is one alternative, but we should consider alternatives to traditional CVOTs for evaluating CV safety in a more pragmatic and more efficient way. There are a variety of ways to do that, such as studies using real-world observational data, registry-based randomized clinical trials, or pragmatic streamlined CVOTs.

Unlike most traditional clinical trials, data from clinical registries are representative of most patients, and these can increase the generalizability and external validity of the results. I want to emphasize that the methods used should be selected based on factors such as the strength of the cardiovascular risk signal and the mode of action of the drug.

We have seen that antidiabetic drugs can improve cardiovascular outcomes in patients with diabetes, and we are only beginning to tap into

this potential. However, traditionally CVOTs are large, long, costly, and complex, and risk factors discourage patients and investigators from participating and drive developers from investing in CVOTs.

When an antidiabetic drug shows potential for cardiovascular benefit and an indication is to be sought, it is utterly important to provide robust, randomized, unbiased evidence. One way to do that is a traditional CVOT, but we should also consider alternative study designs such as pragmatic, streamlined CVOTs, registry based, randomized clinical trials that can also provide robust unbiased data that may have increased real-world applicability compared with traditional CVOTs but will significantly decrease cost and complexity.

A CVOT for an antidiabetic drug would cost around $200 [million] to $400 [million], meaning that just the 9 CVOTs for antidiabetic drugs that has been conducted today to prove cardiovascular safety have cost us $2.7 billion. We need to

encourage development of these drugs and more drugs for patients with diabetes, but we need to be smarter about how we invest these dollars to ensure that we tap the full potential of recent scientific development to help patients.

If we are to use more real-world data sources to evaluate either cardiovascular safety or benefit, more pragmatic methods of safety reporting and revised regulations are needed. For example, health authorities require reporting of suicides, suspected, unexpected, serious adverse reactions within a certain time frame. Suicide reporting includes an assessment of seriousness and causality by the investigator, neither of which are readily available for events derived from wayward data sources.

One way to streamline CVOTs is to change our approach to endpoint adjudication. Centralized, external adjudication of CV endpoints has generally been recommended with the attention of reducing bias and increasing accuracy, but external adjudication of endpoints may not actually impact

study results in any meaningful way.

The figure on the right shows a Cochrane meta-analysis of 47 randomized-controlled studies where outcomes have been assessed both on site and by external adjudicators. Treatment effect estimates for each study or generally similar regardless of whether endpoints were assessed on site or by external adjudicators, and the analysis suggested that adjudication may mainly be of value in an unblinded study, which you have on the bottom here.

External adjudication of endpoints in CVOT is complex, time-consuming, and costly. Adjudication can cost anywhere from $5 [million] to over $50 million for a single CVOT. So using investigator-assessed endpoints in double-blind trials is an opportunity to reduce cost and complexity without increasing the risk of bias.

In cases when external adjudication of endpoints is warranted, automated adjudication also using machine learning are new methods being developed that in the future could be more

efficient alternatives.

In conclusion, conducting CVOTs to evaluate the cardiovascular safety of antidiabetic therapies should no longer be a requirement. Patients with type 2 diabetes are not adequately treated with respect to HBA1C and suffer from comorbidities in addition to their diabetes. We need to reduce barriers to innovation and encourage development or new treatments to meet the needs of these patients.

To do so and to make studies more relevant to patients, alternative endpoints to MACE and alternative approaches to selecting study populations should be considered in CVOTs. We should also consider streamlined and altogether different study designs as options for evaluating both cardiovascular safety and benefit.

In the past decade, we have gained a better understanding of the comorbidities and pathogenic mechanism of diabetes, and we have seen real scientific and technology progress that has made it a possibility to address many of these needs of patients with diabetes. To make that happen, we

need to make use of what we have learned and where science and technology have taken us, and to ensure innovation and continued investment in antidiabetic drugs, we need to be much smarter about how we evaluate CV benefit and safety. Thank you for listening.

DR. WILSON: Thank you very much. Now we'll hear from speaker number 6. Please identify yourself and any organization you represent.

DR. EDELBERG: Good morning. I'm Jay Edelberg, physician scientist, internist, and cardiologist. I'm here today on behalf of Sanofi, a leading global healthcare company that develops and distributes new therapies, including products for diabetes. I'd like to offer Sanofi's perspective on the FDA position articulated in the 2008 guidance on evaluating cardiovascular risk in new therapies for type 2 diabetes. The statement today outlines and accompanies our written comment, which Sanofi submitted to the docket this week.

Sanofi appreciates that FDA recognizes, through holding this meeting and establishing a

public docket, that it is time to revisit FDA's current approach to cardiovascular risk in type 2 diabetes drugs that, as a condition of approval, sponsors of all new type 2 diabetes therapies conduct extensive pre and post-approval assessments to ensure that new products do not pose cardiovascular risk.

While the FDA has articulated their approach in guidance, in practice, these studies have become a de facto blanket requirement. For the past 10 years, with little exception, every drug product indicated for type 2 diabetes has been required to conduct these studies in a postmarketing setting.

Sanofi believes that it is time for FDA to revise this blanket requirement as it relates to antidiabetic drugs. Instead, we believe that FDA should utilize a product-specific, risk-based approach towards cardiovascular risk assessment, similar to the approach taken in other disease areas.

First, the scientific evidence shows no evidence of heightened cardiovascular safety risk

for any of the multiple drugs or drug classes of novel anti diabetics that were tested. Trials conducted over the past 10 years, in over 14 antidiabetic products, enrolling over 200,000 patients, makes clear with a high degree of certainty that these new widely prescribed medications do not increase cardiovascular risk even in patients with high baseline risk of cardiovascular disease. Relative to other therapeutic areas, there is no significant safety risk for type 2 diabetes mellitus products.

Second, Sanofi believes that the FDA currently has the statutory tools, expertise, and technology to follow risk-based, targeted approach to studying cardiovascular risk, to drugs, to treat type 2 diabetes.

Pre-approval product-specific assessments, the maturation of the Sentinel program, and risk-based use of FDA's 505(3) authority are more than sufficient to detect and respond to any potential cardiovascular risk. FDA's use of a risk-based approach has proven to be effective and

is consistent with the approach that FDA already uses to evaluate a signal potential cardiovascular risk for all new drugs.

Finally, there's an opportunity cost for these required studies, discouraging further research in type 2 diabetes and reducing patient options for choice. Regulatory requirements are routinely considered by companies when prioritizing development projects and portfolios.

The size, complexity, and length of these cardiovascular studies is demanding of the limited resources within established multinational companies and can be full and prohibitive for small, innovative biotechnology firms. Instead, FDA should be looking towards policies that encourage innovation in new antidiabetics and facilitate continued learning on drugs that are already marketed. In other words, revising the cardiovascular requirements will benefit patients.

In summary, Sanofi requests that FDA update its practices with respect to the new type 2 diabetes therapies and adopt appropriate

product-specific, risk-based approaches towards any required cardiovascular risk assessment in type 2 diabetes. Sanofi hopes that FDA finds these comments to be helpful and looks forward to continuing dialogue with FDA on this topic.

DR. WILSON: Thank you very much. Next, we'll hear from speaker number 7. Please identify yourself and any organization you represent.

DR. RIESMEYER: Good morning and thank you for the opportunity to address the committee on this important topic. My name is Jeff Riesmeyer. My colleague is Dr. Angie Bethel. We're both full-time employees for Eli Lilly and Company, working in diabetes drug development. She's an endocrinologist, and I'm a cardiologist. We've each devoted the bulk of our careers to patients in cardiovascular outcomes trials. Between us, we have studied over 85,000 patients. I'll cover the pros and cons of the 2008 CV safety guidance, then Dr. Bethel will address our proposal for improvement.

The 2008 FDA guidance on CV safety was a

thoughtful approach to the lack of sufficient events to confidently assess CV safety in diabetes drug applications. It provided a pathway to accrue these events. As we look at 10 years of data, we can see positive consequences of the guidance and some less positive. Here's a list of benefits that have been covered at length previously.

CV benefits, as the effects of new diabetes therapies are better characterized than before; newer agents have not been associated with an increased risk of MACE; treatments that confer CV benefits have been identified; and finally, robust outcomes data have led to updated treatment guidelines. But there are downsides. Many of them have been covered.

This is one that I don't believe has, but I think it's an important one, that their attempts to implement the guidance have led to complicated development schemes that are vulnerable to unforeseen risks. Since this wasn't discussed yesterday, I'm going to take you into the clinical trial kitchen and show you how sausage is made.

The top of the figure is an idealized version of how the guidance might work. This scenario 1, adequate data would be generated in a meta-analysis to provide a meaningful assessment pre-approval. The studies would then be submitted, and the CVOT would continue to discharge 1.3.

In reality, because few events are actually captured in these phase 2/3 studies, the 1.8 hurdle may not have been discharged through the meta-analyses alone. This has led to complex designs with interim analyses of ongoing CVOTs as illustrated in scenario 2 in the bottom of the slide. Early unblinding of CVOTs at these interims has the potential for compromised trial conduct, and interpretability with possible impact on trial integrity delays the submission and even risks to approval.

Speaking then to the 1.3 hurdle, as it was highlighted yesterday and has been highlighted today, every new drug has been studied in a large CVOT whether or not a signal of risk existed pre-approval. The guidance stipulates that the

primary assessment be a composite MACE endpoint, a one-size-fits-all approach irrespective of the molecular profile. With MACE rates of less than 6 percent per year, large studies are needed to accrue the requisite number of events in a reasonable period of time.

To date, over 190,000 patients have been studied in type 2 diabetes mellitus CVOTs. A CVOT may cost upwards of $500 million. The question of the impact of cost to the development came up yesterday. To put this into perspective, we've recently done the math in our own development programs. The CVOT essentially doubles the cost of a diabetes program. This money could be used to fund a full phase 3 program and one of several other therapeutic areas.

The cost of the guidance, then, are not only measured in the billions of dollars spent but also in opportunities not realized, including the impact on patients, investigators, and regulators. For large companies, financial tradeoffs mean that funds may not be available to develop promising

molecules that address still unmet needs in diabetes or other diseases like cancer. As we understand from our colleagues and the public documents attached to this meeting, at smaller companies without access to necessary capital, the guidance is an absolute barrier to entry, preventing innovation.

So while the generation of longer term outcomes data has benefited patients with type 2 diabetes mellitus, the tradeoffs have been significant. There's a higher patient and regulatory burden; increased complexity of developmental programs and risks to approval; larger studies leading to increase overall development costs and longer timelines; research and development reprioritization across all therapeutic classes; and barriers entry that limit innovation.

It's time to reassess our approach to the safety of drugs for type 2 diabetes mellitus. We advocate for a new paradigm. Yesterday, Dr. Archdeacon mentioned another guidance. In

early 2008, prior to the advisory committee that generated the CV document, a draft guidance on diabetes drug development was issued by the FDA.

It appears that the long-range goal for this guidance was to ultimately incorporate CV safety concerns into one finalized diabetes development guidance. So the FDA already has a tool in place to direct sponsors in the new thoughtful assessment of CV risk for new diabetes drugs.

Dr. Bethel will now cover our proposal on how this guidance can be improved prior to being finalized. Thank you for your attention.

DR. BETHEL: Thank you, Jeff, and thank you for the opportunity to address the committee in this public forum. As Jeff has suggested, we do believe that the 2008 draft diabetes development guidance can form a basis to inform a new paradigm for the assessment of cardiovascular and other safety risks in the development of drugs for type 2 diabetes.

The draft diabetes development guidance has many strengths. Its phase 3 safety assessment

exceeds the ICH requirements for chronic therapies, requiring at least 2500 exposures, 13[00] to 1500 of those for at least one year, and 300 to 500 for at least 18 months.

The guidance specifies populations of interest defined by ethnicity and by age, reminding us of the importance of testing safety in geriatric patients who may have altered renal function, hypoglycemic unawareness, or other autonomic dysfunction, or who may be exposed to drug interactions with drugs used to treat other conditions.

But perhaps most importantly, this guidance defines a safety evaluation as one that should be an iterative process based on prior experience; and that experience is to be informed by preclinical findings, the mechanism of action of the drug under study, and any known toxicities either of that drug or those previously defined for the class.

In order to address the described deficiencies in the pre-2008 development programs characterized by a paucity of cardiovascular

events, we believe that the draft guidance should be strengthened by specifying inclusion of high cardiovascular risk subgroups in the longer 12- to 18-month exposure groups.

We hope to work with the agency to clarify best practices and strategies for detecting cardiovascular safety signals using routine pharmacovigilance techniques. We would continue to support robust prospective ascertainment of events using common event definitions and with independent adjudication where appropriate.

We anticipate a continued need for the use of composite outcomes to augment signal detection, and we would encourage flexibility on a case-by-case basis in defining the level of unacceptable risk rather than having prespecified thresholds for harm as has been demonstrated by the 1.3 and the 1.8 goalposts.

We believe that that threshold should be informed by multiple inputs representing the best totality of evidence at the time to include not only the raw event numbers, but any modifications

of known risk factors or changes in relevant biomarkers. And finally, we would like for the guidance to affirm the need for an appropriate cardiovascular safety evaluation, but without a requirement to demonstrate cardiovascular benefit, acknowledging that drugs that reduce blood glucose do have utility independent of their impact on the cardiovascular outcomes.

In the setting where a concerning safety signal has been identified in the pre-approval period, again, the drafts diabetes development guidance offers us advice, specifying areas of interest for all agents, including hypoglycemia, interactions with other commonly used medications, and to look for worsening of comorbid conditions.

The guidance qualifies the investigation of safety signals, indicating that further studies should occur in population enriched for risk and that the timing of that investigation, whether it is pre or post-approval, should depend on the strength and nature of the signal and whether or not that treatment offers a major therapeutic

advance.

Again, we would suggest that that guidance could be further strengthened by adhering to the principles of an individualized safety assessment; that safety assessment to be directed by what is known about the drug, the class, and the nature of the safety signal. And we hope that we'll be able to move beyond MACE as a primary outcome, whether that means revising the components of MACE perhaps to include heart failure, for example, or indeed collecting MACE outcomes as secondary outcomes in another long-term outcomes study that is under conduct.

We would like to consider with the agency alternative or multiple methodologies to collect additional safety data, again, where appropriate, moving beyond randomized-controlled trials, perhaps to consider pragmatic or real-world studies that maintain the principles of randomization or in prospective registries where safety data can be collected in large populations. And where they are robust, we would advocate the use of electronic

health records to facilitate adverse event reporting.

For absolute clarity, we do not wish to return to the pre-2008 era where there was a paucity of data available to adequately assess safety signals, but we would advocate the replacement of the current cardiovascular safety assessment guidance with this diabetes development guidance revised as described.

We believe the advantages of these revisions would prevent unnecessary patient exposure to long-term controlled studies for safety assessment when no prior risk signal has been identified, and where there is the presence of a concerning signal, it would allow greater flexibility to develop a fit-for-purpose safety assessment program, whether for a cardiovascular signal or otherwise.

Under this revised guidance, the study designs would be guided by prior knowledge, including clinical findings, method of action, or other molecule characteristics, allowing study in more relevant populations and perhaps with more

relevant endpoints. We look forward to exploring novel trial methodologies with the agency and using focus safety event collection where it's appropriate. We believe that under this guidance, studies that were done would then allow freed resources to be applied to further innovation in the field.

We thank you for your attention today and look forward to seeing how the guidance evolves.

DR. WILSON: Thank you very much. Next, we'll have speaker number 8. Please introduce yourself and any organization you represent.

MR. RENTZEPIS: Good morning. I want to thank the FDA for the opportunity to speak on this valuable and important policy for diabetes patients and healthcare providers. My name is Peter Rentzepis, and I speak as a patient advocate and aspiring physician. We all can't think the FDA enough for assembling this meeting to discuss the CVOT mandate.

In recent years, the FDA has made such strides in better engaging patients, seeking their

input, and putting their concerns at the forefront of decision making that directly affects them. Everyone in this room wants the same thing. We all want a more efficient system where money is spent on the drugs that are really going to work so that every patient has access to the most efficacious and innovative therapies with the highest degree of safety. However, it's clear that we haven't reached this goal yet.

If everyone is okay with the status quo, then we can all go home, but the status quo is not acceptable, and I would like to posit to you that the potential impact of modifying the CVOT mandate extends far beyond an effect on industry.

Ten years ago, when I was 12 years old, another aspiring doctor named Mark Yarchoan was here for the original CVOT guidance meeting. Prior to and during medical school at U Penn, Dr. Yarchoan published five peer-reviewed articles on diabetes and insulin resistance. Unfortunately, despite these accomplishments, Dr. Yarchoan elected to pursue a career in oncology, stating that

doctors in this field could help more patients faster.

Indeed, a 2007 survey published in Endocrine Practice by Mark, Kelly Close, and others investigated why medical students are not choosing to specialize in endocrinology. The first response was a perceived inability to change or impact patient behavior.

Certainly, although there are many complex elements to diabetes care systems, expensive CVOTs for therapies to which only few have access hasn't improved the situation despite bringing very valuable data to the field. As Dr. Ratner showed yesterday, no safety signals have been found. As such, I would request the FDA explore other approaches, and I hope that those not here today will have an opportunity to weigh in after the vote.

Modifying the CVOT requirement to reduce the burden of these trials and enable participation from more manufacturers in the diabetes industry would be a clear benefit from multiple

perspectives. It would incentivize bringing more therapies to market from different manufacturers and saved money could be put towards access programs, and increasingly important element of care for healthcare providers and patients.

