clinicians are asking, anyways -- is, what do we do with these individuals that are potentially high-risk to begin with.

You know, the Rosi experience has actually been interesting from a post-marketing experience, because when we've had to discuss rosiglitazone with our patients, we present their data about potential cardiovascular risk and then we ask them if they are willing to take that risk even though their hyperglycemia has been well-controlled with this agent. And I think that -- those are the kind of questions that we need to begin to address, and this is the time for this type of process.

I would use active comparators, and this goes along with the theme that we can't use placebo controlled trials. It's conceivable that you may have some subjects with early diabetes that would go on a placebo control trial for a short-term, and that would be part of a Phase 2 and maybe a

small part of a Phase 3 trial. But I think for the most part, we really need an active comparator.

So I would say that that would be important and I would say it would be standardized to either an oral agent and or insulin with some pre-defined goals for hemoglobin A1c.

In accordance with that, in the next part of the question, how would glycemic control be included, I'm not as familiar with some of the trials. There's Judith and Peter and the other people who have sort of overseen those studies. But I know that there are ways in which that can be standardized so that we try to get to the best reasonable level of control. So I'm not sure I can answer that as well. Peter suggested a stepwise approach. I'd like to see the details of that, but I think that that's the approach I would use.

And I do believe that it would be

really critical to encourage all the investigators to use some sort of algorithm to ensure that risk factors are equalized. Because I think that is one area where I think there's so much heterogeneity that it makes it very difficult to interpret the studies.

DR. BURMAN: Thank you, Dr. Rosen.

Dr. Day.

DR. DAY: As a cognitive scientist, I have an initial comment about this question. It is wonderful in that it puts everything together in terms of what would be needed for long-term trials. On the other hand, there are seven different bullet points and it is very difficult to listen to colleagues with different types of specialization respond to each and keep all in memory, and then compare to your own opinions and make adjustments and so on.

Mr. Chair, you've done a wonderful job in guiding us through all this. I think I would have preferred to take these in

chunks. It's well-known in cognitive science if you have a long list of things and you've got to deal with all of them, it's very difficult. But if you take a subset that goes together and everybody talks and then another and then another, it can be more beneficial.

So I might have suggested that there is an initial chunk, which is what's the purpose of such a study to demonstrate the CV benefit versus rule out the risk. And then there's a chunk or package that goes together about the primary endpoint, size, duration, patient type may be the comparative group. And then the last chunk is, how do you manage people along the way. And I think that hearing each of -- something about each of the chunks along the way would have been very useful to some of us, especially to me to then go on to what the next ones are.

So I'm having difficulty in going through all of these for you at this time.

But, I'll do the best that I can.

I don't know if anyone else would agree with breaking this up. I see some heads nodding, and they're next to you, so if you'd look around and just notice --

DR. BURMAN: Well, thank you. As a cognitive endocrinologist, I take these very appropriately. And I'm happy to -- since we want everybody's opinion, it's difficult to have each chunk talked about and I would ask --

DR. DAY: Well, not all seven. But, there's three kinds of chunks --

DR. BURMAN: Well --

DR. DAY: And if we --

DR. BURMAN: That gets into how the questions were made in the first place, and that's a separate issue. So I think however you want to respond. Your comments are certainly appreciated.

DR. DAY: All right. I'll proceed and decline to comment on some along the way.

So what should the study be about?

It would be nice if we could show a CV benefit, but it's never been demonstrated before. So then that impacts one of the later questions, how long should the trial go on. So if it's not been demonstrated, it's been approached once, maybe. It might have to go into perpetuity. So if everybody decided that they wanted a trial for that, then the duration might be exceedingly long. So all of these decisions impact each other.

So given that it sounds like most people are interested in ruling out CV risk, that does seem to be the most important thing before us right now.

And I would agree with considering the confidence interval as well as the hazard ratio. I mean, these wide confidence intervals that also overlap each other are very difficult to deal with.

In terms of primary endpoints, I think there's some agreement about a composite endpoint with real clinical events.

It looks like the duration should be at least three to five years, all other things being taken into account. Impossible to say size without deciding some of these other things as well.

I do have a recommendation with respect to patient type. I think the arguments about patients with increased CV risk has been well made, but how are these drugs going to be used? There's going to be new patients coming in and I'd like to see two sub-sets, not just included but specifically considered as sub-groups and perhaps analyzed separately. And that would be recent onsets and then those with increased risk. Because although you cannot get enough events out of recent onsets, I think it would be important to know about them, since the number of new onsets is increasing all the time. So I would like to see both sub-groups addressed.

As for comparative groups, that's

very difficult and I decline on that one.

And glycemic control, I didn't hear exactly from people what the escape criteria might be. And managing other factors along the way, I think both of those go together in terms of how do we balance the real world use and ethical treatment of patients in the trials with the purity of the scientific analyses we can get afterwards. And I think that sadly enough, in 5 or 10 years, this Committee may meet again and say yes, and we had all these recommendations to do all of these but then these factors are confounding what we got and so on.

