with. If we take patients who are later on in their disease, maybe the horse is already out of the barn. It's too late to affect it or you'll cause more harm than good in people with stiff vessels who can't recuperate from an episode of hypoglycemia.

I don't know the answer, but one must understand the tradeoffs when designing the trials. Societally, obviously it would be ideal to do both because as someone has already pointed out, ignoring the 12 million people who already have cardiovascular disease and are very high risk is a terrible mistake that we've made over and over in diabetes trials up until now.

What about concomitant therapy? Should we be doing placebo or direct comparative trials? Since there's currently no proven winner in diabetes, I'll spare the jokes about diabetes. We have a lot of fun in our steering committee meetings now between diabetologists and cardiologists.

Active (inaudible) versus placebo is an extremely viable approach I think for some time to come. And this is what we commonly do in heart failure trials and many other kinds of trials. As winners emerge though, obviously active control and combination trials will be necessary.

But we have other issues in concomitant therapy, and I noticed it was in the guidance document. We have other risk factors. All these people have other risk factors. And how aggressive should we be in their control? Dr. Nissen castigated one trial for being less rigorous about this than another. So the options are to mandate it, which is very expensive, because the minute you mandate it, particularly in multinational trials where there are different standards for different countries, you're now in a situation where the trial has to pay for the costs that are not part of routine patient care for that country. It really runs up the

cost.

So my recommendation is recommend local guideline based care, have a good electronic data capture system so if people are completely out of line you can use methods of feedback to help the sites get up to speed in what they're doing. And there's a huge on-label/off-label conundrum which, without revealing any details, we're in the middle of now. Since diabetes drugs -- as people have pointed out -- have typically been developed by taking out all the patients that I treat in my practice in a cardiology clinic, they're labeled for narrow populations but then they're used extraordinarily broadly.

So if pragmatic outcome trials are limited to on-label use, they'll not reflect actual use of the drug, nor will they capture the nexus of where most of the benefit and harm is over the period of time the trial is going to be done. And the two big areas here

are rental dysfunction and people with multiple co-morbidities. This is really where the action is and where drugs have both the most harm and the most benefit.

If we're going to do the placebo-controlled add-on trials, we have the issue of glycemic equipoise. This is a nightmare, but there's no way around it. If we start out with people with diabetes and we give drug or placebo, obviously on Day 1, we'll have a difference in glucose levels in the treated and controlled populations. And so if we're looking at net benefit versus risk of drug, then we're obligated to try to treat both groups to the same level over some reasonable period of time, whatever that is.

And so this leads to a problem that's called intensification. It's a common problem in every field of medicine where we do these trials. And you'll end up with different uses of treatments.

And Dr. Nissen pointed out an

interesting one which is that if you have a diabetes drug that raises LDL cholesterol, it is likely that there'll be more statin use in the group that doesn't get the drug. I would argue that you obviously can't stop that. It's an uncertainty that one has to deal with and think about as the trial is designed.

And then we have something that also comes up. You diabetologists cannot resist wanting to know about the biological effects of the drug. Personally, I could care less. I just want to know whether the net benefit exceeds the net risk. And so we begin to insert what I call ornaments on the Christmas tree. We start out with a nice, pristine, simple, pragmatic trial and everyone comes along with their substudy they want to unmass the underlying biology. Sometimes these ornaments can cost more than the tree. And no one wants to take them away, including the FDA, which I think is a fatal flaw in the way things are currently

working.

And then we have outcomes. I wish I could say that cardiology had it all licked. We do not, and you know that. So we have these five issues that we have to deal with. I would like to think that outcomes are hard. We used to be able to say there was very little argument about death, but now with VADTs (?) and transplants all over the place, it's hard to even tell about that. But at least with death, MI, and stroke, there's a logic that these are hard events. People recognize them.

They're palpable, and they make a difference. But within these categories we have issues that one has to think about carefully in designing a trial. The big one in death is all cause versus cardiovascular. What's interesting here in diabetes trials to me is that if you go out on the sixth (?) spectrum, cardiovascular deaths dominate. So you don't have to worry that much about it.

If you go into the less six (?) spectrum as we did in Navigator, you no longer have a majority of deaths that are due to cardiovascular disease in the trials. And you've got to think about whether all cause mortality should really be the endpoint that you're looking at because now you have an endpoint of death that doesn't include most of the people who died, which to me is a tough issue.

You'd like to hope that myocardial infarction was a done deal, but now as supersensitive troponens are coming in, after jogging we're finding we have a little bit of myocardial necrosis.

So in designing a trial, one has to put in place a system -- particularly if it's long-term to adopt the endpoint to the changing standards that will inevitably occur in the tests that are used.

And then for stroke, particularly in countries like the U.S., since a brain CT

is sort of rite of passage for people over age 50, we have to take into account now imaging versus symptomatic strokes and how we're going to deal with that.

So those are the hard events. And there are some tough issues there. They're even tougher with regards to the soft events. What we used to call unstable angina -- it's very complex. For every 10 patients admitted to the emergency department with what we would call chest pain, only one to two have real unstable angina. And this can take a lot of documentation to figure out. And people can argue even after the documentation.

Revascularization is a very hard endpoint, but it's very dependent upon the cultural context. I'm pleased to say now that we're no longer the country with the most extreme rate of revascularization -- Germany has now surpassed us -- per population is doing more

revascularization. And then heart failure admission, which has really hit the radar of diabetologists due to the issues with the TZDs. And it's sort of halfway between. Most cardiologists believe that a heart failure mission is a heart endpoint. It has palpable consequences, but it needs to be measured carefully so that bouts of edema are not mistaken for heart failure.

All right. I'm almost done. Then we get to adverse events. I don't know how I can be more clear about my opinion on this. I'd welcome argument about it. But for the important events of interest -- now, remember, we're talking about outcome trials after we've been through the screening process that Dr. Nissen described -- so we have some signals that we want to look at. And if there's one thing that's clear in studying clinical trials it's that if you want to measure a signal that you're looking for, open ended adverse events is about the

dumbest thing you can possibly do. You only get a quarter to a third of the events that actually occur. And what you should do is construct a tick box that enables people in a very simple rational way to get the information that you need to classify the event.

Serious adverse events must be collected. I'm in agreement with that. But why on earth we have to have this expedited reporting of serious adverse events in this phase of the development of drugs, I challenge you to give me a good reason or it. Working with the FDA in a public partnership we have, we've recently been looking at oncology. We have oncologists now who are getting over 200 serious adverse events a month from pharmaceutical companies from trials that they're not even participating in because they're doing other trials related to the same drugs. If you calculate 15 minutes every time one of those comes in to open it

up, and read it, and decide what to do about it, for a trial that you're not even participating in, for which you have neither numerator nor denominator and no way to deal with it that could be meaningful it's astounding that we're still doing this to people and it hasn't been stopped.

So if we just collected serious adverse events and reported them to a data monitoring committee and did it in a non-expedited, non-Federal Express manner, in one trial that we're coordinating we calculated a single serious adverse event for a global trial for a drug that's being used for multiple indications can cost up to $450,000 to send to all the investigators around the world.