Moreover, according to Dr. Yarchoan and Kelly's survey, changing this practice of long CVOT trials could have positive ripple effects that address the shortage of endocrinologists in the U.S. By modifying the CVOT mandate, you not only invest in innovation and access, but also in the future medical leaders who will treat patients with diabetes and lead the field during increasingly critical times.

As the diabetes epidemic continues growing, the field needs the best and brightest, such as Dr. Yarchoan, who now runs an immune oncology lab as part of his faculty and clinician role at Johns Hopkins. I thank you for considering all the factors at play as you decide how to proceed on CVOTs and whether there may be other ways to design safety trials. We are so grateful for your help.

Thank you.

DR. WILSON: Thank you very much. Now, we will hear from speaker number 9. Please introduce yourself and any organization you represent.

MS. CLOSE: Good morning. My name is Kelly Close, and I'm here representing dQ&A, a diabetes and obesity market research firm that seeks to bring patient insights to the field. By disclosure, there are multiple manufacturers and nonprofits, as well as other organizations in the field that subscribe to dQ&A's service.

What a difference a decade makes. We weren't here 11 years ago with many of you, and I don't know how often people thank you, but you deserve so much thanks. The FDA is so underfunded. What you have done in the last 11 years in bringing so many new therapies and opportunities to market for patients is a really big deal. I don't know how you have done it with such a small staff and with so much complexity. We've heard a lot of different things just this morning alone, a lot of different opinions, and we're really grateful to

you in taking these opinions into account.

Eleven years ago, the guidance did come out without input from the field. It was just a really different time. Safety was -- there were really tragic things going on, Vioxx, other controversial things. It was a different safety field, and I think we have certainly seen in diabetes over the last 11 years a lot of really good safety data come, and I'm grateful for that. But I think you made some hard decisions 11 years ago, and I just want you to know, on behalf of many patients, that we're grateful for that. I've had diabetes over 30 years.

I think that now is a different time, and I hope that when you all go away and put your heads together, I hope that you are also willing to take into account feedback from even other organizations that weren't here today, and I hope that you give time for the field to give you input and that you don't give guidance that is final without seeking input from the field.

So on that note, dQ&A published some data

earlier this year in clinical diabetes. This is one thing that I wanted to tell you about this morning. This was based on a study of 3450 patients, and really just sort of showed that patients are pretty far from feeling successful these days, and this was thousands of patients with type 2 diabetes, taking insulin and not taking insulin.

These patients shared their opinions that were particularly poor results in terms of feeling success in emotional wellbeing, complications, burden of diabetes care, family relationships, and social stigma. And that again was just published earlier this year, and you can find it online very easily. That was led by Richard Wood.

I like it that you have gone out of your way for many years to seek patient perspectives. I would just also ask, as graciously as I can -- it's hard for patients to come here. There would be many more patient groups here if we had a little bit more notice for the meeting. I don't know if it's like an FDA rule that you can only put out the

agenda 2 days ahead of time and the voting question a couple of days ahead of time. But it would be nice for us and many other stakeholders to really understand the challenges that you have so that we can give more input into that.

That's just a question. There is a conference going on right now in Boston, and I wanted to read to you a couple of the things that doctors have said there this morning.

Let's see. Christie Ballantyne [ph] in particular said, "What a difference a decade has made." And I'm looking at this slowly because I'm finding the text. So I want to quote Dr. Ballantyne.

"I used to think CVOT were a waste of time because they didn't show anything, but they've completely changed how we think about drugs and therapy. Remarkable that we're seeing the consistency in classes."

So that's two different things; one, how awesome it is; and two, it's pretty consistent. So there's a question whether or not you want to keep

doing the CVOTs at this cost.

Dr. Jay Skyler said, "The real issue I think they'll have to address is it ethical to keep people with known cardiovascular disease off of GLP-1 or SGLT2? If you do that, reduce risk, it makes it harder to show incremental benefit of what you're testing."

I love what Dr. Skyler brought up, but would that it be, if there weren't these trials, that all these patients would just get the medicines. And we also know that that's not true, and we know that there is a commissioner who really cares about access, and we know that you can do things like working with CMS as you decide what to ask the trials of the different manufacturers and things like that.

Access is the biggest problem of our time for patients, and we just really beg you to think as creatively as possible for how to do better on that front so that so many patients can be able to take advantage of all of the transformation.

This is an amazing time. There are drugs

now that reduce risk of heart attacks, strokes, severe hypoglycemia. And there are so many patients who don't know that, and there are so many doctors that don't know that. And reimbursement is such a major problem. You can have such a big impact on that. So we hope that you will take that into account.

The last thing that I just wanted to say is that there are really good models at FDA. Dr. Tatiana Prowell, as I understand it, is an oncologist and also is on staff at FDA. She said something recently in a tweet.

"To be truly transformative, new cancer therapy," -- just cancer, but this is true in diabetes as well. "To be truly transformative, new cancer therapy must be effective, safe, and within reach of every patient who needs it. I challenge any company to develop even one. Let's see what you've got."

It's amazing for us as patients to hear these challenges, and it's not just challenges to companies at all. It's also challenges to all of

the people that are making reimbursement decisions, so we hope you will take that into account. I was so excited to hear yesterday that there are other strings going on here at FDA that are looking at some of these questions.

Today's question is about CVOT; we get that. But knowing that there is a meeting coming up, I think it's next week, public workshop, clinical trials to optimize outcomes in early breast cancer, that is spearheaded by this amazing Dr. Prowell, this academic oncologist, and FDA regulator. And we really hope that you folks who are running the diabetes division can also look to see what other stakeholder opinions you can bring in because we absolutely need to look at this incredible pandemic as a group of stakeholders. Thank you very much for your consideration.

DR. WILSON: Thank you very much.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at

hand, the careful consideration of data before the committee, as well as what we heard in the public comments.

So we have two action items first, though. We had two committee members who came in shortly after the introductions.

Would they introduce themselves? That's Dr. Yanovski and Anna McCollister.

Dr. Yanovski, first?

DR YANOVSKI: Susan Yanovski, co-director, Office of Obesity Research, NIDDK, NIH.

DR. WILSON: And Ms. McCollister.

MS. McCOLLISTER-SLIPP: Anna McCollister-Slipp. I'm here as a consumer representative.

Clarifying Questions (continued)

DR. WILSON: Thanks very much.

We had a questions for the FDA from their presentations yesterday morning that we didn't get to yesterday. And I have names here, so we're going to go down and Dr. Kushner, Dr. Wang, and Dr. Rosenberg.

Dr. Kushner first, over on my left. Do you have a question? You wanted to follow-up.

DR. KUSHNER: I'm not sure they had time to do this, but I was just curious as to the effect size of the CV benefit in the trials that showed CV benefit in terms of numbers needed to treat.

DR. CHONG: So we've not looked across all the trials for that, but I can speak to one from our evaluation of the EMPA-REG OUTCOMES trial. It looked like it was about 180 to 200 patients needed to treat to reduce MACE event.

DR. WILSON: And EMPA-REG was 2 to 3. It's more than two.

DR. CHONG: The duration, I believe EMPA-REG was about 2 and a half years of --

DR. LOW WANG: I think it was 2.1 years.

DR. WILSON: Anything further on that, Dr. Kushner? We only have that for one of these.

DR. CHONG: We have one of our statisticians here --

DR. WILSON: Sure.

DR. CHONG: -- who will be able to provide a

little more.

DR. WILSON: Please identify yourself for the record before you speak.

DR. ANDRACA-CARRERA: Eugenio Andraca from the Office of Biostatistics? We also have that estimate for CV death EMPA-REG, and the number needed to benefit, the estimate is about 125 with a confidence interval from 80 to about 220, for the benefit of CV death.

DR. CHONG: Thank you.

DR. WILSON: Next, Dr. Tommy Wang.

DR WANG: My question was actually answered during the subsequent discussion yesterday.

DR. WILSON: And Dr. Yves Rosenberg. He stepped out for a minute.

I have a question. In the open public hearing, reference was made to another document in 2008. Should we consider any of that as related to our discussions at hand today, this other draft document that was not directed at our question at hand?

Dr. Chong, could you provide us some

guidance on that?

DR. CHONG: Those were two guidance documents released in the same year. For purposes of our discussion today, we should really be focusing on the December 2008 CV risk guidance. The other recommendations from -- I believe it was January. February? The February 2008 draft guidance were separate considerations. However, your comments and thoughts on the December guidance will be considered, as we do need to consider at some point finalizing this 10-year-old draft.

DR. WILSON: Thank you for your response. That was not conclusive, but it's providing us -- we should specifically focus on the CVOT issues, the cardiovascular issues.

DR. CHONG: Yes. We're really interested on a focused discussion with regards to the cardiovascular safety assessment for glucose-lowering drugs.

DR. WILSON: All right. Thank you.

Dr. Rosenberg, did you have a follow-up question from yesterday, carryover?

DR. ROSENBERG: Yes, but in view of what you've said, I'm not sure it's very relevant or essential. But I think it's still important because there's a lot more that probably we can still learn from the completed studies.

The question was related to the issue of HBA1C control, or flag [ph] thereof, in those trials, and whether or not that might be related to some of the outcomes as micro or macrovascular. Given the differences that we observed, has the FDA also attempted to do some follow-up analysis to try to account for the impact of those differences, both on the level of glucose control and the level of utilization of the other hypoglycemic drugs?

DR. YANOFF: Thank you for that question. Of course, it occurred to us, and this burst throughout [indiscernible] and how the A1C changes impacted the outcomes, and we did attempt to look at that. One difficulty we encountered is that A1C data collection wasn't really rigorous. It wasn't required, to my knowledge, and there was so much missing data with regard to the A1C measurements

that we couldn't even get a good estimate of the changes between groups over time, let alone how they impacted the outcomes. The trials, unfortunately, weren't designed to look at that, and overtime we put less focus on looking at that as we saw that our analytic tools weren't sufficient and the data wasn't sufficient to assess that.

I'm looking at our statistical colleague, and it looks like they agree with what I've just informed you of.

DR. WILSON: Dr. Low Wang, did you have a follow-up question?

DR. LOW WANG: No, I actually just wanted to clarify. So the EMPA-REG was 3.1 years. I was able to look that up. So I think that was the number needed to treat, 180 to 200 over 3.1 years.

Is that correct?

DR. CHONG: I'm going to let Dr. Andraca-Carrera address that.

DR. ANDRACA-CARRERA: This is Eugenio Andraca from the Office of Biostatistics. Those

numbers were per patient year rate, per 100 patient years. So you need about 180 patient-years in the population of the trial to benefit reducing one MACE event. So that's per patient, 180 patient-years.

DR. CHONG: Thank you.

DR. WILSON: Dr. de Lemos, did you have a question?

DR. DE LEMOS: A question for the FDA. We've heard from many sponsors about the burden of these large CVOT trials as if in their discussions with the FDA, the complexity of the trial is driven by the agency in terms of monitoring, adjudication, and some of the things that may drive the cost up relative to these simple trials, and Dr. Wang made this point yesterday.

I'd love to hear your perspective on your interpretation of the guidance and the requirements for some of the bells and whistles that add complexity, but perhaps not value, specifically to adjudication and monitoring and whether that is actually a requirement or just something perceived

by sponsors.

DR. ARCHDEACON: Thanks. Prior to moving to this division, I spent a couple of years in the Office of Medical Policy where we address some of these broader questions. It is true that the CVOT guidance specifically calls out adjudication committees, so that is an element of the standing guidance.

The rest of the issues that you're bringing up, though, and specifically monitoring, are not addressed in the guidance. And FDA has in the intervening years issued new guidance, specifically on risk-based monitoring, and stated very clearly that we encourage that approach.

DR. de LEMOS: And to follow up, is there appetite at the agency -- is there a possibility that the adjudication requirements for safety trials may be considered differently than efficacy trials?

DR. ARCHDEACON: As I said, there's a specific guidance out there that discusses FDA's view on risk-based monitoring, and it would apply

to this area as well. So the whole idea of risk-based monitoring is that the definition of quality becomes tied to what is important for the question that you're asking.

So for instance, knowing what somebody's weight was on visit 17 is probably not important to answering the question, so that would be factored into the risk-based monitoring. So if we were to find that there was some deficit in terms of weight-collection data, presumably that would not affect our opinion of the overall value of the trial. However, missing MACE endpoints would be more important.

So the guidance speaks to those points. I think, to some degree, industry has looked at investment in monitoring as a type of insurance. So how much are you willing to spend on an insurance policy that you probably will never need to cash in? I think they've looked to us to give them a guarantee that if there's a problem with their data, that they won't be penalized for that. And I think we stop short of giving them a

guarantee, but we point to the guidance to say, listen, we intend to be reasonable when we are assessing the quality of your data.

DR. WILSON: Yes? Mary Thanh Hai?

DR. THANH HAI: I'd also like to point to another guidance just to answer your question whether or not FDA provides companies some direction in terms of the amount of information necessary. That guidance is actually called Determining the Extent of Safety Data Collection Needed in Late Stage Premarketing and Post-Approval Clinical Investigations.

That was published -- it's not a draft guidance; it's a final guidance. It was published in February of 2016. And it really does get to the point of there may be in situations where you are very, very targeted. You know that this trial here is designed specifically to evaluate a particular safety concern or an objective. There may be other events, particularly for a product that has already gone through a more thorough development program and has got approved, that you don't have to

collect some of the non-serious adverse events, those things.

So this guidance here actually encourages or invites companies to look at ways to be more targeted in their safety data collection.

DR. WILSON: We've earned a break. We're going to take a 15-minute break, and then we're going to come back and address the panel discussions and the voting question. So see you back in 15 minutes; that's 10:25.

(Whereupon, at 10:11 a.m., a recess was taken.)

Questions to the Committee and Discussion

DR. WILSON: Thank you very much. We're now going to proceed with the questions to the committee, and we're going to have panel discussions on three discussion topics. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

First, can we pull up discussion topic 1?

Because we're being recorded by voice, I'm going to voice out the question for those who may only have an audio recording.

Discuss the impact of the recommendations in the 2008 guidance for industry, diabetes mellitus, evaluating cardiovascular risk and new antidiabetic therapies to treat type 2 diabetes on the assessment of cardiovascular risk for drugs indicated to improve glycemic control in patients with type 2 diabetes.

We're open for questions, and I have one that I would put to our cardiovascular colleagues. It says the word "cardiovascular risk." It says "cardiovascular risk" twice. Would you define, in 2018 moving forward, what is cardiovascular risk?

Maybe we'll get some help from our clinical cardiologists. What would be the outcomes of specific interest moving forward? Dr. Wang?

DR. WANG: I think Dr. Everett actually articulated it yesterday. Cardiovascular disease, the way that many of us think about it, includes not just the traditional atherosclerotic events but

would include heart failure. And within that, the sclerotic events wouldn't be combined to the coronary or cerebrovascular bed but would include the peripheral arterial beds.

So to your specific question, I think the way that it's phrased here is reasonable and broad enough to allow many of the interpretations that have been raised over the last day and a half of discussions.

DR. WILSON: So as I understand it right now, to summarize a little bit what you said, it's beyond myocardial infarction and cardiovascular death. It's to also include those other outcomes: cardiac failure, stroke, and peripheral artery disease, as considerations possibly for -- there could be multiple MACE approaches is what you're saying.

DR. WANG: I would agree with that.

DR. WILSON: Any other comments? Dr. de Lemos, Dr. Burman, Dr. Blaha?

DR. BLAHA: Mike Blaha. I was going to agree, generally speaking, with what Dr. Wang said,

but I think there should be allowance for some adjustment of that endpoint based on the mechanism of action of the drug, because drugs might be more likely to have a heart failure signal or not, or drugs might be more likely to have an arrhythmic signal or something like that.

So I think the allowance to make that cardiovascular endpoint specific to the drug makes sense to me.

DR. WILSON: So if I were to interpret that one, it would be for one product, you might be interested in one MACE aggregate and in another product, or line, you might be in a slightly different composition --

DR. BLAHA: Taking heart failure, for example.

DR. WILSON: -- of the MACE.

DR. BLAHA: Yes.

DR. WILSON: Dr. Everett?

DR. EVERETT: Not to overdo this, but just to clarify, I think we talk a lot about the numbers of events. We heard 600 or so as being the key

event, and that's for a composite atherothrombotic endpoint. It would be important to structure the trials in such a way that you would not necessarily lump heart failure in as an atherothrombotic endpoint. So it would have challenges for the designs of the trial and the statistical powering of the trials, just to be clear about that.

From my perspective, I don't think it makes sense to add more endpoints to the soup, if you will. You have to be a little bit specific because the mechanisms and the pathophysiology are different. You may decide that you want to do that, but you have to at least think about it in terms of the mechanism of action of the drugs, along the lines with what Dr. Blaha said.

DR. WILSON: Dr. de Lemos?

DR. DE LEMOS: I would just say that that may differ depending on whether the primary purpose is safety and noninferiority. I would actually be comfortable with a global composite endpoint that added heart failure to a noninferiority endpoint

for safety, but obviously for efficacy, one would have to tease out what the benefit of the drug would be relative to active control or placebo.

DR. WILSON: Doctor Kushner?

DR. KUSHNER: Yes, I agree. I think we need to think about safety, and this was a guidance for safety initially. And I think that I would agree with adding heart failure, stroke, some of the other cardiovascular outcomes for safety signal, but efficacy, the trial design would probably have to vary somewhat.

DR. WILSON: Dr. Grunberger?