So I don't think that there is a true path to conducting these studies in a real world context enough that does not compromise the clarity of the scientific outcomes without confounding, and vice versa. And I don't know what the balance is between the two of those.

DR. BURMAN: And let me say thank you

for your comments, and I certainly -- I know you're really an expert in developing questions. We talked about that before. And it certainly would be in favor of you being involved of the process in the future. So thank you for your comments.

Dr. Felner.

DR. FELNER: Yeah, I'm going to take this -- I mean, I think you could look at -- I'm going to answer the questions a little differently than they're -- at least in a different order. Because I think the important piece is really the which patient population you want to look at. And you could actually answer, I think, all of these questions for each group of patients. Whether you want to look at pre-diabetes, glucose intolerant, early diabetes, late diabetes, those who have cardiovascular events or high-risk.

I mean, I'm a pediatric endocrinologist, so I don't see, obviously, the type 2 diabetes that most of you guys

see. Although I see a tremendous amount of obesity in kids who I know are going to have diabetes at some point in time. And the way -- after looking at some of the DCCT and UKPDS slides that we've seen and just reviewing that -- I mean, I like to believe that the rosiglitazone information and some of this -- some of the data that the drugs are getting are not necessarily related to the drug.

I think these patients have something going on well before they're actually diagnosed with diabetes, and if they're picked up early enough then it may be much more beneficial from a cardiovascular standpoint to at least help them if they're started much earlier.

We know it's pretty easy to help their glucose, whether they've been walking around for 5 or 10 years with diabetes. You can get that in decent shape for many of the patients. With one of the many drugs that we

have.

But as far as the cardiovascular effect, I think the real look needs to be done early in the disease really in your glucose intolerant patients.

So I would start with that as really the answer to this first question as looking at the impaired glucose or the intolerant patients, starting with them. And then as far as an objective to show a cardiovascular benefit or a pre-specified -- or to rule out a pre-specified increase, I mean -- the fact that if you can show that a drug is not going to cause cardiovascular harm, then I think that would be the beneficial route.

Is it a problem to look for cardiovascular benefit? I mean, I kind of agree with both of these options. And maybe you're not supposed to. But I could see taking both of these sides. And if I chose for the cardiovascular benefit, that really

is looking for a new drug. If you're looking for to rule out a pre-specified increase, a hazard ratio, I think what Dr. Nissen had gone through was very acceptable. Looking at a hazard ratio somewhere in this 1.2, 1.3 range.

As far as endpoints go, I think most people are really on the same page at least that have spoken before me with this composite -- really the primary being composite clinical endpoint. And making the individual more secondary.

As far as size and duration, it should take at least three or more years. And somebody had commented that if you look at the impaired glucose group, it's going to take forever to really find events. Well, this is a progressive disease. And if you pick these patients up early enough -- which you should -- in their teens, in their twenties, you'll have the data. And yeah, it'll take time but that's the whole point of

this whole idea behind this disease is it's a progressive disease. And I think you'll have the three- to five-year -- you could use three to five years and probably looking for for this adequate benefit you're looking about 10 to 15 percent better than the standard of care. So I think that answers.

And then since we're -- since I would really study this impaired glucose group, I think you could simply do a drug X versus placebo or a drug X versus drug Y. I think that would be a very simple way to start. Obviously if you're taking patients that are already have established diabetes, then you'd need to look at obviously a more complicated comparative -- comparison.

As far as deteriorating glycemic control, there's pre-defied goals. But really you want to have your glucose optimized, your A1c is best shape as you can. And if they fail in that sense, you have either insulin or some other algorithm with

an oral agent to use to help normalize that.

And then as far as the blood pressure, lipids, aspirin use, I think you want to equalize the risk factors. So obviously, I think we should be doing both of those jobs.

But, I mean, in looking at the whole thing as an endocrinologist, you know we're being asked here to look at a big cardiovascular part. And I think maybe it was Dr. Nathan who said that most of the endocrinologists don't have anything left to do if this becomes a big piece. Because the cardiologists are wanting to take it over. But, I look at it from the opposite is, I don't want to do any of the cardiology stuff. I don't want to have anything to do with it.

So if we start our job early enough and we get on these patients who are overweight, who have impaired glucose intolerance, who have -- who are going to get diabetes, then we'll prevent most of this

well down the line. And I think to put a drug onto somebody or to give somebody a drug well into their disease of diabetes and then say, oh great, it caused a cardiovascular abnormality, when that abnormality probably existed 10, 20 years before. That's my opinion on it. I think it at least has some substance to it. But I think most of this should be looked at well before they get into the disease. Because you really don't know what's causing that cardiovascular effect.

DR. BURMAN: Thank you very much. Dr. Fleming. And let me just get you an outline -- it's about 10 to 12:00, and we're going to take a lunch break at noon. You know, feel free to make your comments, if we want to continue later we're happy to do that. Then we'll go around and go to Question 3 and the vote later.