Now, for non-serious adverse events, please, please forget open-ended non-serious adverse event collection at this point. I challenge you to find my useful purpose for this. It eats up enormous

amounts of time. And running a coordinating center that does a lot of industry- funded trials, it is a nice source of profit. Every time this happens, the cash register is clicking, but it's not contributing anything to understanding the risk and benefits of the treatments.

Now, a plug for cost analysis in these outcome trials. It's fairly easy to do. In the end, in most cultures there will be different views of what makes a therapy worthwhile. I think that's perfectly fine. We live in different economies with different values. We learned a lot about this in the GUSTO-1 trial with TPA.

The sentinel event for me was when a New Zealand cardiologist called and told me that he had been notified by his hospital board that they had to choose between having a cardiologist -- that is him -- or using TPA. In that case, although TPA was my choice based on the trial we did in the U.S.,

in New Zealand I would say probably having a cardiologist is a better thing to have. But you can't do that kind of analysis for your country unless you've collected the cost data.

So finally, what could the field of diabetes accomplish if it really adopted pragmatic trials as a standard for the field? I think it could do what's happened in the field of acute coronary syndromes. And I do want to single out here the FDA as actually being the group that made this happen. It was only because Ray Lipicky and Bob Temple stood up to people and said we don't need to measure these things -- it's hard to do, it will cost too much money -- that it now is a standard in this field to do large outcome trials to measure the balance of risk and benefit.

If that's done, this is not a panacea. And I think many people have made that point. It's not a panacea, but if

that's done, at least we have guideposts based on evidence that can drive practice with clinical practice guidelines that are really based on outcome data. And when that happens with tens to hundreds of thousands of people randomized in the clinical trials, we now know from studies done around the world that if we measure adherents to those guidelines from those kinds of trials, first of all we can show that we can actually adhere if we pay attention; and secondly, we can show that the risk of our patients dying does go down.

I would submit that currently in the field of diabetes, since we just don't know, it's impossible to exert this kind of a scheme and have confidence about what it's going to do to the overall mortality and other outcomes for the population of diabetics that's growing in all of our practice. And that the key is these highly pragmatic trials.

So in closing, just to sort of add a little levity, you've probably seen this from the British Medical Journal 1999, I don't know any other alternatives other than what I've put forward. Shortcuts will not do the job. They've been proven to be unreliable. Praying may be an alternative depending on your beliefs. But I don't think we should be forcing people to practice nervousness-based medicine because we're widely prescribing drugs for which we don't know the balance of risk and benefit, which is the situation we're currently in.

So as a red-blooded American, I'd say we want evidence-based medicine. I do trust in God. But all others must have data. And despite the fact that I'm passionate about this, I also want to remind you I'm not putting this forth as something that will just be done simply and answer the questions. I think Hertzel said it very well today.

When you get the data you find it's

not as simple as what you believed when you had no data.

Thank you.

DR. BURMAN: Thank you very much. This will be open now for about 10 minutes of discussion and questions.

DR. KONSTAM: Rob, that was really terrific. And I can't think of a single thing you said that I don't completely agree with.

DR. CALIFF: That's the first time.

DR. KONSTAM: I guess the 30,000 foot question we should have for you is where do you draw the line in all of this between the regulative imperative and the arguments that you made about, okay, we need more information in this field and let's go out and get it. Because I think that's going to be an important question. You know, you didn't mention much about the microvascular effects, and I think I haven't heard anybody challenge the evidence of the linkage between those and glycemic control, so I guess I come back to -- and I'll also say,

obviously we've done a lot of trials in diabetes, and there are more trials underway in diabetes. And there are more trials in planning in diabetes. And some of them are pretty large, and some of them are funded by the pharmaceutical industry, and some of them are funded by government agencies. I think that everything you said is a terrific stepping off point for how do we do those trials even better and get better answers.

But how much of that is the regulatory requirement for a drug that shows glycemic control, and does a good job of it, and doesn't have a safety problem? There's a lot to be discussed in that last statement.

But philosophically, I guess, I'd love your take on this.

DR. CALIFF: I appreciate the chance to at least render an opinion on this, because I do believe strongly, and we published about it in the Journal of Health Affairs about four years ago, and my opinion hasn't changed. And

as painful as it is, I pretty much agree with Dr. Nissen on his view of it.

I don't think that we'd be doing the trials we're doing in heart failure and acute MI if the FDA had not said you must do these trials. Because there's too much at stake for the public to get by with less.

But having said that, here's what I believe. I think there should be a requirement to look cumulatively at the data. And there's no better place to do that than at the Advisory Committee when a drug comes up for approval. That process, I think, needs to be a bit more open in terms of the discussion about what comes next. So if there is a signal early on, there should be a discussion about it. And I think the dirty little secret that many of us have who do a lot of consulting with industry is that the problem is not that there's some signal that industry is purposefully avoiding. Usually there's some hint of a possible signal that

there's uncertainty about. And the question is do you address the uncertainty head-on early or do you try to sort of hope it will go away.

And so if there would be a way to surface what the real issues are that are bothering people at the time of approval so the label could be appropriate, and then a requirement for a proper outcome trial, which would be different depending on what you knew before approval -- at least one in my view -- that would be a tremendous step forward.

Now, I've also tried to make the point that one trial is not going to do it. There are going to have to be more than one. And I've also made a plea that the structure of these trials should be so that neither industry nor the practicing clinicians dominate, but there's a balance of power so the right questions get answered. It is very easy to gain outcome clinical trials in ways

that you and I both know. We've both done this for a while. So some public proceeding to vet the study design needs to be done.

And then the final thing I'll say, I mean, the whole message in the morning at the oncology things is that if you put the government completely in control -- no offense to you now that you're a government guy -- but there's a reason in America we don't like that to happen because they showed data that shows your typical cooperative group trial takes three years to get started from the time the concept is finalized. And that's unacceptable. So we need a balance of all those powers.

So I think it should be required and it should have some public proceeding, but not before marketing unless there's a signal in the screening at that point.

DR. BURMAN: Thank you. Other questions for Dr. Califf? Dr. Temple.

DR. TEMPLE: The kind of trial that

you endorse and that Steve suggested -- that is one where you're trying to rule out an upper bound of risk -- is plainly something that FDA can require of a new drug that's approved, but more easily now with FDA than before. But we can't.

Some of the trials you're talking about are more sort of what the field needs. That is they're not about a single drug. They're about approaches to therapy. I think either you or somebody said target versus drug. And I wonder if you had thoughts about how to get those done. It's not as easy for us to insist on those because they're sort of everybody's problem.

The other thing I wanted to take the opportunity to advertise is that we completely agree with what Rob says about simplification of trials. Even though he sounded critical of FDA, those are not our requirements. We make exceptions. Anybody who doesn't want to collect stupid things

just needs to come in and ask. Because the rules are very, very clear. You don't have to collect every drug the person is on. You don't have to collect silly little adverse effects. You don't have to submit immediately the outcome measures of the trial or any of those things. And everyday intelligent companies get permission not to do that. They don't even need permission really because we've written guidance that makes it possible.