DR. GRUNBERGER: Not the make the soup even more complex, but there are no nephrologists here. The question is, do we consider vascular blood [indiscernible] in the kidneys, too? Because everybody's now not talking about possible effects on the current renal disease, so does that also get added as a potential endpoint?

DR. WILSON: Any other comments on kidney disease. Dr. Rosenberg?

DR. ROSENBERG: I was raising my hand to

make that same comment. I think we all know the impact of kidney disease on cardiovascular disease and diabetes. I think it's an important outcome to consider in future studies. All outcomes that are clinically relevant, whether you consider micro or macrovascular, you have to think what is clinical relevance in terms of patient outcome, both in longevity and quality of life.

DR. WILSON: If I could come back to you on that, Dr. Rosenberg, for overall safety, you would consider kidney safety. For instance, in an initial study, if a class new drug class, for instance, did not have a signal, some sort of rather simple approach to kidney disease or as an outcome would be satisfactory or you need detailed information?

I'm trying to ask you about lumping and splitting a little bit here, as you can see.

DR. ROSENBERG: I think it's a hard question to answer, generally. I think we have to move away and -- as has been suggested multiple times for the one-size-fits-all model, each drug, not only class

of drug, needs to be considered individually based on each mechanism of action, physiopathology, and then base the regulatory evaluation both on the safety as well as on the long-term efficacy evaluation.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: I wonder if I could comment on the discussion question to move away from what we've been talking about. I do think that the overall impact has been positive For diabetes care, and the climate now is very, very different from where we were about 10 or 12 years ago. We now have adequate safety data for a number of new drugs; adequate cardiovascular events to assess cardiovascular risk; very, very rigorous adjudication; and this reassurance of safety.

I think that we have also gotten data for other safety outcomes, so things like pancreatitis or other safety concerns, pancreatitis, but now we have new safety signals: amputations, heart failure, et cetera. But I think that it's unclear whether the drug development and innovation would

have occurred anyway, even without these restrictive guidelines. And I think there's been already mentioned that there were a few companies that have stopped or gotten out of this space because of the restrictions and the cost, et cetera. And there's a lot of patient time, effort, company time, effort, et cetera, that's been put into this.

So I think that overall, it's been positive, but I think it is time to start thinking further because it's really a focus on cardiovascular safety when there are so many other comorbidities to worry about.

DR. WILSON: I heard the word "mandatory" and "required" multiple times up till now in the meeting. So I think you're questioning -- that maybe others, as we go forward, could comment on those two adjectives or qualifiers, so to speak.

Next, Dr. Ellenberg?

DR ELLENBERG: As a non-diabetes expert, I have a question. We're going back and forth between safety and efficacy, and there seems to be

some outcomes where there's an expectation of efficacy, but then we worry about a safety signal.

So my question is, all these things that we've been talking about, we have heart failure, and MACE events, and other kinds of things, are they all thought to be equally better controlled? If you control hemoglobin A1C, the mechanisms of controlling A1C, should that reduce problems with -- I know it's expected to reduce cardiovascular events, but is it equally expected to reduce worsening heart failure or some of these other issues? What's the connection?

DR. WILSON: Why don't we table that for a little bit because that's a very fair question to raise. I think we would agree across the board it does for atherosclerotic MACE, but once we get outside that, we get a little bit off topic, but a very fair point to make.

Let's keep going. Dr. Wasserman?

DR. WASSERMAN: Thank you. I want to echo what Dr. Low Wang just said. I think going to what the question is, I think the impact of the

recommendations has overall been quite favorable both for patients and physicians and, in general, our medical knowledge. I do think, though, what started this over a decade ago was a safety concern, and now we've run the experiment for 10 years.

I think we've adequately addressed the hypothesis in that with over 6 classes of drugs tested, over 190,000 patients, according to some of the things I've heard, have been evaluated in these studies and at least 26 trials. We haven't seen the cardiovascular risk signal that led to this. I think, as you're hearing from a number of the different panelists, it's time for us to look at what we're trying to achieve by doing these studies, and I think the studies need to be tailored for what the actual hypothesis is as opposed to just a blanket approach.

DR. WILSON: Dr. Fradkin?

DR. FRADKIN: I agree that the impact of this has been incredibly positive in terms of the fact that it's now given us cardioprotective

agents, which we never would have known about had this policy not been put in place. But I think a negative aspect of this is that it really incentivized studying a very narrow group of patients in the large follow-on studies. The only way that you could answer this question was by limiting the study to people largely with established CVD or at very high risk. So we don't really have broad exposure to these drugs in a more generalizable population. And I think a major unanswered question is, is this cardiovascular benefit that was seen in the selected population going to be seen in the more broad population?

DR. WILSON: Ms. McCollister?

MS. McCOLLISTER-SLIPP: Of course, you come to me just as I'm taking a bite of my Chex Mix. I want to echo some of the comments that Dr. Low Wang and others have referenced. I think the impact has been significant. The knowledge that we've gained from these studies is important and helpful, and certainly has provided insights into what these new classes of drugs can do and how they benefit

patients.

There have also been cost and not just financial costs to the pharmaceutical companies. My goal in life is not to save money for pharmaceutical companies, but I do think that it's important to think more broadly of the costs, not just the pharmaceutical companies. And I do think that there should be consideration of the potential impact of that on the cost of drugs, although I don't think that there's a direct line, but also on the cost to the individuals, the number of people who have been included in the clinical trials.

I don't know if any of you have ever been a patient or participant in a clinical trial; it's incredibly time-consuming. It takes a lot of commitment. It takes a lot of time. It's not a trivial expense both economically as well as from the amount of time it takes for you, for your family member, and in some of these cases. Particularly those who have established heart disease, they probably had to be taken to the study site by family members or caregivers.

Those are not insignificant. So every time we ask somebody to participate in a trial that's kind of interesting to know about, about a very important thing, we're diverting their attention and their time away from other things, and I don't think that's an insignificant cost that should be considered.

In light of that, in light of the way that we can now get data from other sources, I think it's worth considering the broader impact and the opportunity costs that are incurred by not just the pharmaceutical companies but the individuals involved, the families of the individuals involved. We know a lot of clinical researchers who are making a lot of money off of these studies. There's a significant industry that's emerged around doing these kinds of large-scale studies.

So the impact from that perspective, from an economic perspective, is probably beneficial for many people. But from a patient perspective, as somebody who has seen my father with heart disease and the amount of time and effort it takes for him

and my mother to take him to different doctor's appointments, we really need to think very deeply about whether or not the cost benefit equation really does work on the side of patients.

DR. WILSON: Dr. Burman?

DR. BURMAN: Thank you. I wanted clarification from the committee on something that I don't quite understand, and that is, for sure the cardiovascular outcome studies have been very beneficial and useful. I don't have any question about that. But what percentage of those studies that are published now and have been completed actually had a cardiovascular signal in the phase 2 or phase 3 trials separate from the cardiovascular trial?

DR. WILSON: I'm not sure if we're going to get an answer.

Next, Dr. Wang?

DR. WANG: To Dr. Burman's question, if I understand it correctly, based on the phase 2 and phase 3 non-CVOT trials, my interpretation of the data and of the FDA presentation is that we did not

get useful information from those studies.

So to your point, if we were to go to the pre-2008 situation of relying on those studies to guide us to whether to pursue follow-up studies, they would not have provided adequate guidance because they were hopelessly underpowered.

DR. WILSON: Thanks. Dr. Newman?

DR. NEWMAN: Thank you. I wanted to thank the FDA for this 2008 guidance because it really has advanced science and medicine and improved health of our patients with diabetes. We have discovered that most of the drugs that were investigated are safe from a cardiovascular perspective, except there was one class of drugs, the DPP-4 inhibitors, where there was an increased risk of heart failure for one or two of those medicines.

Also, as a result of these trials, the guidelines of the American Diabetes Association have been changed, recommending the use of SGLT2 inhibitors and GLP-1 agonists for patients who have atherosclerotic cardiovascular disease and also

recommending SGLT2 inhibitors for patients with heart failure.

On the other hand, we have we spent, I don't know, billions of dollars on these trials, and some people have said that this money could have been used for other scientific investigations, which is true. But I want to follow on what Dr. Thanh Hai has said about the guidance from 2016 and about streamlined trials, because I been involved in several cardiovascular outcome trials of the statin class of drugs, where the trial methods have been streamlined. Sometimes we call them simple trials.

One of the things that is done is that because these drugs are already approved, we do not collect non-serious adverse events unless these adverse events are of interest to the population. Of course, serious adverse events are collected. In addition, since these trials have multi-thousands of patient's, laboratory tests are done in a random sample of patients, not in all the patients.

Finally, one of the other measures is that

we look carefully at the visits of patients, the visits needed in the trial, and follow-up is often less frequent after year 1, depending upon the patient population. So I think that we could take advantage of this and spend less money on these important trials, which give us a lot of important safety information.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: Thank you. I'm not going to come back on the positive aspect of the effect of the guidance. That's been repeated all over. I think what is much harder to evaluate is the negative impact, any potential negative impact in terms of opportunity costs that we have heard several times, especially from me and from industry about the resources diverted from other research and companies pulling out.

What we really don't know is whether or not those costs would have been invested in any useful research that led to improvement in patient outcome. If these resources had been invested in additional drug-lowering A1C without us knowing

whether or not it has any clinical outcome, that will not be very useful in my mind.

As we know by experience, a lot of investments go to these me-too drugs. So I have a little problem assessing this. What we know for sure is that trials can be made more efficient and less burdensome, both from the investigator and the patient point of view, as was just mentioned.

I also want to address the point that Dr. Fradkin raised, that we only studied a fraction of the diabetes population, and that's phase 2, and we studied practical reasons because they are high risk, and that was a way of doing these trials, the only way of doing these trials.

So that comes back to my previous point. If we make them more efficient, we could enroll more patients in a shorter period of time to study the broader population of diabetes patients. But I would argue that it's not very different from other fields, the patients of the cardiovascular field. We follow -- I think it was mentioned yesterday -- the development of

cholesterol-lowering drugs, where we started with a high-risk population and we proved the effectiveness. We want to try to broaden the indication of those drugs, and those trials were done. Now it's harder to do them.

So I think that's where we need to put our efforts, collectively, FDA investigators, and the public, into making those trials possible. It was mentioned several times that collection of adverse events and 3 phase [indiscernible] money, even more than just the endpoint education. There are areas where we really could focus and will make things happen.

DR. WILSON: Dr. Kushner?

DR. KUSHNER: I do understand the point Dr. Fradkin made about generalizability of these issues, and this is an efficacy issue. I want to thank, by the way, just in preface, the FDA for convening this panel because I think this is an important issue. I think you've done it in a very thorough way. I hope this isn't the end of this discussion because I think after we leave today,

this conversation will need to be continued and perhaps more stakeholders involved in the discussion as well, because I think there are lots of policy implications.

We're faced with this situation where I'm not sure of the mechanisms of these drugs, how they affect -- the cardiovascular outcomes that we noticed was noted in the mechanism of action of the drug. I don't think anybody picked up that the SGLT2 inhibitors would improve heart failure, or renal outcomes, or these others. So we discovered, through the CV outcomes trial, novel mechanisms of action that weren't identified in the safety lead-up studies, and this is a conundrum that we're dealing with right now.

I was going to ask Dr. Fradkin, although this population of cardiovascular patients in the diabetic population is a minority of the population, is it not true that it accounts for the majority of death and disability in that population, of the overall diabetic population?

DR. FRADKIN: Well, cardiovascular disease

accounts for two-thirds of the deaths in people with diabetes. But I think the thing that you have to remember is that diabetes is a disease that people live with for decades. These are drugs that people are going to be taking for decades also.

When Dr. Rosenberg talked about trying to streamline trials so that we could potentially involve lower-risk people so that you could follow and see what the longer term effects are on both microvascular and macrovascular complications, I wouldn't say that we should streamline them in terms of trying to make them shorter.

I really feel that getting longer term exposure to these drugs with a variety of meaningful outcomes -- because even though cardiovascular disease accounts for two-thirds of the deaths, people with diabetes care about kidney disease, and eye disease, and amputation, and depression, and bone fractures, and all of the conditions that are increased with diabetes. And in general, these things do develop over decades. So I think you really want to understand the

effects of these drugs in a meaningful time frame.

DR. WILSON: Dr. Ellenberg?

DR. ELLENBERG: It's certainly clear that these trials have been expensive. One impact we haven't really talked about is whether it's really impacted on the development of new antidiabetic therapies. Now, we saw a large number of cardiovascular outcome trials that have been reported over the last decade, but I don't know how many of the developments were already underway. They had already pretty much completed the phase 3 trials or were in process, so companies were not likely to throw that away and say, well, we're not going to do the outcome trials.

But I don't know whether there has, in fact -- it's a logical supposition that if it's going to cost more to develop these drugs, that it might slow down the development. I'm not sure that we've seen data to show that. Certainly, we've seen a number of outcome trials conducted during the decade.

DR. WILSON: Dr. Yanovski?

DR. YANOVSKI: Sure. I agree that the guidance has been extremely helpful over the past 10 years, and we've also gotten a lot of information over that time that really I think does support a more risk-based approach to requiring dedicated cardiovascular outcomes trials.

That being said, I think Dr. Wang pointed out that pre-2008, you really were willfully underpowered to see enough cardiovascular events to really even provide a strong signal. And we also heard over the past couple of days that even post-2008 guidance, the phase 2 and phase 3 trials really enroll very few higher risk people like older adults and people with preexisting cardiovascular disease.

So if we were going to go to a more risk-based approach, I think we need to revisit the idea of perhaps requiring expanded eligibility in these earlier clinical trials.

DR. WILSON: Dr. Grunberger?

DR. GRUNBERGER: Thank you. When you ask an endocrinologist the question, he or she always

begins with, "It depends." And I always tell my patients, if your doctor doesn't begin the answer to your question with, "It depends," find a different doctor.

So I'm trying to figure out here what's the impact. Dr. Burman already hinted at the fact that there was very little safety signal to begin with, and the one which started it was the consumer rosiglitazone, and as you know, FDA reconsidered that.

So the question is, when did you stop beating your wife? There was no obvious risk to begin with. Now we know, 10 years later, that no risk is still no risk, so we've proven that there's no risk; congratulations. And I'm trying to figure out was it worth it.

We talk about opportunity costs. We talk about large companies which left the diabetes field because of the potential cost of CVOTs. We'll never find out how many small companies and how many mom and pop shops decided either not to go into the business or quit when they realized the

cost. We heard about people maybe not choosing a career in endocrinology and diabetes because of these burdens.

At the same time, I'm here representing not just myself; I'm representing my patients. I'm trying to think about how did they benefit. So there's no question we have learned tons of things which we probably would not learn otherwise. The question is, has that benefited my patients? These drugs would have been approved because they lower A1C anyway. So we're in the market or we're going to be in the market anyway. So now they get to see I guess benefit commercials for Jardiance and Victoza on their TV, and they can ask me to prescribe it for them, and of course they find out it's not covered.

So I guess one of the positive things, in addition to this incredible wealth of knowledge, is that hopefully cardiologists and nephrologists are getting excited about diabetes because they would never go near diabetes before. So hopefully this is good because we can know investigate the

unexpected with SGLT2 inhibitors, the GLP-1 agonists, and maybe attracting a new generation and bright young scientists and clinical investigators who would not pick that field if it wasn't for those positive outcomes.

So again, it depends. What is the net benefit for knowledge? Amazing. Feeling safe, yes, but I was safe pretty much before that. But maybe the new knowledge will generate even more knowledge and maybe more excitement, maybe more people will pick that career, and hopefully they'll come up with more, even better drugs. So I'm closing where I began. It depends.

DR. WILSON: We're going to have three more questions, then I'm going to summarize, and we're going to move on to question 2. Some of the issues we're discussing right now, we'll get a chance again to revisit in question 3. You're not getting cut off. You're going to get more chances.

The three we have left on this are Dr. Blaha, Dr. Low Wang, and Dr. Robbins. Dr. Blaha?

DR. BLAHA: Great. Thank you. Mike Blaha. I'll make two quick points, and one of them I'm going to share with my colleague, Dr. Wang. I think it is interesting to think about, take it to its logical extension, and say, let's just say we decided to continue with the mandate to do a cardiovascular outcome safety trial. What would be the point at which we decided we'd no longer have to do that? How many trials? How many safety signals?

There has to be some endpoint at which we decide you don't need that mandate anymore. I'm just encouraging if we could think about what that would be if it hasn't been reached already.

DR. WILSON: Can we bring that back when we discuss question 3? Because that's going to be a part of 3.

DR. BLAHA: Yes. That's interesting. But I want to also make a comment on Dr. Burman's question, and then Dr. Wang's response, and to lean to Dr. Wang because we had a quick side conversation.

I think the FDA did present data -- for certain of the more recent development programs, we did have enough data in phase 2/phase 3 to exclude a 1.8 upper limit, and I'm going to let Dr. Wang comment on that.

DR. WILSON: We'll get to that in question 2, the guideposts for the cutoffs. Dr. Low Wang?

DR. LOW WANG: Actually, I wanted to comment and address Dr. Burman's question. So that's going to be addressed later as well. I don't know. Do you want me to answer that now?

DR. WILSON: We can come back. Dr. Robbins, anything?

DR. ROBBINS: Quickly, I live my life knowing that I'm getting older and hopefully wiser. And I'm walking away from this meeting feeling this since 2008, I think we are wiser, and the landscape has changed. I'd like to just throw in, too, minor ingredients into the soup here that we should consider. George brought it up briefly, but I think there is market pressure now, and it's good

business to show that the drugs prevent cardiovascular disease. And I'm not sure that the drug companies need to be prodded now. It's just good business.