DR. FLEMING: Great, thank you. Just to begin, general comments. We certainly do need clinical trials, including cardiovascular

safety trials, in order to allow patients an informed choice. Not just a choice, but an informed choice about interventions. And to allow timely and reliable identification of interventions that do have unacceptable safety risks. And this can't just be done post-marketing.

And it's not sufficient to be done through post-marketing surveillance from pharmacovigilance.

Dr. Califf made a good point that it's especially important for these insights, safety insights -- reliable safety insights -- to be in hand for agents that are chronically used in large-scale settings.

There is additional particular motivation for a substantial amount of this insight to be obtained pre-marketing based on the experience I've had of being on many data monitoring committees that have been doing major safety trials, and there isn't the same sense of urgency in the conduct of those

trials post-marketing that exists pre-marketing. The quality and sense of urgency is enhanced when they're done in a pre-marketing setting.

So to get at the specific bullet point questions. Regarding the first question, as my colleagues have said, I agree that based on efficacy -- specifically the evidence for benefit on microvascular complications -- it's adequate to rule out cardiovascular harm rather than requiring that these trials actually establish cardiovascular benefit.

Of course, by conducting these trials to rule out unacceptable cardiovascular risk, it's possible these studies could actually show cardiovascular benefit. And if in fact they do, we talk about the burden to developers. If in fact you show that, there's a major reward when you in fact have an agent that has been established to not only provide the

microvascular, but macrovascular complications, certainly for that agent as well as for the overall use of such agents in the field.

Thinking back to lipid-lowering agents. When the statin trials were establishing definitively benefit on MI and death, the overall volume use of such agents became much greater. So it's certainly to the benefit of developers to be able to reliably establish when there are benefits beyond -- in this case, beyond microvascular benefits.

What should the end point be? I agree with my colleagues, who have advocated myocardial infarction, cardiovascular death, and stroke. These are the most clinically compelling. But furthermore, these are where the signals are. A cardiovascular safety trial needs to rule out what it is that you are worried you've seen before. So these are -- this composite is what was seen in

muraglitazar, at least suggested -- the MI suggested rosiglitazone death in ACCORD. So we aren't ruling out the concern if we don't specifically use as the composite endpoint those measures that in fact have been suggested to be potentially harm.

What about the size and duration of these trials? And this relates to the margin issue. And this, as my colleagues have said, is a difficult question. But it's one that we need to do the best we can to address. And we can address it in an evidence-based manner. The question that was raised here is, do the margins have to be 1.2 to 1.4. Again, I suggest this needs to be handled on a case by case basis. But, in general I would think that possibly somewhat larger margins could be justified.

Something in the range of 1.33 to 1.5 for this definitive cardiovascular safety trial.

So what's the rationale for that?

Well, suppose we are enrolling a population that would have about a 2 percent annual risk of our composite endpoint -- cardiovascular death, stroke, and MI. If you had a 1/3rd increase, that would translate to about 6 to 7 additional events per thousand person years. If you had -- if you were ruling out a 1.5, a 50 percent increase would be 10 additional events.

Now to put this into context, the precision trial that we talked a lot about yesterday that was looking at celacoxib against naproxen was ruling out 1.33 -- 33 percent increase when you had a baseline rate of 1 percent. So that was ruling out three additional events per thousand, saying a positive trial would have to have an estimate of no more than one additional event.

That was based on careful consideration against the benefits. The benefits there being, widespread analgesic

benefit -- although, you could still get that with other agents but maybe not as thoroughly in all cases. And reduction in GI ulceration.

Here, what we're talking about as benefits are microvascular complications. Well, we need to do some numbers here. Let's project what is, in fact, the expected benefit that you're seeing here in terms of preventing microvascular complications.

So the size of this margin may well be specific to the agent. May well be specific to how compelling is the evidence that this specific agent provides benefit in these other domains, such as microvascular complications.

But, my general sense is, when such analyses are done you may well be in a position to say, it's adequate to rule out a one-third increase or the Lipicky-Temple rule of a 50 percent increase.

Now, what does that translate into

in terms of trial size? A one-third increase -- we've already -- these exact calculations with the precision trial. It would take 508 events, or roughly 500 events. If we were doing a five-year trial, it would take 5,000 people: 2,500 treated, 2,500 controls.

On the other hand, if we could say it's adequate to rule out a 50 percent increase, it'd be half that size: 256 events or 2,500 people. Just to put this into context, the PROactive trial had more than 500 events. The ACCORD and ADVANCE trials are twice the size of the 5,000-person trial, four times the size of the 2,560 person trial. So we're talking about the definitive trial being one-fourth to one-half other trials that have already been conducted.

I agree with others. We should pursue pragmatic trials to make this more achievable and more affordable. The burden will be less if we pursue pragmatic trials.

Such studies would be positive if you had some excess. If the estimated excess was no more than about 12 to 17 percent.

That translates to an estimate of three excess events per 1,000 person years. That meets the Califf cut-off that Califf was talking about yesterday, a 10 to 15 percent increase being clinically relevant.

These studies would only be positive if your estimate was no higher than that. And again, its justification for allowing that is the microvascular benefits.