So we totally agree with that. And the time and money spent on collecting that stuff is ridiculous. We just had a meeting yesterday where a company was sending us all of the endpoints. And I asked them why. And they said, well, our safety people are nervous. I don't know what they're nervous about, but they don't have to do that. I'm sorry. That was just an adverb.

DR. CALIFF: What do you do with those things when they come in one at a time like

that?

DR. TEMPLE: Well, we mostly ignore them when they're study endpoints. But you identified the problem. They go to 260 investigators, and then they all send them to their IRBs because they're afraid not to. And then they get buried and put in the garage. And everyone agrees it's stupid. Janet, five years ago, and all of us since. And I don't understand why it persists as much as it does.

DR. CALIFF: So you asked the question --

DR. TEMPLE: But I still had a question.

DR. CALIFF: How do we get the target trials funded. And I think that is a responsibility of the NIH and the practicing community. I will say there are an increasing number of fields where once a drug is on the market being part of a trial which is looking at targets, it becomes a very positive thing for a company to do. So we have a number of examples

of that that are occurring in blood pressure, for example, where we now know the combination treatments look pretty good.

So being part of a combination that is beneficial when you reach a target is a favorable thing. But fundamentally, I think it's a matter of public health to define for the major diseases what the targets of therapy are. And I hope we can do something about the NIH project.

DR. BURMAN: Thank you. Dr. Veltri.

DR. VELTRI: We certainly like simple trials, but many times these global trials have other health authorities as well, and the FDA has been very responsive to get rid of some of the nonsense. But as you know, Rob, we do global trials, and many of those health authorities request us to collect many of these things. And therefore, we're caught in a bind in a way, and somehow as these trials get more and more global, and as you said many of these now are going to other areas of the world,

appropriately so, it just gets more difficult to do. And I guess one plea would be that somehow health authorities harmonize some of these things because clearly these trials are larger and larger, and many requests are just not able to be done in a timely fashion and certain they're very costly.

DR. CALIFF: Yeah, I think we really have to work on this. And it's hard. Culturally I think it's gotten harder the last couple of years because of other tensions that exist internationally. But we need to overcome that.

DR. BURMAN: Dr. Day, you had a question.

DR. DAY: Just a brief comment about the huge difference in treatment effects for U.S. and non-U.S. trials. If indeed trials are going more and more global, I think something needs to be taken into account here. And one possibility is to look at the existing data and see what the effects are for U.S., U.K., and New

Zealand. U.S. and New Zealand are the only places that have direct-to-consumer advertising and drugs. And while we're not here to comment or debate the pros and cons to DTC, I think that Americans are better aware that there are benefits and risks of drugs more than in the U.K. where I visited and looked into this a little bit. And so there actually could be a cognitive component of treatment effects over and beyond what is picked up with comparisons with placebo.

DR. CALIFF: I hope that tomorrow -- although it's not the main issue -- when Steve put out his two things that should happen with approval before the outcome studies, three and four for me would be no direct-to-consumer advertising until the outcome study is done, and an appropriate label that informs the public of the amount of uncertainty that exists. So people could then make rational choices about what they want to do. But that's not the main purpose of this meeting.

DR. BURMAN: Dr. Rosen.

DR. ROSEN: Great talk. I want to ask you about off-target events. And I'm particularly interested in bones since it's my field.

So with the rosy story, I mean, we have an increased adverse or increased risk for congestive heart failure, myocardial infarction, and fracture. What happens in an approved drug when you start piling up adverse events such as this that are off-target in respect to utilization? Do you have any comment on how we can improve on that? Because it's all relative to your perspective in terms of what you think is important or what you don't think is important.

DR. CALIFF: I'm glad you brought it up because, I mean, I reconnected with the blind man and the elephant to exemplify this issue. And we all know that because health systems are all developing data repositories and the bit

initiative from FDA is going to make it very easy to find adverse events now with drugs. They're going to be legion, and balancing these things is really critical.

So I think one of the challenges to statisticians -- again, not the primary purposes of today, but I think as you get into large outcome trials that are carefully done, you're going to see significant differences in things that are not the primary endpoint. And we would probably all agree that as human beings what we want to do is to balance all the benefits and all the risks, not just the primary endpoint of the trial that happened to be done.

So finding ways of appropriately displaying and stimulating discussion on this would be critical. And here's an area where advertising is deadly because all these things have to be listed in advertisements, but Dr. Day's work has shown clearly that they're not going to be listed in bold print

on the upper left hand corner of the thing that people are reading or looking at.

So you know, I would predict we're going to find a lot of things good and bad about drugs as we do more of these long-term trials that will beg the question of how do we put into place -- how do we put into context findings that meet nominal significance but weren't in the study plan.

DR. BURMAN: Thank you.

DR. ROSEN: May I just follow up for just one quick session?

DR. BURMAN: Sure.

DR. ROSEN: So was the mortality assessment in zoledronic acid part of the primary outcome evaluation? Because we've had to deal with this with vitamin D. As you know, there's a study out there where a secondary outcome was found for vitamin D -- that it reduced cancer risk -- even though it was not part of the original evaluation. And I happen to be chair of the data safety monitoring board

for that and trying to deal with that kind of information is difficult. So can you enlighten us about that?

DR. CALIFF: Well, I think you all really -- this is something you do need to talk about tomorrow. And there's a famous written-up interaction that involved Fleming and Temple related to a cardiovascular drug that failed to meet its primary endpoint but where mortality was dramatically reduced. And there was a quote "mortality trumps all." And one could argue maybe mortality shouldn't trump terrible stroke, but pretty much everything else. When you really ask people, and we did it in the support study in intensive care units in the U.S. very vividly, almost everybody, at least in the U.S., would value staying alive over most other imagined outcomes.

And Dave DeMets is about to write a piece about monitoring trials where you might see a dissociation between the primary outcome and the mortality signal in a

positive direction, which I think would be worth people looking at and focusing on. Because we're beginning to see this more often.

DR. BURMAN: One more question for Dr. Califf. Dr. Jenkins, I believe you had one.

DR. JENKINS: I wanted to ask you about the issue of feasibility of actually getting these cardiovascular studies done for diabetes drugs after approval. Going back to Dr. Nissen's proposal he had a screening concept that if you excluded a certain level of risk before approval that would be acceptable and you would do the long-term study after approval. So I'm wondering if we had a scenario where in that proposal, we've adjudicated prospectively the events in the Phase 2 and Phase 3 trials and the point estimate is 25, 26 percent increase in cardiovascular events but it excludes the upper bound of 2 that Dr. Nissen proposed, what are the practical implications of the ability to actually get such a trial done in the

post-marketing setting? Is there equipoise there to enroll people into that trial? Will investigators enroll patients into a trial where they might be getting the drug that you have an estimate of 25 percent increased risk of cardiovascular events? So what about the practicality of actually getting those studies done under that scenario?

DR. CALIFF: Well, I couldn't have imagined a better question to close my part of the session on from what I'm really interested in. And let me just say a couple of things about it.