The second issue -- and I think it really needs to be reemphasized -- is the resource of the electronic medical record. Both Epic and Cerner maintain an anonymized database, which literally has millions of patients in it. And I think this is something that was not available in 2008 and really, again, changes the landscape, and I think really must be taken into consideration of how we move forward and what sort of resources are available to answer these questions.

DR. WILSON: I think that was most -- Dr. Rosenberg.

DR. ROSENBERG: A clarification on something I said. I was not suggesting that we do short follow-up study. In fact, yesterday I suggested the opposite; we do long-term follow-up of our trials. I said we need to do our trials faster, complete them faster. But they need to have a long

follow-up, whether it's a trial of the observational follow-up.

Then a quick epidemiology comment, I think, where Kushner asked the question about where do the events occur, the majority of events occur with cardiovascular or in diabetes? Although the rate of events are high in people who already have a cardiac event or in diabetes, really, the vast majority of events occur in people who don't have cardiovascular events in the lower end of risk.

DR. WILSON: FDA, do you want to make a comment? Yes, go ahead.

DR. YANOFF: Very, briefly, the issue's been raised several times of the unknowns of the opportunity costs. And I wanted to recognize that the FDA nor any of the guest speakers were able to address that specifically in our presentations, and all you heard today was from the guest speakers.

I just wanted to note that, yes, we considered that, but unfortunately there isn't really a good way to assess that because it's a lack of control group, so to speak, and also trends

in the economy that occurred around 2008, as we all remember, around the time that the guidance was put into place. It's very difficult to really know what would have happened. So we don't have enough information to be able to offer a position to you on that specific question.

DR. WILSON: All right. I'm going to attempt to summarize. And this is daunting, so give me a chance here.

We started out on question 1 asking for some clarification for what were the cardiovascular endpoints of interest. The original 2008 guidance was especially directed at atherosclerotic disease, and there's much more enthusiasm now to also pay attention where it's critical and where it's appropriate for heart failure as an outcome to be included. And previous deliberations of this committee have addressed elements of this in individual trials where it's especially been relevant, but it's not part of that 2008 guidance.

We're a little less unsure what to say about some of the other outcomes. There was interest of

course for stroke, for kidney disease, and peripheral artery disease, but again, especially where there may have been prior signals and where it may be especially appropriate. So that was the first, clarifying what is cardiovascular disease.

Secondly, there was overwhelming, almost unanimous. Everybody who spoke to address the issue of where are we in 2008 applauded that the guidance has gone forward, and it's been very successful in terms of changing care and what has happened, and we've had uniformly helpful results.

One little point to add there is we now even have guidelines that endocrinologists are aware of this. In fact, it has not really permeated beyond the endrocrine literature. So only in the last weeks and months, joint groups are applauding some of the specific classes of drugs for cardiovascular prevention, and it was by dent of the 2008 studies that that has moved forward.

There have been concerns. Dr. Fradkin very eloquently said it incentivized narrow studies and we need to broaden the perspective. And that

uniformly was said in multiple voices throughout other speakers. There were concerns of costs, and costs at every level: patient costs, opportunity costs, family costs.

Our trialist expert mentioned I think very efficient trials need to be the future, less burdensome, larger and quicker. Maybe we can do in two years with more people -- if I could dovetail that -- what we used to do in four years, and perhaps using modern techniques as mentioned by others with electronic health records, registry systems, adaptable systems, using 2018 and being on technology.

Dr. Yanovski made the point of using risk-based approach. Does that mean going more narrow? We're going to come back to that in questions 2 and 3. Or does that mean being more abroad, or does that mean effectively using our populations and asking multiple questions with different parts of studies? In that element, she emphasized especially preexisting CVD, older adults, and expanded enrollment. But then

Dr. Rosenberg cautioned us that a lot of the cases are especially coming from those without preexisting CVD.

How many studies, et cetera, a variety of questions. I think I'll stop there. We're going to get to these other issues in questions 2 and 3.

Can we move forward?

(Affirmative response.)

DR. WILSON: All right. I'm going to read question 2. This has several parts. The lead-in paragraph, for each recommendation described in the 2008 guidance, discuss its value in the evaluation of the safety of new antidiabetic drugs. The recommendations we would like you to consider are, A) establishment of an independent cardiovascular endpoints committee for prospective adjudication -- LaToya, should I go through all A through D or should we go through them one at a time?

CDR BONNER: Let's go one at a time.

DR. WILSON: We should do A first?

CDR BONNER: Yes.

DR. WILSON: All right. So we're going to leave this up, and we're going to focus on A. So that means we have to -- let's keep some momentum here; we've got four parts.

Who's first? Dr. Everett?

DR. EVERETT: Brendan Everett. I think when you're considering safety of the new antidiabetic medications of a new NDA, both in the phase 2B and 3 stages of the development, as well as any potential outcome trial, whether it was a kidney disease trial or a cardiovascular outcome trial, I think you need two things.

It's not enough just to have an independent cardiovascular events committee, but you actually need to have dedicated ascertainment for the events of interest. Cardiovascular events is the subject of the day, so you have to actually ask. It's not adequate to simply collect those reports via adverse event reporting, I think, if you're really focused on this as a safety signal.

Much of the data that we saw yesterday looking at the rates of adverse cardiovascular

events and phase 2B and 3 development programs was collected via the standard AE reporting mechanisms. I think those are inherently inadequate when you're really asking a focused scientific question. So I think it behooves us to ask specifically about them, and then to have those data go to an independent committee.

While I think there is a lot of validity and truth to the idea that the PI assessing NMI [ph], yes or no, is probably correct most of the time, I worry about a potential ascertainment bias and subtle shades of unblinding during the course of the drug development process that might shade the investigator's opinion about whether or not this was truly an event.

MI is one thing, heart failure is another. Right? It's much more difficult to ascertain. And I think the other advantage having a central committee review all these events has is that they're applying the same standards across the entire trial and not a different standard in 1 of 200 or 300 recruiting sites.

That's particularly important for somebody who does this for a living. In a lot of industry and NIH-funded trials, there are lots of subtleties there, particularly with respect to cardiovascular death and lack of complete information and clinical judgments that have to be made in the course of adjudicating those events.

There's also discussion about using the phase 2B and 3 data to inform whether to move forward into a safety trial. That makes a lot of sense, except to those of us who have experienced other trials where -- I think of torcetrapib. We were talking about Vioxx earlier, where there's a potential signal of harm that's only detected when you actually do a trial large enough and long enough to detect evidence of harm.

So you have to balance the consideration for requiring that to be done in everything versus the very real likelihood that you're going to miss something when you only have 3000 patient-years of exposure as opposed to 30,000.

Lastly, related to my comments about

endpoints committees, I'm skeptical. I work with NEHR. I work with Epic. I'm pretty skeptical of its ability to accurately and adequately be used for important endpoint adjudication, particularly for heart failure. I think death would work well, potentially, although sometimes I still have patients showing up in my clinic that I know died 6 months ago from their progressive heart failure, and for some reason Epic hasn't picked that up yet.

So I think you have to be careful -- and we talk a lot about generalizability, but first and foremost is validity. You have to have validity before you can have generalizability. And without the validity of the endpoints and the approach taken there, you don't have any generalizability.

DR. WILSON: Okay. Dr. Newman?

DR. NEWMAN: I wanted to agree, now that you've spoken, with what Dr. Everett says about the need for adjudication of endpoints and the need to collect data from hospital records, et cetera, to see whether a patient has had a myocardial infarction or look at a CT scan for a stroke. But

I also wanted to say that's really important in the phase 2 and 3 programs because there are so few events.

I wanted to say something about the investigational drug torcetrapib, where the program was discontinued. There was a signal for adverse cardiovascular events in the phase 3 program. There was an increase in blood pressure of several points. I think overall it was about 5 millimeters of mercury. And despite this, the cardiovascular outcome trial was conducted. But it's possible the drug should have been conducted in a different way.

So we did see a signal. It wasn't that we saw a signal only in the outcomes trial, illuminae [ph] was seen before.

DR. WILSON: Dr. Budnitz?

CAPT BUDNITZ: Thank you. I largely agree with the points made by Dr. Everett as well, and I respect his view kind of looking under the hood of such clinical trials. Let's take a step back from an epi perspective. If we can't have the extended -- the Rolls Royce, we can have everything

we want. If you already have a randomized blinded, a prespecified endpoint with well described outcomes, maybe this is an area that you could give on a little bit, but certainly not in the setting of the phase 2 trials where you would want some kind of validation of those adverse outcomes of high interest.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I wanted to agree with Dr. Everett on that first point because I really think that there's no substitute for rigorous adjudication of cardiovascular endpoints. As you know, I'm a member of the adjudication committee that adjudicates MACE, limb, and bleeding endpoints. There's just no substitute. But I really think that that needs to be in the context of a very, very well conducted, well designed trial. The executive committee, independent DMC, high-quality trial conduct, data integrity, and a prespecified statistical plan, all of those things are important.

DR. WILSON: Any others? Dr. Robbins, go

ahead.

DR. ROBBINS: A quick question about adjudication. Can we get some data as to what percent of events that are sent to an adjudication committee are actually turned over? I think that might help us actually quantify this rather than just saying we strongly feel we should have this adjudication.

DR. WILSON: Maybe Dr. Rosenberg is going to respond to that partly. Go ahead, sir.

DR. ROSENBERG: Many NIH trials -- and it should be a trial to have adjudication. And DMC is like what Dr. Everett was saying. It depends. It varies tremendously from one trial to the other, and depends on the type of outcomes, and depends on the design of the trial. And that's really the point I wanted to make.

It really depends on the risk of bias. It's all come to that. It has been shown that if you have a blinded trial, the necessity of it just to make sure that the internal validity of the trial is preserved, the necessity that part of

[indiscernible] of adjudication is less. What you lose if you don't do it is more in terms of precision, but you're less likely to introduce bias.

I want to question, again, the fact that even in an unblinded trial, whether or not we need those systematically, we've conducted many strategy trials, like the ACCORD trial, and especially in the follow-up phase of the trial, we didn't have the resources to conduct adjudication, so we had to plan where we did 10 percent adjudication and to evaluate whether or not we see any difference. And we didn't see, so we were fine with the 10 percent adjudication.

It all depends on the quality of the design of the trial. So it's, again, a question of quality by design. If you design the trial in a way where you really minimize the risk of bias in term of ascertainment and collection of the event, the way the data on the events are collected, it's not just a passive collection based on adverse events. And if you assess whether or not there's a

potential bias early on, very often you can get rid of the systematic teach adjudication even in those circumstance.

I'm not questioning the early phase premarket approval. I'm talking about these long-term outcome trials.

DR. WILSON: Sure. Does FDA want to provide clarification?

DR. YANOFF: FDA just wants to clarify that. Yes. The question is related to the establishment of an independent cardiovascular endpoints committee for adjudication. If you could provide comment on that aspect of it, rather than the overall approach of the adjudication. And also, what's not included in the question is -- I want to emphasize this is related to a safety trial, and I know there are different considerations for efficacy and safety. If you could comment on the use of the establishment of an independent committee in the setting of the 2008 guidance and establishing non-access of cardiovascular risk.

DR. WILSON: All right. We'll keep that in

mind. We're not finished.

Dr. Wasserman, next.

DR. WASSERMAN: I just wanted to comment on I think a little bit of what Dr. Budnitz said. "It depends" to quote Dr. Grunberger, and it depends, on a large part, on what type of study you're doing. If you're doing a cardiovascular outcomes study, of course, an independent -- and it should be an independent -- cardiovascular endpoints committee makes the most sense. I do think, though, that we've spent some time in this committee talking about forward-looking opportunities of different ways of doing clinical trials.

For example, some of the work that Dr. Budnitz does in large databases may allow for an opportunity to look in a non-endpoint committee way at adjudication. And I see the faces grimacing.

I just would ask people to keep an open mind because I think this is a field that's evolving, and I think with the ability of larger and larger

data sets to look at these things, that if we were to think very futuristically, a lot of what we do on an endpoints committee is rules based and could be applied. That being said, it depends on the completeness of the data.

So I would just ask people to keep an open mind about that.

DR. WILSON: Dr. Budnitz?

CAPT BUDNITZ: Just to make a comment, I'd actually say if you use a large -- outside of a clinical trial setting, I think it's more important to have adjudication of the endpoints as opposed to in a clinical trial setting, where you have randomization and blinding and a prespecified ascertainment of an outcome, then you may not need a triple check of adjudication when biases would be ferreted out by all these other controls in the trial design.

DR. WILSON: We have a couple more questions, and we're going to close this. Dr. de Lemos?

DR. DE LEMOS: I would separate out the

absolutely prospective endpoint collection for cardiovascular endpoints and would just agree with the later people that I'm not sure that there's any evidence to support that the reclassification done by endpoint committees results in a more accurate assessment of the effects of the drug. I don't think we see that because it's an inherently subjective process, whether it's done at the investigator level or it's done in an endpoint committee.

Now, there are exceptions to that, and that would depend on endpoint by endpoint. But I think that really does represent a potential savings, but you have to have well collected endpoints not from electronic records. They have to be searched for, collected, maybe screened through some initial rules-based algorithms, and I do think you could get away without that.

DR. WILSON: Dr. Nason?

DR. NASON: I just wanted to quickly comment on Dr. Rosenberg's point, that he was focused on bias as far as adjudication and that, yes, you

could get some precision. And you sort of dismissed that, and I think when you're talking efficacy, that is something that isn't as important. But because we're talking safety here and noninferiority, precision becomes very important in the sense that if you -- this is similar to a point I tried to make yesterday and may not have succeeded fully.

But anything you can do to minimize noise will help you really figure that out, because if you're adding noise by not having precise endpoint, for instance, that will make the two groups look more similar and make you more likely to declare a noninferiority even if it wasn't appropriate; just decision.

DR. WILSON: Okay. I'm going to try to summarize this quickly, and then we'll move on to part B. The interest is greatest in having valid outcomes, especially related to cardiovascular outcomes. I think there was consensus that cardiovascular endpoints should be valid and that means having good inputs to have a valid output.

Historically, this has been at the highest level with independent committees, but there is also some interest now moving forward with newer ways to collect data, to use electronic health records, and mobile devices. All the different things that we've heard about over the past couple of days is that as studies or products are moving further along in development, perhaps some of these other methods could be used efficiently.

One comment that was made also is that there's tremendous interest in increasing the pace at which medications may collect data and be sure they're safe to go forward. But there's also some signals which may take larger studies and longer. I'd like to think perhaps those are going to be less frequent adverse outcomes, but that's part of the balance that we have to face even within the cardiovascular outcome arena.

One last comment about this is some of the experts who are especially experienced have some degree of skepticism about how well we can use these newer methods. We did not have a consensus.

We have a balanced of different opinions on how this might move forward using these newer methods.

Is that all right? Can we move forward? Is that all right, a summary?

(Affirmative response.)

DR. WILSON: All right. Let's go to part B, inclusion of patients at higher risk for cardiovascular events in phase 2 and phase 3 trials to obtain sufficient endpoints to allow for a meaningful estimate of risk.

Dr. Newman?

DR. NEWMAN: Since there were so few endpoints in the phase 2 and 3 program, I think that we definitely need to include patients at higher risk. In fact, that isn't the way cardiovascular outcomes trials are designed. We look at the risk of the patients and see what we need to get a significant result. But the phase 2 and 3 program has to have these high-risk patients, I think.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: Thank you. I have to say

that in direct response to this question, I would say that this is a yes because this is important for determining cardiovascular safety in that population in a high-risk population, but it's not generalizable to the majority of patients with diabetes and also ignores other endpoints, other noncardiovascular endpoints.

So I wanted to mention that, of course, I think we all realize the pathophysiology of atherosclerosis is very different, so atherogenesis versus atherothrombosis and primary prevention versus secondary prevention. And I really don't think that this inclusion of patients at super high risk with established cardiovascular disease necessarily answers the whole question for the population.

DR. WILSON: Who's next? Dr. Fradkin?

DR. FRADKIN: I don't think it will be sufficient to get enough events, even if you include in a phase 3 study people who are at high risk, but I wonder whether the experience from general drug development in terms of drugs where

they've had a cardiovascular adverse effect, whether the combination in terms of trying to identify a safety signal could include events in a phase 3 but also risk factors.

In other words, if a drug raised your blood pressure, like Vioxx inhibitors did, or even if it perhaps led to obesity or changed your lipids in an adverse way, it might be that a safety signal could be defined both in terms of events in a phase 3 and a worst risk profile.

DR. WILSON: Dr. Grunberger?

DR. GRUNBERGER: Well, for the sake of time I say yes because the previous two speakers pretty much addressed what I was going to say, that we do need to enrich, obviously, the phase 2 and phase 3 trials in people at high risk. But also I'd like to broaden the risk collected so it's not just the very specific MACE events, but actually go broader, and not to wait for a CVOT to include these people.

DR. WILSON: Dr. Blaha? He's looking for other -- any other comments at this point?

(No response.)

DR. WILSON: Can we try to summarize this, Dr. Blaha, and then we could perhaps come back? Oh, you found what you were looking for.

DR. BLAHA: Yes. In reference -- and make sure I get this right -- to the comment, did we have enough data from the phase 2B/3 programs of certain drugs to have some assessment of cardiovascular safety, my assessment of the slides from FDA -- and I'm looking at the presentation overview of design and results of CVOTs, and I'm looking at slide 7.