Now, as achievable as these trials are, I think Dr. Nissen made a key observation yesterday that while it's important to have insights pre-marketing, it is a burden to do this entirely pre-marketing. And so a compromised strategy of saying that a screening assessment could be done pre-marketing and this trial could be done post-marketing is rational.

So just to quickly touch on the

size of that -- from these numbers, the smallest that I can seeing justifying would be the second to the last line in the Nissen slide, which would be 125 events.

A 125-event trial. By the way, that's one-fourth to 1/8th the size of an ACCORD or an ADVANCE study.

If this were a 2-1/2-year trial -- so if you followed these people for 2-1/2 years, it would take 2,500 people, or 1,250 treated patients. A positive result would be an estimate of no more than 25 percent increase. Now, that is ruling out an 80 percent increase. So that's not a definitive answer, but it's at least some reassurance that it's not more than an 80 percent increase.

And it has the property that, if you had a percent increase, you only have 1 chance in 7 that you'd see an estimate of -- as favorable as 25 percent increase or better. So that's the rationale for saying,

this is a screening assessment, doesn't give you the final answer but gives you sufficient encouragement to go on.

Now, how burdensome is this? A 2,500-person, 1,250 of which are treated, contrasts with what we saw from Dr. Parks that pre-marketing we're seeing 3,300 to 4,400 people have been treated. So it's a fraction of that. However, the person years that she referred to as 1,300 to 2,600, the person years here is 3,000. And so in essence, the difference is those experiences have typically been following people 6, 9 months. This is following people for 2-1/2 years. But still the total person years of 3,000 in treated patients is not that dissimilar from what is currently the experience.

Mary, did you want to interrupt?

DR. PARKS: I'm sorry. A point of clarification on the total number of patients exposed in that slide that I provided you.

That's including Phase 1 trials as well.

DR. FELNER: Okay, that's fine.

DR. PARKS: So just to make it clear, it's not 3,000 patients --

DR. FELNER: Understood. And that's the point that I was just making, is that the total treated patients of 3,300 to 4,400 is giving rise to 1,300 to 2,600 person years, whereas this study, which would be 1,250 treated patients, would be giving rise to 3,000 person years. So that here you would be doing a more extended follow-up.

That more extended follow-up has substantial advantages to the sponsor, advocacy for the product, because if it is in fact true that the longer you're following these patients the more likely you would be seeing evolving beneficial mechanisms for affecting cardiovascular death, stroke, and MI to offset shorter-term adverse, than it actually has a better chance of being more

favorable when you have somewhat more follow-up.

One point that was touched on, it's related to Dr. Temple's point. This study, when it's completed, is intended at a minimum to rule out an 80 percent increase. And it has, however, the possibility that your estimate is much better than a 25 percent increase. Your estimate could actually be neutral to favorable.

If you're estimating a 30 percent reduction in this trial, that's superiority. You're done. There's no need for that confirmatory trial post-marketing. In my view, you've proven superiority on this point.

But even if it's less favorable, even if it's just slightly favorable, a 5 percent reduction, that rules out a one-third increase. I think it's relevant to discuss whether that could be sufficient to then not just -- to justify that you've ruled

out an unacceptable increase and you wouldn't need to do the post-marketing, large-scale study.

So let me close here by quickly touching on the last four questions. Very quick comments on the last four components to this. In terms of populations, I'm looking for comprehensive assessments here. If this is an intervention that would be used in pre-diabetics and diabetics, et cetera. This needs to be assessed. Whether we can pool pre-diabetics and diabetics is an interesting discussion. But, in the diabetic's assessment certainly we should be looking at some patients that are high-risk. And in fact, obviously those high-risk patients will contribute a larger fraction of events.

In terms of the design, I would favor a real-world design. I would like designs to represent what the affect would be in a real-world setting, so I very much like the drug X plus standard of care against drug

Y plus standard of care, where drug Y would be restricted only to be an agent without a cardiovascular signal. Because we want to, in this comparison, be able to say if you're comparable, you're comparable safe not comparable unsafe.

Regarding the deteriorating glycemic control, patients should be managed per current guidelines. But everybody counts. I favor the principal analysis of intention to treat. So if there's deteriorating control, then add insulin or add whatever would be appropriate real-world standard of care. And everybody should be followed.

Now, because everything counts, though -- and these are the issues I was talking about yesterday -- there are some key performance standards that have to be met. The first is, you need to have good adherence to the experimental intervention. We're trying to rule out whether there's an excess

cardiovascular risk, and this experimental agent needs to be adhered to at least at a level that would represent best achievable in the real world.

The control arm needs to be provided a standard of care, but first of all there should be no access to the experimental. You shouldn't be able to cross the patients into the experimental. You're nullifying the ability to interpret the data from a safety perspective. And there should be no, or at least very limited access, to standard of care agents that themselves have a suggested increased cardiovascular risk. So wouldn't want a lot of rosiglitazone use or use of agents that might be suggested to potentially have an increased risk in that control.