As somewhat of a specialist in doing trials and drugs that have been impugned for one reason or another to try to get to the bottom of it the last talk at the oncology meeting today almost left me in terms. It was a private practitioner who had been running a private consortium doing one of the largest enrollers in NCI clinical trials. And they had just voted as a group

to stop enrolling Medicare patients because of cutbacks in Medicare funding. And it sort of went like what's to not like about being a clinical trialist in the U.S.? You lose money, you're hated by your administrators, you're hated by your practice peers because you make practice less efficient, and you get a chance of being turned into the FDA, and written up in your local newspaper for being associated with drug companies like it's the plague.

I notice that even here you've got us roped off from everybody else. We're not allowed to touch you, as if we're unclear or something because we've done studies with industry. And yet, this investigator gave an impassioned plea about why he had to fight this and it needs to get done.

There's a drug you may have heard of called nesiritide, which is believed by many people to be dangerous. We, indeed, are doing the outcomes trial with nesiritide, and

we're way ahead in enrollment, largely based on U.S. enrollment. So despite all the bad things -- and it is an uphill struggle right now against many obstacles -- we still find that astute practitioners, when really educated about the truth about uncertainty, and patients when informed about the truth about uncertainty, are willing to volunteer if they're comfortable that the practice environment is appropriate.

So I think these trials can be done. It requires dedication, and it requires absolute honesty with the patient about the uncertainty, and assurance from the investigator that the trial is being monitored and you're going to keep an eye on it. In the nesiritide trial, we have a data monitoring committee that looks at every thousand patients because which is nowhere near where an interim analysis should be done. But just because of that concern -- they've met once. They said go

ahead. I know nothing else, of course. So I think it can be done.

DR. BURMAN: Thank you very much, Dr. Califf. I thank you for your presentation. At this point, from about now until 5:30, we have on the agenda clarification and questions from the panel to the speakers for specific questions. There's no microphone, I don't think, in the back, so if the speakers are addressed, if you would be kind enough to come up to the microphone up here, that would be great.

I'd also like to remind you both Dr. Nathan and Dr. Gerstein won't be here tomorrow, so if you really want to focus any questions to them as well.

Paul says Dr. Nathan might have left already. Thank you.

So let's proceed and open it up for the panel for any specific questions or points of clarification they'd like from the speakers.

MS. KILLION: As a patient representative, I have probably a layman's concern. But I'm seeking clarification and some of it I think I've already gotten from Dr. Califf. And I think maybe Dr. Nissen may be able to enlighten me a little bit.

One of the statements that was made by Dr. Nissen is that there are 10 drugs available to lower glucose. So we know how to lower glucose. And as a patient I have to say we don't always know how to lower the glucose levels. Drugs lose their efficacy over time for many diabetics. I know I've been on quite a few of the 10. And some diabetics can't tolerate the side effects or can't take some of the drugs for other reasons. So it's not really accurate to say that there's 10 options available to diabetics. For some there are significantly less.

So I guess as a diabetic my concern is increasing the pharmacological arsenal to

deal with diabetes. And when I think about adding these kind of trial requirements, either pre-approval and post- marketing, my concern is that -- there are two concerns that I have. One is that this kind of approach, while I can see the benefit of it, I'm afraid that it'll have a chilling effect on development. And I think Dr. Califf addressed this a little bit. If you can simply if to bring the cost down, then you can sell it that way. You can get it done.

I think that's admirable and I think it's something we should strive for, but I'm not sure how we accomplish it. Because if it was easy to do, it would be done already. It requires a lot of behavioral and perspective changes that are not easy to enact.

And the second thing that I'm concerned about is that these kinds of requirements and focus would delay the rate at which new drugs come on the market. And I

know there are some that said, oh, it won't. And I'm just sort of wondering how it doesn't. And I think that Dr. Califf again addressed this a little bit on making it a post-marketing event unless there's a signal prior.

So I just would like some comfort from some of the speakers for those two concerns.

DR. BURMAN: Thank you, Ms. Killion. Dr. Nissen is on his way up.

DR. NISSEN: Well, I fully agree with you that we need more strategies to help patients with diabetes. But, we don't want new strategies that increase the risk of morbid/mortal events. We want strategies that at the very least are going to lower blood sugar without harm. And hopefully we're going to set the bar even a little bit higher and show benefit.

Now, that is why -- I mean, I gave a lot of thought to this process -- and

that's why I recommended a two-step process. There are certainly people that would say we really ought to have an outcomes trial before we launch these drugs, and I didn't say that. I said we ought to exclude a certain level of risk. If you do the calculations, what you see is it involves a modest increase in the number of patients that are exposed to the drug prior to approval, and it requires that we give the drug to some patients that have higher baseline risk for cardiovascular disease. We actually study the population where the adverse events are more likely to occur.

You know, again, only time will tell, but I think by having a two-step process -- by doing that -- what Tom has called a screening trial, which I think is a very reasonable way to look at that, and then getting the big outcomes trial going, I don't think we have a chilling effect. I think what we've done is we've taken a

moderate -- an intermediate step towards stronger levels of evidence about benefit. It's very important for diabetics to understand that we understand the benefits of lowering blood sugar, but if we take drugs forward that lower blood sugar but increase the risk of death or heart attack, we haven't done diabetics any favors at all. And unfortunately, we've seen some examples where that's probably happened.

DR. BURMAN: Thank you. I wonder if I could ask, Dr. Nissen, if you're up there, just a quick question. I understand the hypothesis of your proposed plan. But do you have an estimate? The one negative aspect theoretically would be if a drug is approved and has a signal for cardiovascular events that doesn't quite reach the threshold in the pre-marketing circumstance but does in the post-marketing where there's an increased number of cardiovascular events -- and it's going to take several years for this to be defined -- do you

have any estimates or thoughts on how many people would be at risk for these cardiovascular events once the drug is approved but in retrospect would have been at higher risk had we known more information?

DR. NISSEN: Look, I can't -- nobody can make all the risk go away. You know, drugs are risky. You know. With all good intentions we -- and I mean all of us -- have been involved in approving drugs that subsequently we thought were going to turn out to be great drugs, that turned out to be a hazard. We cannot get to zero risk. And so what I'm trying to propose is having some upper level of risk that's acceptable. Now, does that mean we're never going to make a mistake? No. It's going to happen. And it has happened, and it'll happen again.

But the way things are now where we say, look, you don't have to study high-risk cardiovascular patients. You don't have to rule out an upper confidence interval. I

mean, what I showed you for rosiglitazone is that it was approved with an upper confidence interval of 3.6. And I think that was too loose. And I think we've learned from that. And we can now move on and we can come up with a standard which is somewhat more rigorous.

Now frankly, when I did this slide, I frankly thought about using the 122-event limit. The argument being that, again, an 87-event package still means that you could have a point estimate of 1.3. You could have 30 percent more events and you'd still say that drug was approvable.

And John Jenkins' is asking the question can you enroll patients in a big outcome trial when it's approved with that kind of a signal. Well, we've done outcome trials previously with drugs that had a signal of 3.6. So you know, all I'm doing is saying let's tighten it up. Let's reduce the uncertainty. But we're not going to reduce

it to zero.

DR. BURMAN: Thank you. Other questions?