My understanding, if I'm interpreting this correctly, from the dapagliflozin and canagliflozin programs, for example, and even the alogliptin program, I think there are events to exclude the 1-point upper boundary within around 100 or 200 events accrued.

I think to answer the question in some programs, was there enough data, especially the more recent development programs, to exclude a cardiovascular harm signal, I believe my answer to that is yes, in certain programs. But of course

clearly before 2008 or just after 2008, I think in the exenatide program, there were 18 events total.

But if we were to look at those slides, I think the point FDA was trying to make with this slide is that in the more recent development program, there actually was -- and in more larger phase 2B/3 programs, there was enough events to make an assessment, potentially.

DR. WILSON: So we're going to talk about the cutoffs in a little bit.

DR. BLAHA: It's a slightly different point in response to a comment that was made earlier.

DR. WILSON: Okay. Can we pull up the slide? Is that the slide you had in mind?

DR. BLAHA: You can see here, if I'm interpreting it right, in the dapagliflozin and canagliflozin phase 2/3 -- for example, on dapagliflozin 2/3 meta-analysis, there are 178 events and an upper limit of 1.09 of the confidence interval from the phase 2/3 program.

So I don't think it was exclusively true that in none of the drugs did we have data to

exclude an upper boundary of 1.8.

DR. WILSON: FDA would like to make a comment on this.

DR. ARCHDEACON: I think this speaks a little bit to what Dr. Everett was talking about earlier with regards to event ascertainment and needing to have a sense of validity before doing a deep dive. So I think while this slide seems to present all of these as similar types of data, I'm not sure that that's actually true in terms of the event ascertainment that was underlying the dapagliflozin analysis compared to the CVOT data. So I think maybe that's one caveat I'd have of interpreting the dapa data here.

DR. CHONG: I had another comment side.

Dr. Blaha, I wanted to congratulate you on a very observant eye. I was looking at this slide, too, as Dr. Wang was addressing Dr. Burman's comment. As you point out for dapagliflozin, the meta-analysis did seem to accrue enough events. I would like to remind committee members, dapagliflozin actually went through two review

cycles. The initial review did get a complete response. They did accrue additional data before they got approved.

As Dr. Thanh Hai has reminded me, the additional data was done in a slightly high-risk population of patients who all had hypertension.

DR. LOW WANG It's very helpful to know that.

DR. WILSON: Ms. McCollister?

MS. McCOLLISTER-SLIPP: One thing that I think would be important to consider -- and I as a consumer representative and a patient would love to see FDA consider or require, or consider requiring -- is the expansion of the definition for cardiovascular risk beyond MACE and potentially incentivize or encourage the collection of other markers that could potentially signal cardiovascular risk.

Given our understanding at this point and projecting two to three years ahead, our understanding and the emerging science around particular markers, I would rather see the

collection -- or rather than just looking at major cardiovascular events, the collection of data points associated with therapies, looking at things such as markers for inflammation, hypoglycemia, the impact of hypoglycemia and potential risk for cardiovascular events, and if we can see a connection there, teasing out some of the stuff that we've seen from other studies, connecting hypoglycemia with cardiovascular issues.

I think it's important to have a diverse group of people within the study population, but rather than looking specifically for people that are only cardiovascular, I think we need to look very seriously at the inclusion/exclusion criteria and make sure that the complexity of the patients within the study, and the complexity of the diagnoses and all of the different medications they take, are actually reflective of what the general population is going to be, as opposed to some of the study designs that I've seen where there's an attempt to tease out the complexity, so that when the drug actually makes it into the real market and

the real world, you're beginning to see what it looks like in real life in patients that actually reflect a broader patient population.

DR. WILSON: Tommy Wang?

DR. WANG: I just wanted to follow up on Dr. Blaha's and Dr. Chong's discussion, mainly just to clarify for my understanding. If a sponsor achieves the exclusion of the 1.3 upper bound in the premarketing studies before they've even gotten to the postmarketing phase, then that should be sufficient to meet the guidance. Is that correct?

DR. CHONG: Yes, the guidance does say if you can exclude 1.3 premarket, but that is on a composite of the harder outcomes. So sometimes we'll see them exclude 1.3 with a composite, including things like unstable angina or other components to accrue additional events. And we have examples of where that has occurred.

Semaglutide is as an example where they definitively excluded 1.3 premarket. They were not issued a postmarketing requirement. Lixisenatide is another one where they completed a

cardiovascular outcomes trial pre-approval to exclude 1.3, and they were not issued a postmarketing requirement.

DR. WILSON: Okay. Any other comments?

(No response.)

DR. WILSON: All right. I'm going to try to summarize this. The question is addressing need for patients at higher risk for cardiovascular events in phase 2 and phase 3. In general, there was enthusiasm across the board for this, but there was also balancing that not everybody is going to be at high risk, so how much is this needed? I think part of the interpretation of that is especially as a product goes further along in development.

There was interest especially in a collection of cardiovascular risk factors and a careful consideration, especially if there are signals of adverse effects. We have examples of this in the diabetes medication class, and I won't go through them. But they can be related to blood pressure signals. They can be LDL cholesterol or

other lipid signals, et cetera. The point is, if that's identified in some studies, especially within a class, as that class development goes forward, that those would be collected systematically.

There was also a comment, potentially, since there's enthusiasm about inflammation and also concern about hypoglycemia potentially, information could be collected, especially with biomarkers that may be related or for case reporting related to severe hypoglycemia.

The FDA even mentioned something that we had not mentioned so far, is that within these classes of medications, at various times, non-hard ASCBD events have been considered. We haven't really discussed that, but angina has been part of the consideration for medications as they go forward, and I would think that would be another realm of consideration. If something was good in the long term but it aggravated angina or improved angina truly remarkably, that would be of interest as well moving forward.

Let's move on, if that's okay, part 2C. 2C is exclusion of 1.8 from the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio prior to approval. I know this is hard for those who are not used to hearing these. This is the upper bound, not the 1.8 the estimate. It's whether the upper bound includes 1.8.

Do we have any comments on this? I'm glad Dr. Ellenberg raised her hand. Maybe you could even help guide us a little bit with what we're actually being asked to weigh in on, so to speak.

DR. ELLENBERG: Well, what this will mean is that your estimate of the excess risk would have to be low enough in the phase 2/3 setting that when you say, given what we observed, how big could it really be, it probably wouldn't be bigger than 1.8. So it depends on how many people you have studied, but maybe you might observe a 1.2 or a 1.3. And if there were enough people, then the upper end of the confidence interval might be under 1.8. Of course, you would hope that the estimate is actually less

than 1, meaning there's not any excess risk observed so far.

My thinking about C and D as well is that I would like to see consideration of a different paradigm for how we assess cardiovascular risk. I'm not ready to make a proposal on this, and I'm not sure it should be separate, phase 3 and then something else; but I think some consideration of how many people really should be studied, and what kinds of people, and for how long in a diabetes development program.

I do think that some simplified approaches to some studies, I think these studies would be larger, needed to be larger than what we saw prior to 2008 given the size of the population and given the different kinds of signals that we have seen. But there are a lot of considerations here.

I remember that when the FDA asked for the RECORD study to be done to clarify the rosiglitazone risk, there was a lot of concern about whether it's ethical to do a big clinical trial to see whether something's really dangerous.

In fact, that was referred to the then Institute of Medicine to consider whether this kind of study was really ethical, so it was controversial. And I do wonder if we have a signal of harm, how feasible is it going to be to then do a larger study to see whether that is borne out.

So I'm just not sure that this is the optimal paradigm and would think that needs to be re-thought.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: I wanted to echo what Dr. Ellenberg said, which is that I think that using an upper bound is a little bit too narrow, it's a little bit short-sighted. I think the initial intent was great, but I think that you can do -- as long as you study enough patients and have a large enough sample size, you could potentially exclude 1.8 but still have a point estimate that's concerning. I do think that some ways around that would be to mandate certain trial sizes, et cetera.

So looking back at the slide that was provided by the FDA yesterday in Dr. Condarco and

Dr. Niyyati's presentation, the upper bound there, the highest one was 1.5 that was quoted. Then looking also at Dr. Ratner's presentation yesterday of the subset or subgroup of patients without established cardiovascular disease in these large CVOTs, there was a wide range of patients without established cardiovascular disease, ranging anywhere from about 75 up to about 700 patients in those trials.

The upper bound of those confidence intervals of course were quite wide on certain ones because of a population of small as 75. So the upper bound for one trial was 2.46, but I think there is a concerning point estimate for in SAVOR-TIMI in that group of 1.3.

So I think the FDA should consider including in the new guidance the possibility of considering point estimates as well in the revised guidance.

DR. WILSON: Dr. Budnitz?

CAPT BUDNITZ: I'd just like to expand a little bit on the point that Dr. Low Wang made about the point estimate, and that's what we really

do care about. The sample size issue is one thing with this confidence interval, and that tells you how many people you have to bring to your study. But what patients care about and what we should care about, really, is the effect, and that's the point estimate, is the best estimate of that.

So what we pick as the point estimate that's of interest is depending on the incidence of the outcome for how many patients will be effective. Certainly I'd be less concerned about two [fold] or three-fold increase in risk if the incidence of the outcome of concern is a rare cancer. That's 1 in 100,000. But I would really be more concerned about maybe just a 20 percent increase if the incidence of the adverse cardiac outcome is 20 percent.

As more and more higher risk folks are going to be given the drug, then I think we have to think about it different; that there are cutoffs for what is an appropriate level of risk might change. So again, it's getting at this different paradigm for what is acceptable risk, and I think it has to be

based on incidence of the expected event.

DR. WILSON: Dr. Everett?

DR. EVERETT: I look at this question as a way for us and for the FDA to think about getting out of this current 2-stage box that we're in, where we have approval for marketing based on reduction in hemoglobin A1C and then a safety trial that is after that, typically after it's been approved for marketing. So I think there's room to think creatively about combining questions A through C here.

For example, if you had specific AEs of special interest that were cardiovascular, a specific ascertainment of those AEs that's not through a classical AE paradigm but rather through specific CRFs in trials that were enriched for patients for cardiovascular disease, and were a little bit larger and had a longer duration, and these things could potentially be required by the agency and allowed substantial enough patient follow-up, you might then be in a situation where you would be comfortable having established

cardiovascular safety if you could meet a lower bound in a one-step process.

So you have a more robust phase 2B/phase 3 development program that includes higher risk patients, follows them for longer, collects some amount of cardiovascular endpoints that gives you more certainty, in exchange you lower that 1.8 to -- I'm just going to pick a number out of the hat -- 1.5. If you want to add a point estimate threshold, too, fine. But there what you have is a one-step process or one-approval process that potentially establishes both efficacy with respect to hemoglobin A1C, assuming that's what the manufacturer is seeking, and cardiovascular safety with a reasonable degree of satisfaction.

If upon review of those data, the point estimate is above your threshold or the upper bound of the confidence limit exceeds whatever you set that to be, then you trigger a larger cardiovascular outcome trial. That might be one approach to, potentially, it's going to be more resources than is required for the current phase

2B/3 approach but less than requiring every single drug that comes through to then conduct a 10 [000] to 15,000-patient cardiovascular outcomes trial.

Just an idea as I tried to link those three questions together into a particular approach that might be more efficient. And that would potentially weave D off the program as something that you didn't have to achieve after that process.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: Basically, I agree with Brendan. He proposed an approach that is a different paradigm that was mentioned earlier that we need I think. We need to move away from this boundary-based approach of approval, especially this multi-step process that doesn't make sense, as was outlined for [indiscernible] point of view. It depends on the type of events you're considering at the incidence.

So I think we really need to have a more tailored approach based on better, earlier data. But I think what the FDA does here, usually, is they base their approval on the estimate of risk

without any specific artificial boundary. And based on the experience on multiple drugs and multiple classes, and there's not been any adverse risk, we need a different approach. It doesn't mean that there doesn't need to be a good evaluation of risk before approval, but I don't see the point of this, of this whole [ph] anymore.

DR. WILSON: Dr. de Lemos?

DR. DE LEMOS: Just to be clear, I do see the point of the rigorous -- I know I can read the tea leaves on the wall, and I see tremendous value in D, I reject the idea that I should be giving a drug to a person with cardiovascular disease based on results for lab tests only. So I'll start with that construct that I don't agree with that; that we should be entering drugs into the market that affect lab tests and no measurable clinical outcome.

Having said that, there's a lot of enthusiasm from others in the room for a more moderate approach. I will say I have little sympathy for the industry complaints about

resources. The market here is enormous, and the path to market, if we eliminate D, is extremely easy. You're fortunate in industry that you're coming to this part of the FDA and not cardiorenal. These are drugs given to patients with cardiovascular disease, and to not have to demonstrate cardiovascular outcome benefits of some sort or some clinically meaningful outcome is a low bar I think.

But having said that, I would agree with Brendan that there is a pathway forward. If D is eliminated, C must be more rigorous. There's a compromise position. I think the upper bound is reasonable because it drives event numbers, and I think that 1.8 is not sufficient to get a drug on the market for safety with 122 events.

That's not enough for any of us to be confident. And there shouldn't be a rush to get to market. We have plenty of drugs available. Why allow a drug to market before we have whatever that boundary is? Make the C boundary more rigorous, 300 events, and require that that boundary be

established either with an active control or on background therapy of drugs that have cardiovascular benefit in that population.

So if you're going to study patients with cardiovascular disease, they should be treated with either a GLP-1 agonist or an SGLT2 inhibitor, and we should know what the upper bound is relative to those agents in this population, because giving a drug that doesn't offer comparable benefit is unsafe in my view. If you're demonstrating 1.5, whatever that upper bound is, and it's not against a drug that is efficacious in that population, we can't be sure that it's actually safe to give patients that drug instead of the evidence-based one.

So I do think there's a compromised position. I'm not in favor of it. I don't think that the bar's too high. In fact, you could argue that it should be higher because the market for these drugs is enormous, and the risk of these patients is high.

DR. WILSON: We've had a lot of mission

creep into section D, so why don't we keep going a little bit more here, but can we do C and D together? If we need to, we could split them, or at least try to summarize, we'll do it, because they are very closely aligned, so to speak, at this point.

So next comment, Dr. Wang?

DR. WANG: Certainly, at least, I agree with the concepts articulated by Dr. de Lemos. A couple points; one, in fairness to the original guidance to the questions brought up earlier, this text here is a high-level summary, but the actual full guidance from the FDA does comment about the importance of point estimates and the fact that a point estimate of 1.5, even if the upper bound is less than 1.8, would not be reassuring.

These issues were not ignored by the FDA 10 years ago. That being said, I think it's certainly reasonable to consider being a little more explicit about paths to approval that might not require multiple steps and multiple stages, which is one reason I asked the question earlier. There

currently is a path to approval that's all premarket. It's just a relatively high bar. So it seems like most sponsors haven't been able to achieve that.

The second comment that I would make, again, echoing a little bit of what Dr. de Lemos pointed out, I hope most or all of us would agree that to demonstrate either safety or efficacy, we need cardiovascular events. There are no surrogates currently in this space that replace cardiovascular events. The history of surrogate endpoints in cardiovascular disease has generally been poor outside of LDL and blood pressure.

So to Dr. Ellenberg's point earlier in the discussion, hemoglobin A1C lowering is not an adequate surrogate to make any statement about the safety or efficacy of cardiovascular drugs. And to echo the comment earlier from our patient representative, while inflammatory biomarkers and other things are of great interest, they are also not adequate surrogates to comment on the cardiovascular effects of these drugs.

DR. WILSON: Dr. Ellenberg?

DR. ELLENBERG: The new paradigm that I had in mind was along the lines of what Dr. Everett suggested, larger studies premarket. And what I would hope is that those studies might be large enough to at least detect a signal, not just in safety, but in clinical efficacy; that you might have enough information that you would be able to see, perhaps not definitively, statistically significantly, but at least a trend toward improvement in reduction of cardiovascular events, or of heart failure, or of any of the other things, the whole reason we treat people for diabetes it's supposed to do to lower the risk.

That would be a complicated effort, but it's kind of hard for me to see that if there's no signal whatsoever, that there's any reduction in risk of the clinical outcomes that we're worried about with diabetes. Even if it doesn't seem to cause excess risk of cardiovascular events, it doesn't seem very exciting.

DR. WILSON: Dr Newman?

DR. NEWMAN: I have a question to clarify the guidance. Right now, it must be demonstrated that the upper bound in the phase 2 and 3 program of the two-sided 95 percent confidence interval has to be less than 1.8. Is that correct? If it's 1.9 or above, would that require another safety study before approval?

DR. CHONG: So in short, yes. That would raise concerns that either there was the potential for excess risk or that the risk had not been adequately evaluated and would mean the drug could not be approved.

DR. ELLENBERG: Right. So if we lowered that to 1.5, there would be a greater chance that drugs would require additional safety studies before approval; because I heard someone talking about lowering the upper bound to 1.5.

DR. YANOFF: I believe the comment also came along with the elimination of the 1.3, but that's really for the committee to discuss. But that's what I heard.

DR. WILSON: We'll come back to that.

Dr. Grunberger?

DR. GRUNBERGER: We heard from a lot of smart people, so there's not much more to add. I'd like to also eliminate the two different numbers there. But something bothers me, and I heard yesterday, is that the 1.8 and 1.3 were sort of arbitrary. And I didn't hear any definition why and how to inspect [indiscernible], going back to what Dr. Budnitz said about the incidence.

Also, if we include the phase 3 to include the sicker people at higher risk and actually broaden the signals or things we look at beyond just the classic MACE -- I'm just wondering, is there any way to ask clinicians and patients what kind of risk is acceptable because this is [indiscernible] statisticians.