Last point. In terms of managing the blood pressure, lipid levels, aspirin use, et cetera. My overall philosophy is, I want a real world answer. And therefore,

yes, we want to manage these according to, in my words, the best achievable real world adherence to current guidelines. So what are current guidelines for managing these risk factors? Then we should be getting the best achievable real world adherence to those guidelines.

That might yield, in the end, some difference. But that's inherently part of the regimen. It's part of the impact of that intervention. But, this is not -- this needs to be done with rigor. This needs to be monitored during the course of the trial and there should be pre-specified performance standards as to what would be best achievable real world implementation of the supportive interventions. And that should be what we would strive to achieve.

DR. BURMAN: Thank you very much. We're getting a lot of very good information, and eloquently and quickly. And with that, we're going to adjourn for lunch and then we'll

reconvene at 1:00 in this room.

Please take any personal belongings you may want with you. The ballroom will be secured by FDA staff. You won't be allowed back into the room until we convene. And remember, there should be no discussion of the meeting during lunch among yourselves or other members of the audience.

Thank you.

(Whereupon, at approximately 12:04 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. BURMAN: Why don't we get started for the afternoon session? Let me sort of give an outline of the afternoon session and see if the panel agrees.

We definitely want to end by 4:30, everyone -- a lot of people have plane reservations.

And hopefully, we'll adjourn even earlier than that. And we have several issues to continue to discuss. What I propose, from now until about 1:45, I hope, we'll go around the room and get everybody's individual opinions, as I think it is important for the FDA and everyone to hear them.

And then, from about 1:45 to maybe 2:30 or so, we'll have an open discussion of this question, so there'll be some interaction between the committee members and I think that's important, as well.

Then we'll go to Question No. 3 and vote on that and give specific -- and everyone will give their specific reasons for voting. And then we'll end up with Question No. 4, which I don't think will take as long as some of the other questions. And I realize that Question No. 2 is the most comprehensive question, so it will take the longest.

Dr. Goldfine, are you ready?

DR. GOLDFINE: Welcome back from lunch. I'm going to take these questions in a slightly different order than which they are presented, because I think they actually address different questions. And I'd like to begin with what type of patient population should be enrolled.

And I think, when you look at the different patient populations who enroll, you're actually asking very different questions. So I think I'm going to start by saying that any study to look at those with

acute coronary syndrome are going to have the greatest event rate. But you have to have a premise that the drug is actually going to be beneficial in that setting to ask that kind of question. And it is very plausible that a drug could be developed that is felt to have an important indication to health and acute event, that then may show to be found to be beneficial from a cardiovascular point of view.

An example might be an ACE inhibitor that will do afterload reduction; therefore it's a plausible reason to be using it in this population -- and yet may ultimately have been shown to have benefit in diabetes or diabetes prevention.

I think if you move to pre-diabetes, however, there's no potential benefit of lowering the blood sugars at this point in these people, for protecting them from microvascular disease complications that's been very well-established. And the

whole reason to treat pre-diabetes is that you actually are going to be either significantly delaying the onset of development of diabetes, and or its complications. And we're not there yet. And the trial size would need to be much, much larger, and as Dr. Ratner pointed out from the DPP, the incident rate of events in that particular population is extremely low, and so this would be part of a staged program development.

So I think we get into patients with diabetes and we must consider those who have a high-risk, which are the patients with diabetes and pre-existing cardiovascular disease, but who are otherwise stable and not in an acute event setting.

So once we say that that would be an initial group to study, we can then extend into the other populations in the logical manner. I think the question, then, as we go up to the beginning of it, should the trial

be to show cardiovascular benefit of a new drug or to rule out unacceptable increase?

I think that it is possible to do a non-inferiority trial and actually demonstrate that you actually have benefit, and I think that would be a wonderful blessing. But I think, again, what we actually feel that we need after yesterday is a neutrality in this, or at least a margin that we would find excludes intolerable risk.

And I think that there, again, as Dr. Fleming said -- suggested that it might also be possible to modulate what the amount of the risk that we're willing to tolerate is. And that, at this moment in time, would be willing to how beneficial or efficacious it is for our glucose lowering and our presumed other benefits of actually lowering the blood sugar.

So the objective of the trial really should be to demonstrate safety and the duration of it, then, needs to be

modulated based on whether or not you're preventing an acute event in a rich population versus doing primary and secondary preventions. And it may take much longer to go from the endothelial dysfunction early atherosclerosis to form plaque and that maybe a very different question than actually preventing the person who's gotten established and formed lesions.

So then, the next question about what the ratio is, I think -- that I think it actually may slide, based on the drug. But I also just want to point out the conundrum from the clinician -- that to say that you could accept a drug with a margin of 1.4 risk, yet you would approve a drug that had a 20 percent, or 1.2.

You know, a 20 percent benefit is actually a conundrum, and so I think it's very clear that these might be -- in staged ways -- to allow a drug to go forward, but may not be acceptable limits as you move into

the larger trial designs, that I think are going to be absolutely necessary. So I think it's very important to say when you have a margin of risk that acceptable for moving forward into a more definitive trial from what that limit is going to be when you're actually going to be in a definitive trial.