Dr. Konstam.

DR. KONSTAM: You know, I wonder, picking up on Rebecca's question, whether we couldn't give our FDA colleagues a little bit of homework to come back to us with tomorrow. Because we're going to be thinking about ways of considering tightening up the pre-approval requirements. And the question I think that I'm hearing is, okay, well, what will that cost in terms of delaying or increasing obstacles to get a drug approved. I mean, I'm sort of wondering based on what we're currently doing in our typical pre-approval programs how much of what we have to do is focused on the nature of the population being enrolled in trials so that we get an increased number of cardiovascular events pre-approval; how much of it is standardizing the way we collect cardiovascular events; and how much of it is really increasing the overall

sample sizes compared to what we're presently doing.

I mean, are we talking about doubling the size of typical pre-approval programs? I guess I'd like some sense of that. If we can't get that today, tomorrow would be great to have some of that information.

DR. JENKINS: Just a comment on that and maybe to help direct the people who need to go find that. Dr. Joffe presented this morning kind of what our current expectations are for the size of the database, but Dr. Nissen has proposed -- his slide there is patient years. So we would need to go back, I think, and look at the recent packages of diabetes drugs and see how many patient years of exposure are there. Because what we presented were number of people exposed for a certain period of time and total number exposed versus patient years.

DR. KONSTAM: Well, the number one issue is events. Okay. I mean, I think the

point has been made, and it's an important one, about exposure time and differences between different durations of exposure. That's a critical issue. But the thing driving this analysis is just events. And so that's number of patients, number of patients enrolled, but also what kind of patients are we enrolling.

DR. JENKINS: Well, Dr. Nissen showed you a couple of examples of the number of events in databases. He also, as you know, is proposing that we study higher risk patients. Increase the number of events probably. But we may be able to pull something together.

DR. BURMAN: Thank you. I think, Dr. Proschan, you were next.

DR. PROSCHAN: Yeah. Dr. Nissen's suggestion about the screening trial and a definitive trial afterwards -- Tom Fleming made a comment on it, and the comment seemed to imply that there would be some consequences if the definitive trial showed unacceptable mortality risk, for example. And that's not what I hear

Dr. Nissen saying. I thought that you said that there wouldn't be any regulatory consequences even if a larger definitive trial did show the excess mortality. Is that right?

DR. NISSEN: You know, there are always consequences. I mean, if you do a trial and the trial shows evidence of harm, then that becomes a regulatory decision. And I would fully expect that the Agency would do as they did with the rosiglitazone panel -- bring people together and say here's what we've got. Take it or leave it. You know, and help us think this through. Or they may decide in some cases that the evidence was sufficiently strong. That a drug should be removed off the market, and the Agency certainly has removed drugs from the market.

The bottom line is that if the studies are well-designed, we will get an answer. And we'll get it in a timeframe that's as timely as is reasonably possible. And that's what I was seeking by having this

two-step process. You know, again the alternative was true draconian, which was to say you've got to have that degree of precision before you ever bring a drug forward, for exactly the reasons that you stated that we do in fact have reasons to want to bring new drugs to market. So that's again the thinking process behind this.

The consequences of a trial that shows harm I think the Agency would welcome the opportunity to reevaluate drugs and to have that clarity of data, and would try to act accordingly.

DR. BURMAN: Thank you. Dr. Temple.

DR. TEMPLE: Mary and her people will have to look at what the implications are for the diabetes group. But it's worth noting there are some classes of drugs where there isn't any short- term benefit to measure. So the only way to get them into the marketplace is to do outcome studies.

Essentially every anti-platelet

drug is in that category. And companies do manage to do very large trials. Right up front, pre-marketing. Not as long in many cases as these, but they do manage to do them.

It's also worth noting that if you're developing a non-steroid anti-inflammatory drug, you companies have managed to get 10,000, 20,000 people into trials because they planned to do it because they thought it was necessary. So it's obviously more difficult than what's being done now. But with a little planning you can make a study that was going to drop off at 12 weeks go for a year and collect the people, and then putting sicker people into trials is common on cardiovascular medicine because the effects are more easily demonstrated in them.

So these things are not alien to the industry, I think.

DR. BURMAN: Thank you. Other questions? Any speakers? I wonder if I could

just ask Dr. Ratner a question. This is sort of a general question. I don't know that there is an answer, but you presented some slides talking about the benefit of lowering blood sugar and decreasing microvascular complications. And I think everyone agrees with that for sure.

But in terms of either cost or biologic effectiveness, how do you factor in the cumulative effect if a drug lowers blood sugar, lowers HbA1c, decreases the events for microvascular disease as we saw in the DCCT but has let's say a 10 to 20 percent increase in non-fatal MIs? How do you put all those together? I realize it's just a difficult question with just thoughts.

DR. RATNER: Well, Dr. Burman, I was with you until you got to the increase in MIs, and then it became a whole lot more difficult.

There are numerous cost-effectiveness studies that have looked at the value of intensive glycemic control and intensive overall control in patients

with diabetes. There is a paper that is currently online to be published in Diabetes Care looking at the cost-effectiveness of the Steno-2 trial where you target glucose, blood pressure, lipids, smoking, and anti-platelet therapy, showing clear-cut cost-effectiveness changes to the benefit of the interventions.

So there is a lot of data there showing benefit. There have been direct clinical trials as well as computer modeling doing all of that. The question of how do you balance microvascular benefit with macrovascular deterioration is a whole lot harder. And I think my answer to Dr. Konstam earlier I still think pertains. First of all, do no harm. And we do have alternative ways of treating glycemia in type 1 and type 2 diabetes that if one therapy does have this side effect, we would go to another therapy. And I think the best example of that is to simply look to see what has happened in the marketplace in the last year

to the use of TZDs.

So that there is a marketplace decision that says we're not going to use a drug to lower glucose if, in fact, there is evidence of risk. So that becomes very, very important.

I think what we end up doing is really going back to Ms. Killion's point, trying to find those drugs that have the best benefit-to-risk ratio in each individual patient. And we discover that as we go along, because type 2 diabetes, in particular, is an evolving disease. What works today won't work in three years. And so we end up moving through a sequence of events to try and find out what the best combination is. So I would actually go back to this distinction between what is the regulatory requirement versus what is the therapeutic decision tree.

And a regulatory decision, in my mind, clearly is looking at populations and

looking at risk versus benefit. The therapeutic decision tree is based solely on that individual -- what works for them. Now, that also takes into account the clinical trials that have been done in terms of the initial decision-making. But I think that we end up deciding on our therapeutic regimen based on the natural history of the disease -- what we observe to be the primary defects in the patient sitting across the desk from us that day -- and then seeing how it works and modifying off of that.

I don't know if that completely answered your question.

DR. BURMAN: I appreciate your thoughts tremendously. Other questions for the speakers? Dr. Parks.

DR. PARKS: Yes, my question is to Dr. Nissen. I'm looking at this slide here and I'm just wondering if you can help me. How is it that FDA could justify -- if these are screening studies -- so this is your Stage 1 or

Step 1 studies -- how we could justify approving a drug that had a point estimate of as low as 1.26. I think 1.17 we might be able to explain, but 1.26 and above, how could we justify approving that? Especially given that we have already 10 classes of drugs out there to treat type 2 diabetes.