I'm just wondering, depending on the type of risk we're discussing, shouldn't there be some point estimate on the part of people who matter, i.e., the prescribers and patients? Because there might be a willingness to accept either a high risk or maybe demand much lower risk.

So this one size fits all, which is arbitrary to begin with, sort of bothers me.

DR. WILSON: Let's hear a little bit about, D, the 1.3, and the 2-stage approach, and then try to summarize both C and D together, if that's possible. Because I think if we try to summarize C, we could repeat a lot of this discussion with D.

Is there a way to comment about the 2-stage and the two different cuts? Dr. Yanovski?

DR. YANOVSKI: I just have a broader question as we're discussing this, which is, really, what our definition is going to be of MACE, because we talked earlier about the fact that often we're using that for atherosclerotic cardiovascular disease but that we also have agreed we want to include heart failure, and we've also heard that maybe we shouldn't be folding in heart failure with our MACE definition because there could be opposite effects.

So I guess my question is, if you're talking about these, do we then have these boundaries for both heart failure or other aspects of

cardiovascular disease and traditional MACE?

DR. WILSON: Nobody's jumping to answer her questions.

Dr. Low Wang, you're next, not that you have to try to answer her question, though.

DR. LOW WANG: I do think that the heart failure and MACE endpoints are very distinct, and as we've seen, there are distinct effects of the different drugs. But I wanted to go back to a comment that Dr. Wang made, which was that the full guidance -- we're just looking at the high-level version of the guidance here, but the full guidance does mention some information about the point estimate.

I do think that the upper bound should be lowered. That's the first thing. I think that in and of itself is going to mandate larger trials, longer follow-up probably, more exposure to be able to show that, and that will also bring down the point estimate. But I do think that some information about what type of point estimate is acceptable would be important as well as guidance

from the FDA.

I know this was mentioned earlier, but in the 2008 draft guidance for development of diabetes drugs, this was also mentioned, that larger trials would likely be needed with larger exposures, longer treatment, when there's many sufficiently safe alternatives already existing.

So I think we're in that space right now where there are many safe alternatives. We have a couple that show benefit. So I think we do need these longer, larger trials, but I think that that upper bound can be lowered to do this. And I don't think we need two different ones.

DR. WILSON: Dr. Yanovski, you had one? No. Dr. Rosenberg?

DR. ROSENBERG: I think Dr. Yanovski pointed out a very important point related to defining a specific boundary, which it's a boundary for what? Can we still rely on the MACE? We're going back to the first question in the evaluation of risk. If we use a boundary, that doesn't seem to make sense. On the other hand, there are very good arguments

why you cannot necessarily put heart failure within the MACE events.

So we need a global assessment of risk, but can we use one value to have that assessment? I don't know if we can do that.

DR. WILSON: Dr. Blaha?

DR. BLAHA: It's Mike Blaha. I'll just agree with many of the things that have been said, which I think are extremely good points. I was coming on the idea of are we lowering the bar or are we raising the bar. I guess it depends on the point of view. I loved Dr. Everett's kind of quick, on the fly proposal for re-doing this, which I need to think a lot more about, but generally speaking, I agree with.

I like the idea that in premarket approval, the lower bound or whatever it is that we choose this pathway, if that bar, so to speak is raised -- they go hand in hand. If we're going to do away with the postmarket CVOT, clearly the bar for approval would have to be raised, which could be accomplished by lowering the upper bound to 1.5

or some strategy.

So I don't see it I guess as -- and I wouldn't want to ever say that we're lowering the bar for allowing drugs to come on the market. We could be changing the approach of what is the initial bar to cross and what would be the requirement for a large postmarketing study.

So I'm in favor of raising the bar at first and then maybe not requiring a CVOT afterwards, which is what Dr. Everett said. But just clarifying, I don't think any of us in the room would be comfortable with saying we're going to lower the bar for access of these drugs to the market.

DR. WILSON: Dr. Everett?

DR. EVERETT: I just wanted to respond or echo Dr. de Lemos and Dr. Wang's comments earlier because I think, in general, we agree. What I will say is that I've taken hemoglobin A1C as a lab test that is a defined and appropriate surrogate outcome for retinopathy and nephropathy for patients with diabetes. So I view it -- I guess, on the advice

of my endocrinology colleagues and on the fact that the FDA is very firm and its position that we're not to discuss; that's inviolate at this point -- much like LDL and blood pressure in the cardiovascular realm. And I'm, just for the sake of argument, taking that at face value.

I will say that when I've sat on this committee and we've considered agents for LDL reduction -- before I get there, I want to say that I also think it's important not to have -- we had many beautiful figures about the varieties and types of morbidity that patients with diabetes face, and to solely drive treatment options based on nephropathy and retinopathy to the exclusion of macrovascular disease, or for that matter to chronic kidney disease, which has come up as well a number of times, is I think short sighted.

So I would hope that the trials in this 10-year experience has opened Pandora's box, if you will, where the market will demand that you have drugs that actually affect heart failure risk; that affect cardiovascular mortality; that affect

atherothrombotic events in order to actually gain any market share. And to what extent the FDA should serve as the gatekeeper to that market I think is an important question.

In particular, I think when we've considered other drugs that have lowered surrogate endpoints, LDL cholesterol, what we've considered is unmet clinical need. So if there is a significant unmet clinical need that's in the marketplace, then maybe we're more willing to approve a drug based on its effect on a surrogate endpoint than if there's not an unmet clinical need.

Now, if I ask my endocrine colleagues, there's always a need for more glucose-reducing agents. As a cardiologist, I don't necessarily see it that way. I see an array of drugs with names that I can barely pronounce and a wide array of classes and agents within individual classes, and there doesn't seem to be, as James put it, an urgent need to approve more drugs in an already expansive armamentarium.

So that would give me some pause about sort

of rushing through a number of NDAs just based on the surrogate endpoint of hemoglobin A1C without demonstrated benefit in other key important categories of disease risk for patients with diabetes, macrovascular disease, chronic kidney disease, et cetera.

So that's I guess to agree and perhaps differ a little bit with what Dr. de Lemos said earlier

DR. WILSON: Dr. Nason?

DR. NASON: I agree with much of what's been said, and I won't go back through it. I do agree on this idea of flexibility and some of the differences in paradigms. The one thing I wanted to point out that I don't think anyone said explicitly, at least, is one of the very early slides we had from the FDA talking about the regulatory framework states that FDA could require a post-approval study to assess known serious risk, asses signals of serious risk, or identify an unexpected serious risk when available data indicate the potential for a serious risk.

To me, it looks like the last 10 years have suggested that there's not much signal of serious risk. And based on this regulatory framework, I'm not sure that it is justified to continue with a lower bound of anything after post-approval.

Having said that, I definitely do agree that if this is dropped, more creative and especially more long-term follow-up before approval would be crucial because you'll lose this information But I've had it in my head that given this regulatory framework, I'm not sure I see that there is a compelling argument that the FDA even can -- "can" isn't the right word, but should be mandating post-approval studies at this point.

DR. WILSON: Can I try to summarize C and D? This is where there's been probably more opinions and lack of consensus than any of the topics we've had so far. But we had a few strong statements, I think, that we're encouraging. One was really questioning whether we need two different thresholds; for instance, a 1.8 upper bound before approval and 1.3; could that be consolidated? And

one, Dr. de Lemos, if we pinpoint him, said do we really even need the D, the 1.3 post-approval. Could it be simpler?

Then after those discussions, we had a fair amount of how about focusing on the number of events and the actual point estimates. And some of this, for sure, the FDA has considered since 2008. But I think we would all like to see it simpler, if possible. Should everything move forward with the current paradigm? We would endorse moving towards a simpler paradigm, not a total shift necessarily, but something simpler I think is the best way to synthesize it.

The focus is on safety. Some of the discussion got into combined safety plus efficacy, but remember, our real mandate for this meeting is safety. And some of the studies that have come before EMDAC committees have combined safety and efficacy. But the point is especially to focus on safety.

Is that a fair -- anybody want to add something? You're going to get other chances here

as we summarize moving forward, and some of this is addressed in question 3 or discussion topic 3. So let's move on to 3.

I'm sorry. Any clarifications? Dr. Fradkin, go ahead.

DR. FRADKIN: I just can't leave what Dr. Everett said.

(Laughter.)

DR. FRADKIN: I'm challenged. Blood glucose is not analogous to blood cholesterol. Nobody is hospitalized with acute elevations of blood cholesterol. Lowering blood glucose is important irrespective of the effects on long-term development of microvascular complications. People need to have their blood glucose within a safe range.

Even though there are 12 drug classes, and I too have trouble pronouncing all of the names, there is no optimal drug for every patient, and there are still a lot of patients for whom the side effects of these drugs are very challenging. And I do think we need additional options for people.

DR. WILSON: We're moving to discussion topic 3, and it's a short one, but that doesn't necessarily mean we have little to say. Discuss how cardiovascular safety findings from members of a drug class should or should not be applied to all members of the drug class. Let's start with Dr. Burman.

DR. BURMAN: Thank you. I know this is controversial. My thoughts are that drugs within the same class still have different chemical structures and have the potential to have different safety and efficacy profiles. Torcetrapib, which we've talked about, as well as other drugs illustrate that point.

The additional issue is to consider how many drugs in a given category need to be approved or evaluated to indicate the next one is likely to be safe? And that's an impossible question to answer. You have 4 drugs approved. Is the fifth one going to be the same as the earlier four? It's impossible to know. So I recommend that each drug be considered individually in a given class.

DR. WILSON: Dr. Blaha?

DR. BLAHA: Mike Blaha. In short, I just will agree with that. I did want to add to your summary in the last one. Although I think we like a simpler framework, I think we also like a simpler but flexible framework. So in some ways we'll simplify it, and in some ways it will become more flexible on a case-by-case basis. So in this simpler, flexible framework, I would say all drugs would have to pass that hurdle.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: I do want to say that I think that
we've seen very good presentations over the past couple of days about how general safety findings cannot be applied to all members of the same drug class. But I think that we've seen that there's no cardiovascular safety signal in the multiple CVOTs that have been done since the 2008 guidance.

So I actually think the answer to this is that we can apply cardiovascular safety findings as long as there are no cardiovascular safety signals

seen in the drug development program in the phase 2 and 3 trials.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: Well, that depends on what you call cardiovascular. If you extend it to heart failure or amputation, is that cardiovascular? That's a safety finding if you believe, then.

The point I wanted to make is you cannot apply the same safety criteria to the first member of a drug to the 10 members of the drug. If you have 9 that have been tested showing that they have no safety findings, even cardiovascular or otherwise, you still need to assess safety long term but not especially use the same criteria for the 10 drugs that you used for the first one.

DR. WILSON: Dr. Grunberger?

DR. GRUNBERGER: This was actually my comments. I basically agree with comments of Dr. Burman and Dr. Rosenberg, is that, number one, each of these drugs have a different molecule, so a priori, you cannot expect they have exactly the same characteristics. But I think the next one

should be informed based on the previous one. So there are specific signals or potential signals raised with one, and probably that bar should then be raised for the next guy to make sure that those safety signals are also addressed.

DR. WILSON: Ms. McCollister-Slipp?

MS. McCOLLISTER-SLIPP: I completely agree with what's been said previously. I don't think it makes any sense at all to conclude that because one particular drug in a specific class is either safe or effective, that we can assume that there's a class effect in either one direction or the other.

I'd also like to say I really hope, after we're finished discussing point 3, that we can come back to discussing the broader impact because I feel like that section of the discussion was really rushed a bit. This is an incredibly important meeting with significant implication, so I'd really like to be able to have a little bit more time to discuss the broader impact before we get to the vote. It looks like we have plenty of time left.

DR. WILSON: Dr. Wang?

DR. WANG: I just wanted to agree with the prevailing opinion that every drug should be considered on its own and to point out what I'm sure everyone probably recognizes, that we don't really understand the mechanism for the cardiovascular benefit for those drugs that look like they have cardiovascular benefit, nor of the potential harm for those drugs that might be linked with, for instance, excess heart failure.

So absent an understanding of that mechanism, it's impossible to generalize to a drug class.

DR. WILSON: Dr. Nason?

DR. NASON: I agree with what's been said, but I just wanted to say that it seems like you might make a different decision, that if there had been a safety signal from a member of the same class, that might be something you would want to take into account. Mostly people are addressing if other members of the same class had appeared to be safe, would you lower your bar? Would you need less evidence in a sense? But if it went the other

way, if there had been another member of the same class that appeared to have a cardiovascular signal, I think that might be enough to push this back into the category of something that did need a CVOT or did need extra follow-up from what you've otherwise decided it would need.

DR. WILSON: Dr. Fradkin?

DR. FRADKIN: To amplify what Dr. Wang said, in addition to not knowing the mechanism, I think what we do know about the mechanisms suggests that there would not be the same profile necessarily.

If you look at SGLT2 inhibitors, the specificity for SGLT2 versus SGLT1 can vary across the agents, and there's huge pleiotropy within the incretins in terms of both the molecules and the receptors. So I think there's a lot of reason in terms of the biology to think that they in fact would be different, potentially.

DR. WILSON: Dr. Newman?

DR. NEWMAN: I just wanted to agree that drugs in the same class differ in their safety profiles and that we have to take that into account

when we're deciding how these drugs should be used. This has been demonstrated. You can see this in the DPP-4 inhibitor class. Also, in terms of the statin class, and I'm not talking about cardiovascular safety, but other adverse events, the drugs differ in whether they cause liver problems or muscle disease.

DR. WILSON: Dr. Everett?

DR. EVERETT: Just at the risk of stating the obvious, I think the FDA and the investigators do a great job of iterating and adapting both their efficacy endpoints, as we heard yesterday from Dr. Sabatine with respect to dapagliflozin and looking for heart failure and cardiovascular death as a key primary endpoint of that trial; as well as their safety endpoints.

I would imagine that the FDA has asked them to look very carefully at peripheral artery disease and amputation in that study because of risk signals that have come from other agents within that class.

That said, I don't think you paint all of

the agents with the same brush, but you use information from agent 1 to inform your approach to testing agent 2.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: I just wanted to state that I do understand that different drugs are different. They have slightly different structures. They have sometimes other different features that make them distinct. But I think that here there's a difference between safety signals, in general, versus cardiovascular safety signals. So I think that the trials that we do have the results from, all of these CVOTs do show very, very reassuring consistency across different drugs in the same class for cardiovascular safety. But for other non-cardiovascular safety signals, they've been very different.

So looking at this discussion topic, I think here we're talking about cardiovascular safety. And to me, I think that we have enough information that the cardiovascular safety is very consistent across the classes, across the class with different

members of the same class. So I agree that the different drugs are different, that there are differences in potential hepatotoxicity, GI side effects, and other safety findings. But for cardiovascular safety in particular, I think that this has been fairly consistent.

DR. WILSON: Any more comments?

(No response.)

DR. WILSON: Everybody said that they were saying the same thing, but you all said something different.

(Laughter.)

DR. WILSON: If you take notes, you start noticing this. Dr. Wang said some of the simplest things to summarize, that each drug should be considered on its own. And I think, importantly, we lack mechanisms for the drugs that have been proven to show cardiovascular improved efficacy, reduction in events.

This is a very hot field, and we have good studies. Considering each on its own, as we move forward, we may find out much more about this

cardiovascular protection that has been observed in at least two major classes of drugs.

So many of the panel said the drugs differ. A few of the voices said for cardiovascular safety, they're more the same. I would raise the issue, for instance, though, that we've observed for the SGLT2 class, as for cardiovascular overall safety, they may be beneficial, but for peripheral artery disease/amputations, there may be adverse events.

So we have surprises, so to speak, and we didn't have any great uniformity. But I would say the majority was in favor of considering drugs as individual drugs, even within the classes as a drug development is assessed and reviewed by FDA and committees, et cetera, in the future, with some element of flexibility, for sure, because some of the different endpoints beyond the simple 3-point MACE have some differences.

Is that fair enough? You get to comment, make alterations.

(No response.)

DR. WILSON: All right. We would like to

move to the voting, but Ms. McCollister-Slipp, you wanted to make a comment. Can you go ahead and make your specific comments about that? We would like to go ahead for voting, though.

MS. McCOLLISTER-SLIPP: Well, I feel like the impact discussion was pretty quickly run through, and we seem to have plenty of time. So the impact of the 2008 guidance was significant. And whatever the agency does as a result of this hearing and the additional work they're doing is also going to be significant. So I think we really need to think deeply about what are the options, where are we, and what will the impact be for whatever the agency does moving forward.

As somebody who's here as a consumer representative, as a patient, as a daughter of a patient, I think it's important to consider the impact that the agency has on setting the research agenda and the focus of both drug makers and the broader research community.

There are a lot of things that really matter to patients and people who live with the disease

beyond cardiovascular events. And there are a lot of things that can happen between the time of diagnosis, and going on these medications, and staying on them for decades, and ultimately a major cardiovascular event.

Like in the case of my father, I think his heart would probably be in much better condition if the drugs that he had been on for decades didn't cause weight gain, and he wouldn't have had osteoarthritis and had to have two different knee replacements for which he you didn't really do the exercises.

Now, is that relevant here? I would say it is relevant here because we need to think more broadly about what the impact of the agency's ability to set the research agenda and the focus is. And I'm not blaming the agency for that. I think the agency acted very responsibly in response to both the political and scientific environment at the time in 2008.