I think that for adding drugs or controlling diabetes, we certainly have to have safety limits, and I think these safety limits may actually slide with out current understanding of diabetes. And so if you look at trials that were conducted at the time of the DCCT, the limits and control groups are much higher than any of us would be comfortable with now. And we might have suggested that they needed to be lower than our current rates, but the ACCORD data suggests that that may not be the case.

So I think that the -- when the trial is designed, you have to use the information available at that time and we

have to have a little bit of flexibility as to what these cut-offs, these safety cut-offs, are for adding drugs. As the armamentarium grows, the complexity of interpreting your results will become much more complicated if everybody is allowed to add whatever they want, in whatever order they want.

And while that may be most real world, it will also be most difficult to interpret. And therefore, I actually do like the staged or step-wise edition of agents, following some of the cardiovascular trials that have been underway. Because at least those will be able to be interpreted to a best way -- and I think there is a stage way in which most clinicians would be recommended to be adding drugs. And so I don't think it should be terribly off from real world.

And I think that at this point in time then, the final question really had to do with the management of the -- aggressive

or appropriate management of blood pressure, lipids, aspirin, and other cardiovascular risks. And I think at this point, this is standard of care and should be enforced standard of care across our country. And therefore, we need to talk about additive benefit or additive risk to what is already a clearly lowering our incident in disease in our patients.

DR. BURMAN: Thank you. I'll just summarize my views briefly here. I agree that the objective for long-term studies should be to show no unacceptable adverse cardiovascular effects, and should not be primarily to show cardiovascular benefit.

Diabetes is a complex disorder with multiple confounding issues, including progression of disease, use of multiple agents, and varying genetic background. Treatment of microvascular events is extremely beneficial to patients in cardiovascular diseases, of course,

correlated with diabetes mellitus. I think it is impossible to demonstrate no unacceptable -- I think it is important to demonstrate no unacceptable adverse effects of the anti-diabetic agents.

The hazard ratios, where we'll -- I recommend that we'll be discussing shortly in the group discussions. I think the endpoint should be the composite endpoints and the size and duration of the trial should be similar to what has been mentioned earlier. I think the high-risk -- that patients with diabetes should be studied primarily, especially those with high-risk disease. And I think, as I already mentioned, add-on therapy with comparator agents seems to be the most appropriate for these groups of patients.

And lastly, the parameters for treating blood pressure, lipid profile, and aspirin, all should be managed to goal in both groups, so they can be comparable.

DR. HENDERSON: The first bulleted question is an either/or scenario. We don't have the choice of both of the above. So given either/or, I would say that showing cardiovascular benefit would be nice to know, but the second one, being able to rule out risk is a need to know. So I vote for ruling out the cardiovascular risk as a need to know basis.

As far as relative risk, my main mantra is that we need subgroup information. We need definitive data for subgroups. And to me, it's even an ethical issue that we come up with a 1.0 estimate for all diabetics. Like a diabetic is a diabetic is a diabetic is saying even if we agreed on a 1.3 point estimate, will Dr. Felner's pediatric patient be a 1.3, such as a 40-year-old man, overweight, newly diagnosed?

Such as a 65-year-old woman being diagnosed with diabetes for 30 years? We just can't say that it's a 1.3 risk for all of those types of patients.

And yesterday, Dr. Califf talked about truth -- about uncertainty on the label. And I think that is an admirable, noble goal. It's not truth in labeling if we have information that some people are more at risk than others, and we don't put that on the label. And I'm thinking about the Rosi study last year. From the preliminary data, it was very obvious that some people should not be taking Rosi, because of the different subgroups. But we didn't have enough data for it to be definitive. And so then that couldn't be put on the label. And again, I just think that we need to account for that variability.

So wanting this data by subgroups characterizes the rest of my answers. I do -- the next bullet point, Wanting a Standardized Definition, and look at total mortality, CV deaths, strokes, and MIs.

The third bullet point, Comment on the Size, again, I think we would need a

larger size if we're going to be able to do a power analysis among the subgroups. Such as those by age, it looked like, in other data, that people were at varying risks by age. Also whether or not they're taking insulin. Male/female groups, for example. Maybe overweight/non-overweight. Different groups, so that we can not have just one estimate for everybody. And I think it should be a minimum of five years.

And the next bullet point, again, What Types of Population, I want a large enough study so that we can have power among those subgroups. I agree with what's previously been said for the next bullet point, that we need real-life active comparators.

The next bullet -- my main concern is that when someone is withdrawn from this study, that we do follow them for a little while, even after they're withdrawn from the study, so that we can look at are there any

lingering side effects or prolonged effects.

And for this, I'm referring to a couple of years ago, we had a study on a weight control drug, and over half of the people had withdrawn from the study, and our main concern two years ago was, like, what happened to those people once they discontinued the drug? And that was a huge piece of missing data. And if it turns out in these clinical trials, we have a substantial number of people withdrawing, it is a good question to ask, what happened to them?