DR. NISSEN: Well, what you're arguing for is for moving down the table. And where in this table you want to set the threshold is, in fact, what the job I think of this committee and of the Agency is to decide. What I think we have to think about is if you have a point estimate of 1.31 -- well, here's an example of a drug. Okay, the second example where you had 48 events in the active arm and 39 in the control arm. The relative risk is 1.23, which does not exclude a benefit of around 20 or 25 percent, and does not exclude a risk of 2.0. So that's a drug that I believe equipoise would exist for an ongoing clinical trial.

Now, the reason that I made this

more moderate suggestion, unlike what's required for let's say anti-platelet drugs, is that we do know there are some benefits of lowering blood sugar, and we do know that we do struggle with multi-drug regimens to try to get blood sugar down. And so I was looking here to draw the line and I have no lease on wisdom here.

I mean, you might want to look at this and say, hey, we want 256 events in the development program. And frankly I don't think that's a wrong decision. This committee may make that recommendation. If you do that you've ruled out an upper confidence interval of 1.5. And that means the point estimate is going to have to be less than 1.17. And that gives greater clarity.

And so the question that we're asked here is how much clarity do we require before we will allow the imputed benefit of lowering blood sugar to dominate our

thinking. This is a really tough call.

It's a really tough question. When I actually did this, I was going to propose to this committee -- I vacillated between 87 and 122 events for that reason. But I also recognized that if you take that bottom-line -- if you need 12,800 patient years of exposure to approve, well, that's going to set a pretty high bar. And maybe the bar should be set that high.

You could make the argument we have so many drugs there now to treat blood sugar that that's an appropriate bar for a new drug. I felt -- I'm convinced -- and I do take care of these patients -- that we could use some additional ways to lower blood sugar. And that might be a bar that would be sufficiently high that it might discourage innovation. And so I didn't propose that. But it's certainly not an unreasonable way to go.

DR. JENKINS: Can I follow up on that?

Because I'm struggling with the 1.3 estimate as well or as our comfort level in approving a new diabetes drug that has that risk estimate, particularly in the scenario where you describe where these will be pre-adjudicated. You'll have a protocol in place to adjudicate. So this isn't the old days where you had events that you weren't really sure about. These would be events that had been adjudicated. And 1.3 isn't very far from the 1.4 that was the rosiglitazone meta-analysis that led a lot of people to recommend withdrawal of the drug.

So I'm just interested in the 1.3. That seems like a lot of potential risk of a bad outcome.

DR. CALIFF: I feel like I ought to add a comment on two of these things but they're related.

I mean, if you look through FDA approvals over the last decade, you would find many cases where risk like this has actually been put in front of the panel.

Because the confidence intervals are from here to here, no one pays attention to it.

There's another -- this reminds me of a lot of things. When you objectify something and call attention to it, all of a sudden it looks different. But there's another nuance here. Within a composite cardiovascular endpoint you're going to see variance in the components of the endpoint. And there's a very high risk that if death is a minority of the endpoint that it could be a radically threefold increase where the overall estimate is 1.3 just because it's the least frequent event.

And this obviously has to be balanced. So with regards to the question about balancing microvascular and macrovascular, I just -- I think it's really important to point out there's a good literature on patients being able to make these judgments. But the key, which I think is a very American value, is the informed

consumer can make a judgment. But obviously in the absence of information, can't make a judgment.

So I would disagree a little bit with Professor Ratner in this regard. I don't know how you make an individual judgment if you have no data.

So if you have microvascular data but you hove no data about macrovascular, I don't know what you're trading off. So the key to me is to provide the consumer with the information. I would actually disagree with Dr. Nissen. Some rational people may say I'll go ahead and take a 10 percent higher risk of death if it's going to reduce my risk of renal failure by 20 percent.

But right now we're not providing them with that information because it doesn't exist.

DR. NISSEN: And I would also agree. I mean, I think that historically drugs have been approved in diabetes that would be far

outside -- in fact, drugs have been approved that would not have met the standard for the top line. In fact, as I showed you, many of the previous development programs did not even have 50 events available for analysis.

So you know, how this is not this is something that's been done all along. And I also think that if you have this degree of clarity, then physicians and patients can make decisions. I think that there will be some people that would look at a drug approved that had a point estimate of a hazard ratio substantially above one and say I'm going to wait until the outcomes trial is done before I use the drug, except as a fourth- or fifth-line drug.

And that is absolutely a rational behavior. I tend to do that now. You know, when a new drug is approve, and I have in my own mind a wide confidence interval around risk versus benefit, I tend not to use that drug except when other drugs have failed. So

to speak to our patient's point here is maybe when you approve a drug that has a signal like that you say given this signal, this drug should only be used when other drugs have failed. You approve it as a fourth-line drug. And we as physicians look at that and say this is a fourth-line drug until this signal is either confirmed or refused by the more definitive trial.

So I think we can deal with uncertainty, as long as we know what the bounds of that uncertainty actually are.

DR. BURMAN: Thank you. I think Dr. Proschan, did you have a question?

DR. PROSCHAN: No.

DR. BURMAN: Let me see if any --

DR. KONSTAM: You know, I just was thinking that the cardiologists in the room -- and I'm one of them -- we're slipping into really accepting a dividing line between microvascular and macrovascular effects as if that dividing line means something to the

patients. And, in fact I defy any of us to measure up the clinical impact of going blind to that of a MI, for example. And so looking at this -- and I think that Steve's proposal here has slipped us into that -- and I think when we discuss this tomorrow, we really have to look at that very critically. And one might consider expanding -- you know, so Rob makes a great point. You know, the patient needs to decide. But the dividing line between macrovascular and microvascular clinically is completely arbitrary. I mean, there may be some mechanistic basis for it, but there's no clinical basis for it.

So you know, one of the things to consider tomorrow is how to consolidate that information into the so-called safety signal. So in fact, if there are fewer retinal hemorrhages occurring, I mean, I think we have to face the question of what does it mean that there are a few more MIs? And I think we have to think about it that way.

DR. BURMAN: Thank you. I think Dr. Genuth was first and --

DR. GENUTH: I'm sort of having trouble coping with this discussion. On ethical grounds, theoretically we should want a point estimate of 1.000 with the narrowest confidence intervals possible. I don't understand exactly why we expect that we have to have a beneficial drug with an increased risk. Why we can't direct the pharmaceutical companies to focus their research and development efforts on drugs that are both effective and safe, rather than sort of thinking so much about, well, how much danger are we willing to expose patients to in order to get some benefit.

And the other part of my difficulty coping with this is I haven't heard enough discussion about what other quality the drug should have -- beneficial quality -- if we're going to think about some point estimate for danger that we can accept. So I'm thinking that I would require that a new drug have

more benefit in blood glucose lowering than the best comparative drug that we have -- best in terms of efficacy and safety -- before I would even consider designing a trial to find out how much real danger it has.