We've learned a lot. I think we have a lot more confidence in the cardiovascular safety of the

drugs that are out there, and we've learned some really interesting things that I think will be clinically beneficial. But there are lots of other things that I think we should be focusing on that ultimately have a broader longer term impact on what really matters most to patients and to the people who are impacted by patients.

These are very serious issues. Over-focusing on major cardiovascular events means that we don't focus on other things. There's also an increase in -- especially over time with this disease, there's a significant risk both in morbidity and mortality because of suicide, and alcohol related deaths, and drug addiction because there's a significant, and I would say, understudied connection between depression and mental illness. Sure, we understand what that connection is, we know that it's there, but we don't understand the mechanisms behind that connection.

I would say that would be a more useful investment, whether it's on the part of

pharmaceutical companies or the other research avenues that we have available to us. And I as a taxpayer, consumer, a patient, daughter of a patient would much rather see the agency think more broadly about the risks. And again, I'm not saying that to be critical about why the agency created this guidance. I think it made absolutely perfect sense given the environment in which it was developed, but we've come a long way in 10 years.

I think as a committee, we need to think about what sorts of guidance and counsel we can provide the agency that will give them the ability to pursue things beyond cardiovascular disease, because whether or not we choose to focus on it or not, this happens in a political environment. What we do, what we say, and the comments that are reflected give them either the ability or their permission to think more broadly than cardiovascular disease.

So yes, we're here today to talk about cardiovascular disease. I don't want to die of a heart attack. I don't want to have a major stroke.

There's a really good chance that if I live long enough that that's what's going to happen. But there are lots of other things that can take me down before that. And that's I think the way most patients who live long term with this disease think about this issue.

There are a lot of other safety concerns beyond the heart. There are a lot of things that I think we could look at. And I agree, we don't know enough about inflammatory markers and the connection to cardiovascular events at this point, but why don't we know that?

We've known that inflammation is a significant cause of -- there's a significant link to cardiovascular issues for a really long time. Why haven't we studied that more closely? Because we're only focused on major cardiovascular events. I think that's a little short-sighted, and our science and our ability to measure and assess things has moved on since then.

I would love to see the agency encourage and incentivize looking more broadly at broader markers

because we've also seen a connection between inflammatory markers and depression and mental illness and a whole range of other things that impact people who live with the disease.

I could keep going, and I won't. But I do think that what we decide today is incredibly important and impactful, not just for pharma companies that are spending $6 [billion] to $7 billion on this, but for the people who live with disease.

Heart attacks and strokes are horrible, but a lot of things are horrible with this disease. And I don't think that we as a committee should let the agency go without telling them that they need to broaden their perspective, and giving them permission and the ability to be able to do that within the environment within which they exist.

DR. WILSON: Thanks very much. Was there going to be a comment?

Mary, did you want to -- Mary Thanh Hai?

DR. THANH HAI: Yes. Thank you, and thank you for your comment there. Before you go to the

voting question, I've heard several members today and yesterday talk about mandatory required. When you go to the voting question, this is about our guidance. And I think it's important to remember that the guidance is actually allowing the agency to invoke one of our authorities under FDAAA.

I think Dr. Mason, I believe, brought that up again. I don't know if members need to understand the regulatory framework of postmarketing required studies under FDAAA. If you need to see that again once more before you look at the voting question, we can put that slide up. If you feel like you understand it, then we can pass.

DR. WILSON: Could we pull that up again?

DR. THANH HAI: That's slide number 3, I believe, from Dr. Chong's presentation yesterday. I'm not going to read it, but just so that people can see that, and then you can move over to the voting question.

(Pause.)

DR. WILSON: As I understand this, to assess known serious risk could include cardiovascular and

many other realms of complications. Or is this directed towards cardiovascular?

DR. THANH HAI: The voting question is directed towards cardiovascular. But again, it's another framework.

DR. WILSON: This framework includes the entire spectrum, so to speak.

DR. THANH HAI: It does, but the voting question is only to the cardiovascular risk guidance.

DR. DE LEMOS: Can I ask for a clarification?

DR. WILSON: I think we have a couple of requests for clarification. Dr. de Lemos?

DR. DE LEMOS: So the voting question does not involve the term "pre" or "postmarket." It just asks whether -- do you want to clarify that point? Are you specifically asking the postmarketing question or are you asking --

DR. CHONG: If you read under sub-bullet A or I guess option A of the voting question, at the very end there is a request for discussion of what

assessment would be appropriate and when it should be conducted.

DR. WILSON: Dr. Everett, you had a question?

DR. EVERETT: Just to clarify, the agency can set certain standards for safety prior to approval. The slide that you showed is for postmarketing approval, but for premarketing approval, you could establish any set of benchmarks that you felt were appropriate for efficacy and for safety.

DR. THANH HAI: Yes. That would be part of the -- under our guidance for drug development and our advice to companies as they come in during drug development.

DR. WILSON: A very simple question; is there a definition of the word "guidance" from the point of view of the FDA?

DR. THANH HAI: It depends.

(Laughter.)

DR. THANH HAI: There are several definitions or examples of it. A guidance isn't an

actual written document. It can actually be a draft guidance or a final guidance, but there's also guidances giving us advice as companies come in for milestone meetings.

DR. WILSON: But a formal FDA guidance is to guide the decision process for the FDA and a sponsor for a new product for how it should be developed to gain potential approval. It's to guide how it should go forward. That's the point. It's a guide word, not a mandated or other types.

Is that how it's understood up until now?

DR. THANH HAI: Yes. In fact, if you look at FDA guidances, these are not requirements. But in this particular instance, a PMR is a requirement.

DR. WILSON: Okay. Thank you. We're ready to move forward, I believe. Yes, Dr. Mason [sic]?

DR. NASON: It's Nason, technically, but okay.

DR. WILSON: I'm sorry. Nason.

DR. NASON: That's all right. I just wanted to clarify. Were you bringing this up because you

thought I'd misunderstood it or because other -- this regulatory framework slide. I'm sorry.

DR. CHONG: We thought you understood it.

DR. NASON: I see.

(Laughter.)

DR. CHONG: We just wanted to make sure that everybody understood what you understood.

DR. NASON: Great. I just wanted to make sure. I thought you were saying at first that I misunderstood. Thank you.

DR. WILSON: We're going to move forward. We have more comments before we move forward? No? You're done? Dr. Wang? I'm sorry.

DR. WANG: I hope this is an overkill, but since we're getting to the voting question, I just want to point out, there's a lot of discussion about the limitations of the CVOTs and things that could be done to address those, make them more cost effective and whatnot. Those all still exist within the realm of a yes vote, meaning not eliminating the guidance but keeping and modifying

the guidance to address the current limitations, which I think all people acknowledge.

So maybe that's a question. That's a clarification. Voting yes doesn't mean the guidance exists word for word the way it was written in 2008. It still allows substantial revision to it.

DR. WILSON: We're going to go to the voting question, and first you will have instructions. You have a microphone with lights on it in front of you. We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. LaToya Bonner, the DFO here, will read the vote from the screen into the

record. Next, we will go around the room, and you will each be asked to state your name and how you voted into the formal record. You can also state the reason why you voted as you did if you want. We will continue until all questions have been answered or discussed. We only have one voting question here. I'm going to read this.

Should an unacceptable increase in cardiovascular risk be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes, regardless of the presence or absence of a signal for cardiovascular risk in the development program?

If yes, provide your rationale. Include in your discussion what changes, if any, you would recommend to the 2008 guidance and why, and what kind of assessment would be appropriate and when it should be conducted.

On the other hand, if you vote no, provide your rationale. Include in your discussion what might constitute a signal of cardiovascular risks that would warrant conduct of a cardiovascular

outcomes trial or other form of cardiovascular risk assessment.

We have a question. Yes?

MS. McCOLLISTER-SLIPP: Yes. And I'm sorry. I should have asked this previously. I'm not completely sure what these questions are asking or what these two different -- I mean, this is -- and I'm not saying this to be critical of whoever wrote this, but I don't completely understand what this is asking me to vote yes or no on. So I would love to get a little bit more clarification on what yes versus no means.

DR. WILSON: We'll turn to Dr. Chong there for some help on that.

DR. CHONG: So what we're really trying to get from this question is should we be mandating these trials. And some of the additional further kind of nuances in the yes/no responses are really to understand what we need to know; when do we need to know it; and what is something that we should be concerned about in your opinion? And I recognize that a responsive yes or responsive no may

ultimately lead to you asking for the same thing.

I apologize that the language in this question is somewhat difficult to interpret.

MS. McCOLLISTER-SLIPP: So we're not voting on whether or not there should be a guidance for cardiovascular risk. We're voting on -- what are we voting on?

DR. CHONG: You could interpret the yes/no vote as yes, we need a guidance that mandates cardiovascular outcomes trials for all antidiabetic drugs, regardless of the presence or absence of a signal of cardiovascular risk in the development program. That would be one way that you could interpret the question.

MS. McCOLLISTER-SLIPP: And no would be -- if there is a signal, if we vote no, it's not like that signal is going to be ignored.

DR. CHONG: We would not be ignoring signals, no.

DR. THANH HAI: Just a hypothetical, not trying to suggest that you vote like this, it's just an example, but if you think that there should

be a mandate that there be cardiovascular outcomes trials -- and again in the preceding paragraph, "an unacceptable unacceptable increase in cardiovascular risk regardless of the presence or absence of a signal."

If you think that that should be mandated, but you think it should be changed with respect to what is currently in the guidance, then you can put that in your discussion. If you think that there should not be a mandate for it but you're still concerned that cardiovascular safety needs to be assessed -- because we still do have authority if there's a signal. That's why I wanted to bring up that slide that Dr. Nathan [sic] --

DR. CHONG: It's Nason.

DR. THANH HAI: -- sorry. I don't see your tag; that's why -- had brought up, so that you understand that we still have those authorities, and you have an opportunity to talk about what would constitute a signal for us to consider mandating a trial under FDAAA.

Does that help?

MS. McCOLLISTER-SLIPP: Yes. Thank you very much.

DR. WILSON: I think we're ready. You're going to get 15 seconds or so to vote, and then it will be closed out.

Let me clarify here. If you vote yes, that means you're saying that there is an unacceptable increase and it should be excluded. You're concerned about that. That's the bottom line as I understand it. You believe that you really do need to have these studies. If you vote no, it's the opposite of that. But what really counts when we go around is what you say and how you support how you voted. And it's a difficult question, so what you say is extremely important.

Anything further here?

(No response.)

DR. WILSON: So press the button that corresponds to your vote. Yes means that it's an unacceptable increase; should be excluded is the key thing. You have 20 seconds. Press it firmly. After you've made your selection, the light may

continue to flash, and if you're unsure of your vote or you wish to change it, please press the corresponding button again before the vote is closed.

(Voting.)

CDR BONNER: For the record, 10 yes; 9 no; zero abstain.

DR. WILSON: We're going to go around, starting with Dr. Burman, so please state your name, state how you voted, and provide a rationale, and then we'll move toward Dr. Rosenberg in this direction.

DR. BURMAN: Thank you. Ken Burman. I voted yes. A standard phase 2/3 trial for efficacy and safety is not generally adequate to detect sensitivity and specificity and to detect a relevant cardiovascular signal. I think the next issue is whether a CVOT can be appropriately modified to improve efficiency, the so-called streamline CVOT.

This issue in my view is more in inchoate. There are multiple suggestions that make sense,

including increase of high volume centers, use of mobile devices, adoption of specific endpoints, and a risk-adapted monitoring schedule, to name a few. I agree with these appropriate modifications, which will hopefully increase the efficiency and decrease costs without detracting from the high standards expected from such a trial.

In my view, there is no adequate substitution for a controlled prospective randomized, open-label study. Observational studies, meta-analyses, and chart reviews without specific definitions and adjudication seem inappropriate. Primary endpoints should include MACE, congestive heart failure, cardiovascular mortality. Consideration of secondary endpoints includes retinopathy; neuropathy, which we haven't spent much time on; chronic renal disease; quality-of-life issues; frequency and extent of hypoglycemia; and relevance regarding amputation.

I do appreciate the excellent lectures and discussions regarding both sides of the issues related to this important question. In summary,

the balance of these issues regarding the possible benefits of a controlled CVOT for each new antidiabetic agent outweighs, in my mind, the relevant issues of cost, time, and inconvenience. The CV safety of new diabetic agents is unequivocally the highest priority. Thank you.

DR. WILSON: We're going to skip for Dr. Yanovski. She has to catch some transportation. Please state your name and how you voted, and any rationale.

DR. YANOVSKI: Sure. Susan Yanovski, and I voted no. I do think that there should be a pathway to approval with the 1-stage trial for drugs that have reassuring point estimates, no signals of significant cardiovascular risk, and some reasonable upper boundary, whether that would be 1.5 or something else that's later decided.

I think to accomplish this, it's going to require larger trials with expanded eligibility to higher risk participants and likely longer follow-up to provide adequate events and also an enhanced likelihood of detecting any adverse

signals. I also do think we need to address carefully how we're going to define cardiovascular outcomes in these trials, for example, heart failure when it's not incorporated into a traditional 3-point MACE.

DR. WILSON: Thank you. Dr. Rosenberg, and let's proceed around the room.

DR. ROSENBERG: Yves Rosenberg. I voted yes. It's a yes, but it could have been a no. However, I think, as was outlined, the distinction between the two is thin. And I think the comments between the previous two members outlined these. I didn't hear major conceptual difference between the two statements. They basically requested the same thing.

I voted yes because I think this needs a strong message that we need a careful assessment of the efficacy and safety of those drugs. However, excluding risk is not necessarily a requirement for necessarily a long-term cardiovascular outcome trial. There should be a more flexible, pragmatic approach for the evaluation of risk and potential

efficacy early on in well-designed late phase 2, early phase 3 studies that encompass relevant clinical outcomes.

The problem that's been outlined is that we rely on the approval of those drugs on a surrogate endpoint that is relevant for a number of reasons, but we are very concerned about what's relevant for the patients, and that's maybe different to this. So we need to have a careful discussion about what is needed in terms of the requirement for a eliminating any safety risk, which could be a long-term potential for efficacy in terms of all the relevant clinical cardiovascular outcomes that go beyond and above the MACE that was required in the previous guidance.

DR. ROBBINS: I voted no.

DR. WILSON: Please state your name.

DR. ROBBINS: I'm David Robbins. I voted no. I think the agency and the industry should be given increased flexibility in an environment of the knowledge that we've achieved in the last 10 years and the new tools that are available to

answer these questions.

Since these are being done largely as phase 4 postmarketing studies, I think there are the tools to observe and detect these signals at the time of registration and afterwards that would result in faster drug approval, lower cost, and encouraging more innovation in the field, which is needed desperately. But I think that we all agree that safety and quality of life for our patients is paramount, and this can be achieved.

DR. WANG: This is Thomas Wang. I voted yes. I'll start by acknowledging that the CVOTs conducted since 2008 have had their limitations. These have been nicely summarized during the meeting and include the high cost of conducting these trials and the restricted generalizability to the broad population of patients with type 2 diabetes. On the other hand, I think many members of the panel agree that the information gained from these trials has been extremely important.

As new drugs are added to our armamentarium of drugs for diabetes, it's hard to imagine not

wanting to know how these drugs influence the risk of cardiovascular disease, which is certainly one of the major sources of morbidity and mortality in diabetes. Given the current state of knowledge, I don't think we have an appropriate substitute to the CVOT for generating information about the cardiovascular effects of new diabetes medications.

As discussed, hemoglobin A1C is a useful surrogate for microvascular disease but not from my macrovascular disease. We also have no other surrogates to guide us for cardiovascular, in part, because we really don't understand the mechanisms underlying either the cardiovascular benefit or risk of these medications, which may in large part be due to non-glycemic processes.

So to summarize, rather than addressing the imperfections in the current system by eliminating the guidance and returning to the pre-2008 situation, it seems preferable to focus our efforts on considering how the design of these trials and the endpoints might be improved. This might include considering more cost effective or flexible

designs, thinking about the incorporation of heart failure and/or renal endpoints, and considering alternatives to the placebo control. I would favor considering how the guidance might be modified to provide this flexibility while preserving the fundamentals of randomized allocation and adequate statistical power.

DR. ELLENBERG: Susan Ellenberg. I voted no because I am not convinced that this 2-stage approach is the right approach. I would like to see more information developed premarket and to think about whether safety signals are seen there. I think the focus on cardiovascular safety is too narrow. We've heard about a lot of other things that can happen with these drugs, and I think a broader assessment of both safety and efficacy is needed.

I think that studies that would be able to assess, for example, an effect on myocardial infarction, even, which occurs at a high enough rate, those studies would not need to be huge. They would be bigger than the pre-2008 studies, but

they wouldn't even necessarily have to be as big as some of the CVOT studies we have seen.

I do think doing studies postmarketing when safety signals are seen is going to be problematic for the reasons I said before. If all you have is a small reduction in A1C and no indication of any beneficial impact on clinical outcomes but a safety signal, I'm not sure how easy it is going to be to do another big randomized study to try and see whether that signal is real. So I think that is a problem.

By no means is my no vote indicating that I think we should go back to the way it was before 2008. I think we need more data. I think cardiovascular outcomes are clearly extremely important, but there are other outcomes that need to be factored in to the decision about whether a drug is likely to provide more benefits than harms to the population.

MR. LUMLEY: I'm Dan Lumley, and I voted yes. It was tough for me. Usually when I'm on one of these panels, it's for a drug, and it's pretty

easy. This one, I kind of felt like I had my feet planted firmly in the air the entire time. But when I heard Dr. Wang's final comment just before we voted, that pushed me over.