Maybe six months to a year, at least, after withdrawal.

And the last bullet, I think we are ethically bound to have optimal therapy for the clients.

DR. BERSOT: Well, I think that the purpose of these drugs is to control glycemia and not to prove cardiovascular disease benefit. But I think if the drug companies think that

they have a drug that will provide cardiovascular disease benefit, they should be encouraged to have a trial that proves that.

But in most of the cases, we're going to be looking at a non-inferiority trial result. And I think, practically speaking, to be able to have a study that has enough people in it and enough events, we're going to be talking about adults, probably middle-aged people who have a prior history of some kind of coronary disease or cardiovascular disease to be able to have enough events over a period of time -- a reasonable amount of time.

Now, in terms of the hazard ratio, that, to me, depends on what the absolute event rate is, of course. And since I'm a lipid guy, I sort of -- I went to the outcome of the diabetes arm of the recently done -- to new targets trial, where they looked at the outcome of 10 versus 80 mg of Atorvastatin in diabetics treated over 5

years; to an LDL cholesterol of either 100 or 77 mg per deciliter. And the groups were matched in terms of drugs taken for diabetes. And about -- in the group that had -- and this also I think, speaks to the issue of what current therapy is, in terms of events.

So the group that got 80 mg of Atorvastatin on treatment LDL to 77, about 14 percent of them either had a stroke, a cardiovascular disease death, or non-fatal MI. So if you're willing to accept the 20 percent increase in events related to the new agent, that would be about three people, additionally, having an event over six years -- a 40 percent increase -- six people having an event over five years.

Now, you could say, that's bad, but it also depends on the agent's ability to control microvascular outcomes and also the side effects. There might be that the agent could be used instead of Metformin in people with end-stage renal disease, in a safe way,

that perhaps this additional 20 percent increase in cardiovascular disease outcomes might be outweighed by the beneficial effects in terms of the glycemic control in people who can't tolerate other drugs.

So I think this issue of what's an acceptable hazard ratio is going to depend on what the current state of treatment is in terms of major cardiovascular events and also the benefits of the drug under consideration, with regard to microvascular outcome.

End points -- I think the endpoints should be what I just suggested, based on TMT. But of course, all of the other secondary incomes/outcomes should be evaluated. I think five years is a reasonable duration, given what's been commented on about, in terms of two years to three years not being enough time to see longer duration effects.

If you're going to be dealing with patients who are secondary prevention

diabetic patients who are pretty far down the pike in terms of their diabetes, it's highly unlikely that they're going to be able to be treated with placebos, so you're going to be adding drug X to standard of care, versus another drug.

So then the other point with regard to deteriorating glycemic control, I am not a Diabetologist, but I would presume once there's some excursion above a 7 percent glycosylated hemoglobin, then some, in my opinion, predetermined algorithm ought to be employed to eliminate the variability of different investigators using different agents to control glycemia.

I also concur with the points that have been made about treating patients to currently targeted goals for blood pressure and lipids. However, there is much more attention now being focused in the lipid world on reaching goals for HDL cholesterol and triglycerides. And the agents that are

added onto statins for that are primarily Niacin and fibrates.

So if you don't pre-specify how those drugs should be used, if you have some investigators who are big niacin fans, who want to raise HDL with niacin, you're going to be affecting insulin resistance with niacin, and perhaps affecting glycemic control.

With that class of drugs, on the other hand, fibrates, there's some indication that fibrates, which are primarily used to lower triglycerides, may actually have an ability to reduce cardiovascular disease events independently of their ability to change lipids. And there are also follow-up studies. For instance, the Helsinki heart study showed that after 18 years of follow-up, the original Gemifozil group had a substantial risk reduction, despite the fact that those patients stopped taking Gemifozil some 10 to 15 years before.

And there are also from the field study, are indications that, at least in that study, there may be an improvement in efficacy, and improvement in retinopathy and microalbuminuria associated with the use of Fenofibrate in that study.

So I think that there needs to be some careful thinking about these add-on drugs that are used to get people to the stated goals for raising HDL and lowering triglycerides, that already exist. And then there's the whole issue of what to do about changes in HDL cholesterol when and if CETP inhibitors hit the market, in terms of changes in HDL, as well.

Thank you.

DR. FLEMING: Starting with the first question, I think the problem before us is the increase in risk and not, per se, demonstrating benefit. Of course, we'd all like to see benefit demonstrated, but I think the trial's objective should be to not exactly rule out an

increase in cardiovascular risk, because you can't really rule it out. But have it be at a very low probability of if there's any increased cardiovascular risk.

And I think it would be good to have some risk benefit calculations of some kind in there. Looking also at microvascular benefits as well as potential cardiovascular risk increase.

I guess in terms of the risk, I consider it relative to what? For instance, relative to any benefits, but also relative to what comparator and what is the absolute risk in the group that you're looking at? So I think that's something that has to be looked at carefully, in terms of what is the magnitude? Because the magnitude of a relative risk of 1.2 is different depending on whether the baseline risk you're looking at is very low or very high.