So I would like to hear the presenters focus a little bit more on what drug they would compare a new drug to when they're trying to decide if it's too risk to use even though it has some benefit.

DR. BURMAN: Thank you. In the spirit of focusing on questions to the speakers, do any of the speakers want to address Dr. Genuth's salient questions?

DR. HOLMAN: So welcome to our world. I'm not surprised you're wrestling with these problems. It's what we diabetologists do all the time.

The issue of combining -- and that's a fact -- I mean, there are different ways of doing it and quality adjusted life

years will pull together in a patient reference frame what they feel the impact of really quite disassociated events are -- whether it's going blind, having a MI, having a stroke. So there is a metric by which you can do that.

This discussion today has had two almost opposite polar concentrations. One has been the glucocentric story and the other has been the cardiocentric story. It's true that cardiac death is probably the commonest exit for our patients, therefore, any adverse signal tends to be seen there first. But in the holistic view of what's going on with our patients, the problem is that agents that treat glucose often have multiple effects, both good and bad. We're talking about weight gain, hypoglycemia, nausea. You name it. There's a whole constellation. Sadly, we don't have a statin for glucose or a drug which lowers LDL reliably with very few side effects, and basically seems to work over

many years.

We have a problem, as we've heard, of an evolving disease in which increasing therapy is needed. We're balancing the side effects and the reducing effectiveness over time. And we just have not had sufficient long, head-to-head trials that have allowed us to get the information basis that Rob alluded to just now. If we are going to go forward with new drugs and put them into outcome studies, I support totally what's being suggested. But we do need to collect this additional information, of which the cardiac safety signal is one.

Now, if there isn't a cardiac safety signal up front, we still need the outcome study because there may be other off-target effects. There may be off-target benefits. And what's really missing is the ability in clinical practice to evaluate the effectiveness of the drug in the wider population. Too frequently the drugs that

come to market now have been put through niche studies that have been designed to get the maximum A1c lowering, to avoid the high-risk patients, and to provide the information that current regulator requirements are asking for.

If we're going to treat people in the round in the future, then we need much wider base studies. You've heard the designs. We agree totally between us. Pragmatic, large scale, simple studies will collect the real information that we need with directed focus on the outcomes that we might expect to see being counted in a proactive manner as we move forward.

This approach to do no harm up front -- to have a gated entry into what you might want to put into limited circulation until an outcome study is available -- I think is reasonable. But it's an incremental process. We need to be looking as the data come in, just like a DSM in a trial and the

net effect. And put together, as Saul was just saying, the issue of the various complications that occur balanced with the cost, both in terms of side effects and, of course, eventually with cost of providing the drug.

In the U.K., we have NICE, the National Institute for Clinical Effectiveness. This is what they spend their time doing. Once a drug is approved, they then go into a mode looking at the net effectiveness of it. And there are drugs like metformin which actually, if you believe the UKPDS data, reduce events and actually, because of the cost of the drug, are actually cost saving in the end. And that's one of the few examples of a drug that does it.

So there are different ways depending on your viewpoint as to how you might want to assess these drugs. In the end, the consumer, the patient, must have a voice, but they cannot have that if we do not

provide the long-term data so that they can truly judge the long-term benefits and the long-time harm that occurs.

DR. BURMAN: Thank you. Excuse me one second. Ms. Killion, did you have a question from before? And then we'll get to Dr. Temple.

MS. KILLION: I think I had more of a comment. I think that patients -- diabetes patients and the physicians that treat them are dealing with a daily 24/7 evolving, changing, variable situation. So information is excellent. Information is critical in order to move forward. But, I guess I'd make two points. One is that you deal with short-term immediate problems, and you deal with long-range trends. And you can't -- and those are very hard to meld.

And they're also very hard to maintain focus on because if you want to keep your blood sugar low but not too low, you're dealing with that on a management basis every day, hour by hour. If you're worried about

the effects of cardiovascular risk, then it's probably stretched out more over time. That's a little bit harder to focus on when you're dealing with the immediacy of your every day struggle.

So that's something that the patient and the physician work in concert with during the course of their entire treatment. And I think that good information is critical to make the decisions that allow the patient and the physician together to make the decisions about their individual treatments. In a very diverse population group some may not live long enough to face the cardiovascular risk at the out term.

So I think it's a struggle to make sure that in thinking about regulatory changes, that you don't let the perfect be the enemy of the good. And it's not an easy process for anybody involved -- the clinicians, the physicians, the patient, the pharmaceutical companies -- and working

together to make all that -- well, that would be utopia if we could approach it. But it's a struggle. We appreciate it.

DR. BURMAN: Dr. Temple.

DR. TEMPLE: With respect to the slide up there, I thought I understood it, but some of the conversation here has made me uncertain. So I'd like to ask either Tom or Steve.

Those are what I understand to be the worst case that could still go forward. For example, if you wanted to talk about -- say you way to exclude two. One way to exclude two is to have events evenly distributed into two groups, so the hazard ratio would be one. The upper bound would be less than two. That wouldn't take 2,500 people. That might take 1,000. It would take many fewer.

What this is is the worst it could be and still make it under the threshold. So it's being discussed as if that would be the typical result. I don't think that's what

you meant at all. This is the worst it could be. And as some people have said, maybe that's bad enough. We don't really want it. But most of the time it would be a much smaller database because you don't expect these drugs to be harmful. And it's only when they are a little bit potentially harmful or uncertain that you'd get up into these kinds of numbers. And then as people have been saying, there would be a consideration of whether you really want to risk it, or you might ask for another 2,000 people or so.

DR. NISSEN: You said that very well. What you're really hoping for, Bob, is the first line. You know, where you've got a balanced number.

You know, it's .98 and you know what the confidence interval is around that. And you know, there's clearly equipoise to go forward. And as you move to the right you get into areas that we all have our own

comfort level with. I'm not sure what the right answer is.

You also really would hope that it's example number three where the point estimate is well under one and the upper confidence level is barely above one. You'd have no trouble at all with that drug. Where you clearly get into trouble is in the second and the fourth example. And that just becomes a question of where you set the level. And I think that some of this can be addressed in whether a drug, when it's first launched, is one that one wants to put some pretty significant language into that says if it's the second example there where the point estimate is going in the wrong direction, there's some uncertainty here.

I would argue, however, that from an equipoise point of view, in the second example, there's still plenty of reason to do a trial because you have an excluded benefit. And I also want to make a point that several

others have made that's very important. You could have an example like the second example there where most of the hazard was in -- these are going to be relatively short-term studies in the screening phase. What if the drug has a late benefit? You're never going to get there if you set the bar so high for that first screening study.

And so I'm prepared to accept the fact that there may be drugs out there that have an early hazard that after three, four, five years turn into a benefit. And if you're ever going to find that out, you have to take some amount of uncertainty at the time of drug launch and resolve that uncertainty.

What I am unwilling to accept is that you have a signal, like the one in the second example, and you never answer the question. And that's what happened, obviously, with rosiglitazone. And it's happened in some other circumstances. And

that's a mistake because we don't get the answer that we ultimately need.

DR. BURMAN: Thank you, Dr. Goldfine.