On a personal note, I especially enjoyed as a patient hearing Dr. Everett say he couldn't pronounce some of these generic names. There isn't a patient in and captivity that can pronounce those. But I really enjoyed listening to everybody here, very, very good. And I really enjoyed listening to people from the audience.

The last comment, I do workshops on how to conduct effective meetings in the real world. Dr. Wilson doesn't need my skills.

(Laughter.)

MS. McCOLLISTER-SLIPP: Anna McCollister-Slipp. I voted no for a variety of reasons. One is I feel like the environment that precipitated the 2008 meeting and guidance was some of the discussion around Avandia. And I wasn't that focused on it, so I'm not going to pretend to be an expert on it. But my recollection is that the

issue there wasn't that we didn't see safety signals; it was an issue that those signals were hidden. And there was a problem with transparency and ethics on the part of the company that manufactured the drug, not so much on the fact that we didn't have a sense that there could be a cardiovascular risk.

So I certainly understand why the agency took the action that it did, but that was the real issue that we -- as we're looking about how do we do policy moving forward, we had signals then. They just weren't explored, and they were buried. That to me is an issue that could be solved through other means besides requiring large-scale cardiovascular outcomes trials.

I know the agency is experimenting with the release of clinical study reports. I haven't really dug that deeply into exactly what that means and how that would work, but perhaps we could look at exploring the use of those with diabetes drugs as a way of mitigating some of the concerns around transparency.

Then ultimately, I feel, as somebody who does a lot of stuff, the digital world, and big data analytics, digital medicine, and the future and where that's going, there are a lot of different data sources that have been developed over the years, particularly in the last 10 years. And there are a lot of problems with electronic health record data.

I've seen them up close, I understand that there are significant errors involved, and there's a lot of mess. But we have gotten a lot better at cleaning, and normalizing, and curating that data. We're now able to use natural language processing to understand and structure doctor's notes.

We're getting better with using that kind of data to do secondary analysis that is truly meaningful and in many respects preferable to randomized-controlled trials. I think we need to look -- I know the agency -- I was part of the National Academy of Sciences meeting that the agency requested last year on the use of real-world evidence in evaluating drug safety. I'm not sure

where that stands at this point, but it's certainly something the agency is considering, and I think that that's something that these reviewers, the endocrinology division, should take a look at as well. Because the hope of being able to look at a broader patient population to do phase 4 analysis I think offers a lot of promise for the kinds of evaluations that need to be done in these kinds of drugs and others.

Then ultimately, there's been a lot of discussion about the interesting things that we've learned from the data that aren't related to cardiovascular outcomes necessarily, and I think that's great. I think that's really important, but I don't think it's something -- it's a nice thing that we've discovered. I don't think it's something that warrants the agency mandating these kinds of trials. I would much rather see the agency focus on other issues that I think are much more meaningful and impactful for those of us who live with the disease.

DR. NEWMAN: My name is Connie Newman, and I

voted yes with some caveats. I think sometimes there is no safety signal in phase 2 and 3 for cardiovascular risk. And because patients with diabetes have such a marked increase in risk of cardiovascular disease, it is important that we assess cardiovascular safety for these new medications.

I think it is recognized that the gold standard for assessing safety is a double-blind, placebo-controlled randomized trial, and I still maintain that is true, that you need to have randomization to reduce biases so you can interpret the results. I think placebo, as in some of these trials, can be given on top of usual care. Because these trials take such a long time and cost so much money, I recommend streamlining the trials so they collect only the data that is absolutely needed.

In making this decision to vote yes, I struggled with the data that we have from the SGLT2 inhibitors and the GLP-1 agonists because all of that data shows cardiovascular safety. And in fact, in some medications, there is a decrease in

cardiovascular risk. So I question myself as to whether if a new drug in this class was being developed, whether that drug would need to have a cardiovascular outcomes trial, and I'm not absolutely certain of the answer to that. I think we'd have to really carefully look at the phase 2 and 3 program, and we'd have to enrich the program with patients with high cardiovascular risk, so perhaps we could detect a signal.

I'm not sure if I said this already, but we need to also assess heart failure in a phase 2 and 3 and in the cardiovascular outcomes trials.

DR. DE LEMOS: James de Lemos. I voted yes. Although not the intended purpose of the guidance, the unintended consequences have changed everything in terms of our expectations of what a diabetes drug should do in patients with cardiovascular disease, and I think we can't ignore that. The landscape is different, and I agree with Dr. Wang that we have to know how new drugs perform for cardiovascular endpoints in patients with cardiovascular disease, so it's a strong yes.

I also think there's no substitute for randomization in sufficient duration and numbers of exposure so that you have adequate outcomes, but I would endorse a Dr. Everett's compromise proposal in which an upper limit confidence interval or a medium number of endpoint events around 300 would likely be suitable to exclude cardiovascular risk and also give information that sponsors could use to decide whether they would pursue a cardiovascular indication, which I think is tremendously valuable to patients with diabetes, and that can be done.

I would say that that sort of size of study and duration of exposure doesn't limit it to the narrow cardiovascular outcomes trial that people are complaining about. There's no reason why one couldn't study other relevant diabetes outcomes in the same trial and use that patient exposure to maximum benefit for scientific advancement and for patients.

These trials, I think we could eliminate the postmarketing studies altogether; that these must

be done premarket because there's no pressing need to get drugs on the market without adequate patient exposures and endpoints. And I support streamlining to modify monitoring prospective endpoint collection, but perhaps not adjudication, and the expansion of endpoints from a safety standpoint to include heart failure and peripheral arterial disease events.

CAPT BUDNITZ: Dan Budnitz. I voted no. I think that was for a triple negative; I'm not quite sure. But not because we didn't learn from the current guidelines, but just simply because I think they can be improved. I agree that the traditional phase 2 and 3 studies are often underpowered to detect small and even moderate increased risk of adverse events that are clinically relevant because of high baseline incidence, and that continues to accrue over time.

So I do support continuing to prospectively identify prespecified cardiac CV endpoints and phase 2 and 3 trials, and to be liberal in requesting follow-up studies of CV risk but may not

be necessary for drugs that show absolutely no risk or are protective, and then it's up to the company after that.

I would suggest that there is flexibility in the postmarketing studies. I won't go into all those opportunities. I think those can be discussed at other times, but I would caution on three things. One is that ICD based outcome assessment from NEHRs or other administrative data probably lack sensitivity and specificity and really do need to be validated before even considered to be used in any of these postmarketing assessments. I think registries also have problems with unmeasured confounding based on early adapter characteristics and with open trial issues as well, as well as different characteristics of the patients' prescribers.

Finally, I think folks might have heard me say this before, is more attention to studies using U.S. based patients because it's hard for me to assess what all the confounders might be or other circumstances might be for studies done outside of

the U.S. and other circumstances.

DR. WILSON: Peter Wilson. I voted yes. I voted yes because we need guidance in this field. We need updated guidance for sure, but we need guidance. I reflect when I was early in my career, we had the university group diabetes program with adverse cardiovascular events, and then we had ACCORD, and then we had the thiazolidinediones, and we continued to need guidance; especially our cardiovascular colleagues have really emphasized that. I think we need to move forward with relaxation of the rules, simplification, and flexibility. Thank you.

DR. EVERETT: My name is Brendan Everett. I voted yes. Yes, I believe an unacceptable increase in cardiovascular risk should be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes. Now, how you exclude that and what unacceptable means varies according in the eye of the beholder and can be defined by the agency. It does not have to be in a postmarketing trial as we've heard from Dr. de Lemos and others

in terms of structuring the approval process, so that it could be excluded prior to approval with the right study design, the right numbers of patients, the right patient exposure-years, and the right I guess baseline risk status of the patients.

To Dr. de Lemos' point, these assessments could happen in a study that was focused, for example, on CKD, but nonetheless, the cardiovascular endpoints could be collected and verified. It could be on a microvascular endpoint, or it could be on a quality-of-life trial. As long as you're collecting with an instrument in a questionnaire and eCRF that is specifically designed to ascertain cardiovascular endpoints and not just the standard AE reporting mechanism, I think you could fold that safety assessment into the preclinical and clinical development program of a drug prior to its approval.

I think, as others have mentioned, that randomized comparisons are essential and that double-blind randomized placebo or active-controlled comparisons are essential because

otherwise you don't get an accurate assessment of the risks and certainly the side effects of the medication.

I think longer term exposure, particularly in the development plan, is key. The idea that you could get approval with the change in a lab test for 52 weeks for a drug that is proposed to be used for decades seems outlandish, but nonetheless, it's true. And I agree and fully endorse that heart failure and peripheral artery disease are important safety and efficacy endpoints to be considered as you move forward looking at the cardiovascular safety of these drugs.

DR. FRADKIN: I'm Judy Fradkin, and I voted no, although I think there's a lot of consensus across the people who voted yes and no. I was impressed by the number of trials that have been done over the course of the past 10 years, what we've learned from them, but also the fact that we haven't seen a significant cardiovascular risk, and also that the rosiglitazone meta-analysis, which precipitated this decision has really subsequently

been called into question.

I was also influenced by the opportunity cost of these postmarketing studies, not just the economic cost to pharma so much but actually more the lack of attention to components of diabetes other than MACE, including congestive heart failure and also the lack of diversity that I think this focus on reaching a power for MACE has engendered.

I do think that we need to have attention to cardiovascular safety, and I endorse a solution such as the one proposed by Dr. Everett, where the phase 3 trials might be enlarged so that we could have a little bit more rigorous boundary than 1.3. But I would also take into account not just whether we're going to see a safety signal in terms of events in those phase 3 trials, because I don't think we're ever going to really have the power to rule out cardiovascular safety based on that, but I think many of the drugs that have subsequently been shown to have cardiovascular risk have other safety signals like changes in lipids and changes in blood pressure and weight gain. So I would try to create

a compound evaluation that would take into account whether there looked like there might be any trend in terms of events, but also changes in risk factors.

DR. BLAHA: Mike Blaha. I voted no. And whether we've learned a ton from the postmarket CVOTs, they've fundamentally changed my cardiology practice for sure. I use these drugs in my practice for cardiology patients. My vote was informed by the notion that no study to date has shown increased MACE, shown an increased signal for cardiovascular safety, making it hard to justify a mandated postmarket CVOT for all new drugs in my view.

I think reflects the fact that, as have been said, the landscape has changed. Development programs like, for example, the dapagliflozin one that I saw the data for, evolved to include higher risk patients and more events and a potential framework going forward for raising the bar a little bit in the premarket approvals to get enough safety data to feel comfortable with the one-step

approach.

Also, guidelines have changed, where those guidelines now appropriately say to use drugs with proven cardiovascular benefit first, which has raised the bar. And if a company wants a foothold now, they will need to show a CVOT benefit but that can be their choice rather than a mandate from a regulatory body.

So I favor a simple yet flexible one-step approach with a higher bar to premarket approval but without a mandatory CVOT requirement. And although he voted separately, I support the Everett approach to have premarket approval and of course still a CVOT if there's a safety signal, which all of us I think agree on.

DR. LOW WANG: My name is Cecilia Low Wang, and I voted no. Of course, I'm not proposing that we return to the pre-2008 state of affairs. I think that we need a higher bar and a lower threshold for what constitutes a cardiovascular safety signal in the drug development program. I think in terms of actual signal of cardiovascular

risk, to echo what's already been said, we need to look broader than just MACE, and also look at heart failure and possibly other outcomes, but specifically for cardiovascular MACE and CHF.

I think the upper bound should be lowered possibly to about one 1.5, given the information that we've been given over the last couple of days; possibly a point estimate threshold of about 1.2 and think about mandating a certain minimum number of events.

I think that this of course needs to have the flexibility to be modified based on the totality of evidence from phase 2 and 3 trials. The 2008 draft guidance, already mentioned before, has already required trials that are large enough to demonstrate consistency across subgroups, minimum exposure, trial duration, and longer follow-up. I think right now the draft guidance mentions a year; I think that possibly longer, 18 months to 2 years, in the phase 3 trials, so something in between where we were before 2008 versus now with the current restrictive guidance.

I think that randomized-controlled trials are absolutely critical for initial approval, but we may consider -- I'd like the FDA to consider mandating long-term cardiovascular safety studies using registries and observational data because I do think that the patients who don't have established cardiovascular disease are being missed.

DR. KUSHNER: I'm Fred Kushner. I voted yes. I think at this time there are no surrogate markers that can adequately obviate the need for real hard outcomes trials. I think that's the standard of care at this point in time. I think we need outcomes data. I think currently, as constituted, the phase 2 and 3 preapproval trials cannot adequately address safety concerns for this space.

So I'm worried, what if another new class of drugs that is not one of the drugs that have already been discussed, comes and lowers hemoglobin A1C by a certain amount and we have no data? I think that we need to have enough data, and I agree

with a hybrid approach, Dr. Everett's approach, to try to accommodate the safety signals earlier on so that a large trial like this wouldn't have to be done. But I think as currently constituted, we need outcomes trials to make sure that there's adequate safety.

DR. NASON: My name is Martha Nason, and I voted yes due to the exact wording of the question that said, should an unacceptable increase in cardiovascular risk be excluded. I felt like I had to vote yes, but of course the devil's in the details, and not only what you mean by "unacceptable increase" but what you mean by "excluded" as far as what level of certainty is malleable.

I agree with pretty much everybody around this table, certainly with Dr. de Lemos, Dr. Everett, and Dr. Low Wang, I noted particularly that I agreed. Yes, I think that cardiovascular risk needs to be looked at. I think it's important. I don't think I would keep in the guidance the post-approval CVOT, the 1.3, three

because I honestly think with the regulatory framework as it was presented to us, there's not enough of a safety concern to really justify in that particular framework a post-approval requirement.

I would hope, as other people have said, that many of these companies would want to get that information either for licensing or a label, and that would lead to the post-approval trials even possibly. Certainly if there's a signal, you would need to do it, but as far as mandating it for a drug that has no particular signal, I don't think we really have enough concern now to mandate it for a post-approval.

Having said that, I agree with all my colleagues who say, therefore, I would want more data pre-approval. I'd want more diversity in who's included. I'd want longer term follow up. I can't read my handwriting.

(Laughter.)

DR. NASON: I feel like the phase 2 and 3 information in some ways is stronger than the

postmarketing anyway, whether you're require or not, because of randomization and blinding and less drop-in and drop-out, and that it can be controlled better as far as what your information is. So I would love to see those expanded to longer term and more inclusive but not post-approval.

Then finally, the registry I think is great as far an easy way to collect data long term, but I'm always skeptical of observational data as far as the biases and the conclusions drawn from it. I would say, though, that I think it would be important to follow up trial participants because those people were randomized and were therefore on it for a long time, or at least it's been a long time since they were first offered it. So those people I would want to see included in a registry or included in that long-term follow-up, if possible.

DR. GRUNBERGER: George Grunberger, and I voted no. And I'm the last guy who stands between you and lunch. If you actually turned off the screen so you don't see how people voted, it was

fascinating. Everybody said exactly the same thing. My neighbor to the right said exactly what I'm going to say now, so I'll save you some pain. Yet, she voted yes; I voted no.

I voted no not to get rid of the guidance. I voted no not because I want to lower the bar for entering new drugs for diabetes. I voted no because what made me nervous was the same wording and reading, but it also said "regardless" of the safety signal during. So to me, that makes no sense.

To me, the idea will be, as we discussed before, to broaden the phase 2/3 trials; to broaden populations involved in those trials; to broaden the risks we're discussing. Not to repeat myself, but it should include the heart failure, and we talked about kidneys, and peripheral disease, and everything else.

So if you have more robust, larger phase 2/3 trials, as you said, you'd get probably better data. And if there's a signal, yes, then you do the dedicated trial. If there is no signal, then I

don't think there's a reason to do dedicated CVOT. But the agency should require that every patient who is prescribed the drug anywhere in the world will be followed in real time -- the methodology and technology hopefully exists -- so we don't have to rely on imperfect EMR registries, but the mandate will be that every person taking the drug will be followed in real time, and then signals, hopefully as they occur, will be reported.

Last, I will make sure that we also go on the record that I don't think we can justify doing trials now against placebo. So I think that all the trials would need to have an arm which has in it a medication which has been shown to have a cardiovascular benefit. Thank you.

DR. WILSON: Thank you all for your voting.

FDA, any final comments?

DR. CHONG: Yes. First, Dr. Grunberger, I'm the one holding you up from lunch. But I do want to thank everybody for their thoughtful consideration and discussion over the last two days. I realize we presented you with some

challenging questions, perhaps worded very confusingly, but I do appreciate all the thought that you put into it.

I'm not sure if our speakers are still here or not, but I also wanted to thank our outside speakers who presented yesterday. They provided some very good perspectives, some stark contrast, and I think that was informative both for us and for our conversation today.

You've given us a lot to think about. I also wanted to thank our public speakers who may or may not still be here. We do appreciate all that you have to add. We do consider those comments as we take back all that we've heard today.

I lost my train of thought. I probably need lunch. You've given us a lot to think about. We'll take all of this back and digest. At some point, we'll finalize that 10-year old guidance. At some point, we'll come out with what we are going to be recommending for people to do moving forward. But rest assured we are going to think

about everything that you guys have said today.

Adjournment

DR. WILSON: Thank you very much. Just housekeeping. Please take everything. Don't leave your computer plugs and your phones. You can leave your name badge here or at the check-in desk, and travel safely.

(Whereupon, at 1:23 p.m., the meeting was adjourned.)