DR. GOLDFINE: Thank you. He actually just in part answered my question. But I think I'm going to phrase it slightly differently because I think -- don't sit down, please. Sorry.

So many have actually considered diabetes to be a cardiovascular risk equivalent. And if you take somebody with diabetes who has already had a MI, many of which are actually included in our pre-FDA-approved studies -- these are actually a particularly high-risk and vulnerable group. So if you actually now are exposing our highest risk individuals to the newest agents before you're actually having FDA approval -- and I'm sort of pointing on your three step pre-approval development program where you just commented on useful, at least one study in patients with CV risk,

perhaps 1,000 patients for one to two years -- you actually run the risk of exposing these people and missing those where the benefit may be over extended time. And I wanted you to comment on that possibility as well.

DR. NISSEN: Well, again, unless you're willing to say we need a five year outcome trial before approval, we're not going to know about that.

We're just not going to know about the long-term effects of the drug.

One of the questions that was implicit in what you're asking is is it appropriate -- is there equipoise -- for taking a group of people that are at the highest risk and exposing them to a drug that we know the least about? Let me point out something to you. If we approve drugs ACCORDing to the current standard, that's exactly what's going to happen.

I'm going to tell you what my

experience has been at the Cleveland Clinic. When I send the patients out of the CCU, they go upstairs.

You know, in the post-rosiglitazone controversy era, the first drug they get put on upstairs by the endocrinologist is a DPP-IV inhibitor for which we have the least amount of long-term data. And so look, high cardiovascular risk patients in the diabetic population are everywhere. And they're going to get exposed to these drugs. Wouldn't you rather know what the risks look like before the drug gets on the market rather than after?

And so that's why I'm proposing that you have to go into a population that's vulnerable. If you don't do that, you have the possibility that you're going to turn a drug loose into hundreds of thousands of people for which the hazard has not been adequately defined. And so I'm trying to say we've got to define it earlier on -- or at

least define what the limits are around it -- relatively early on.

DR. BURMAN: Thank you. We just have a couple more minutes. Any further questions?

DR. KONSTAM: Steve, while you're still up there. So could you defend MACE as the appropriate safety endpoint -- primary safety endpoint, let's call it here. So you know, it certainly makes sense -- well, I think it makes sense as a composite efficacy endpoint for cardiovascular interventions.

You know, maybe it makes sense mechanistically because we've heard a lot about the distinction between microvascular and macrovascular effects. But, we have the ACCORD study that had a diversion a difference of direction between the composite endpoint, and mortality, and cardiovascular mortality. So it didn't really work there.

And then, so if it doesn't really work there, then I'm sort of back to wondering, well why isn't retinal hemorrhage

a safety endpoint? And so if you had a drug that clearly shows benefits in the microvascular effects, maybe it exceeds a model based on glycemic control. Why isn't that the safety endpoint?

DR. NISSEN: Well, if you get these kinds of sample sizes, you're going to get a lot more information than we have now about these other adverse and favorable effects.

I can argue either way. If you wanted to debate me on MACE, I could take either side of the question and argue it. That's why I gave you a table that had exposures for both. I think it's going to be one of the challenges of this committee to decide whether that left column, which is based upon rates of death, MI, and stroke, is the more appropriate endpoint, or whether you're comfortable enough with adding hospitalization for acute coronary syndromes, which enriches the event rate and makes the bar a little bit lower. You know, I tend to

prefer those events of death, MI, and stroke, because they're the clearest, the most easily adjudicated, the most objective. But there are choices.

DR. KONSTAM: I guess I'm asking a different -- I think I'm asking a slightly different question. I'm wondering why isn't retinal hemorrhage in there?

DR. NISSEN: As a composite?

DR. KONSTAM: Yes.

DR. NISSEN: Because I'm not going to mix macrovascular and microvascular endpoints. We already know that there's a very robust effect on microvascular endpoints.

DR. KONSTAM: Okay, well -- and maybe we'll talk about this tomorrow.

DR. NISSEN: It dilutes the signal.

DR. KONSTAM: But, again, when we look at the data from ACCORD, it sort of flies in the face of saying there's a single mechanistic explanation for macrovascular events and they're all going to go in the same direction.

Your points are well-taken. I'm just wondering where to wind up on this because we have a clinical spectrum. And I'm just a little bit fuzzy about why this is the key safety endpoint for this population.

DR. NISSEN: Well, again, I would not throw together the microvascular and the macrovascular endpoints because I think -- one thing I was convinced of by the talks this morning is we know a pretty good amount about the relationship between blood sugar lowering and microvascular outcomes. In fact, one of the reasons why I am proposing not requiring a very large outcomes trial prior to approval is because there are microvascular benefits. And so, now what you want to do is in a context where microvascular benefits are assumed, you want to rule out that those are counterbalanced by macrovascular harm. And that's why I focused this on the macrovascular events.

Now, whether it should be death, MI, and stroke, or death, MI, and stroke plus

some softer macrovascular endpoints, this committee can opine. And Bob Temple, you've been looking at this for a lot of years. I don't know what your feeling is about it, but you know, I would keep in mind that some pretty good trials used MACE, including Prove It, which changed our practice in the use of statins in the post-MI world. So it's not a crazy idea, and it does conserve sample size to some extent.

DR. BURMAN: Thank you. I think the hour is approaching. Are there any last questions for the speakers? One last question, please.

DR. DAL PAN: I have one question for Dr. Nissen. If you go to the slide with the 4 scenarios of 87 events, it seems like your proposal for the bottom scenario, where you have the point estimate of 1.56, is you do further pre-approval testing --

DR. NISSEN: Absolutely.

DR. DAL PAN: For scenario 2, the

estimate of 1.23 you do post-approval testing. How about scenarios 1 and 3? Would you go to the second step in each of those?

DR. NISSEN: Yes. Yes.

DR. DAL PAN: Okay.

DR. NISSEN: You know, but I think that I would be pretty comfortable with the Agency approving those drugs to lower blood sugar -- that is scenario 1 and scenario 3 -- under the provision that the large outcomes trial is underway. Why? Because we clearly need more information.

And particularly in scenario 1, the upper confidence interval is still in the direction where we could see some pretty significant hazards. And because these are going to be based largely on short-term trials. And we need to know what happens over, say, a four- or five-year period of time.

So regardless of whether you think it's likely to be risky or not, there may be

a dissociation between short-term outcomes and long-term outcomes. And I want to give every drug a chance to prove benefit or harm in that setting -- in the long-term setting -- the setting where it's used. Because, frankly, my patients with diabetes are getting treated for years, and years, and years.

And I hope if we get better at this they might be treated for 15, 20 years. I've got patients who had diabetes for a long time. Thank goodness. Because we're able to keep them alive.

DR. BURMAN: Thank you. Any last burning questions? Dr. Parks, do you have any announcements or anything? No? Okay. Then I think we will -- we want to thank the speakers for their excellent discussions and for staying all day. It was really a wonderful session. Thank the panel members. And we'll adjourn now and re-assemble tomorrow morning at 8:00.

Thank you.

(Whereupon, at approximately 5:28 p.m., the MEETING was continued.)

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