In terms of the primary endpoints ACCORD really showed an effect on total

mortality and I'm a little bit concerned that a composite endpoint might not be completely specific as to what the potential issue is here. And maybe we shouldn't depend too much on ACCORD per se, but it does show somewhat different results when you look total mortality, which is what the trial stopped for or the composite endpoint, which looks much better.

So I think there -- I don't think cardiovascular or surrogates would be a good thing to look at. But I wonder if total mortality should really be the primary endpoint and a composite endpoint, and a secondary endpoint.

Size, I would think, of the trial depends on what you're trying to detect and what power you want? In terms of the patient population, I think this is a very tricky question because, on the one hand, people who are at very high-risk, you're going to get more advanced and so your sample size is

smaller, but they may be a very different kind of population. And in that regard, I would ask, exactly how would you identify people with diabetes who are at high-risk? Like, what characteristics would be the best way to identify them? And are there any special characteristics of their diabetes, as opposed to other characteristics which should be used to kind of stratify this population?

The risk may be very different in different people of different duration, for example, of diabetes. And so you want to find the group -- if you think there's an increased risk, you want to find the group that has the most increased risk because those are the people you're worried about. I don't know if you have, like, a lot of cardiovascular risks for other reasons that can be harder to pick up any effect with the drug? Or because it's kind of blotted out, so to speak, by the additional risk conferred by other characteristics? I think that's a

tricky question to address.

Just in general, I think from a core -- we really don't know are these drug effects or are they effects of the intensity of therapy, or the strategy that was followed? Or something about the subgroups? So we wanted to zero in, we want to look at the effect of the drug itself -- how to distinguish that from these other kind of characteristics of how these studies are being conducted, because ACCORD doesn't look at specific therapy.

In terms of active comparators, I think it also depends a lot on the types of patients in the study, and especially if you have people with longer duration or advanced disease. They're going to placebos, not an acceptable comparator. And you may have changes during the trial.

You do want to have drugs that have similar adherence, so you don't introduce that as a difference between these groups.

In terms of deteriorating glycemic control, I think there should be some kind of staged algorithm for addition of agents, so that there's something to reduce some of the variability in this whole process. And similarly with the other cardiovascular risk factors, I think you should treat optimal levels as much as possible, but follow current guidelines. In the extent that can all be standardized, too. And that's also likely to change over time.

I worry that event rate -- not worry, but event rates may been lower than expected.

They usually end up being lower than expected. Treatments for other conditions may improve, so that will definitely be something that needs to be thought about carefully and kept track of during the trial.

Thank you.

DR. PROSCHAN: Yeah, I definitely

think the trials should be to rule out a certain level of harm. What level of harm -- you know, I think ultimately that will depend on the HbA1c difference. But I like the Steve Nissen-like approach, and I would modify it in a couple of ways.

One would be to have the large outcome trial -- the large safety trial -- start certainly before approval. And then, in that trial, after there are 160 events in that trial, then I would take a look at it and see if the 90 percent one-sided competence interval rules out 1.50?

If it does, at that interim analysis, I would say, okay, you can go ahead and approve it but you continue that trial until the end, to figure out ultimately what the hazard ratio is. That has the property that if the true hazard ratio, not the observed one, but the -- if the true hazard ratio is 1.0, there's a 90 percent chance that they will pass that hurdle and get the

approval.

So I like that strategy. And then, as I say, ultimately though, at the end of that large safety trial you'd have to make a decision on what's an acceptable level, partly on the basis of what the HbA1c difference is. But I would think that levels around 1.3 -- hazard ratios in the neighborhood of 1.3 would be desirable.

Now, what should the primary endpoint be? I agree that non-fatal MI, CV death, and stroke is a good primary endpoint, but, as was just pointed out in ACCORD, the problem was total mortality. And so certainly -- I mean, obviously the FDA is going to always look at total mortality anyway. So I don't need to say that they should also look at that.

Size and duration? I think such a trial should be five years, because some of the problems in other trials weren't discovered until after at least two years.

And in terms of patient population, I would think that you'd want high-risk patients. Patients at high-risk for cardiovascular events. And I was thinking in terms of a drug X versus drug Y type design.

And then, deteriorating glycemic control, obviously I'm a statistician, so I don't know. You know, I'd assume, ethically, you'd have to give drugs for that, but -- you do? Okay, good.

And then, also I think ethically you do have to manage blood pressure and lipids, and so forth. The current guidelines, I mean, I would say you have to provide them with the current guidelines and say, this is what they should be. As far as forcing them to, I don't know about that.

DR. BURMAN: Dr. Lesar?

DR. LESAR: I'll start by stating, here is a member of the Drug Safety and Reduction committee, so my comments are based thinking a lot about risk. I'm not an

endocrinologist. I'm not a cardiologist, or a statistician, but just to address the first part, I do not think that there should be a requirement to show cardiovascular benefit, nor do I think the objective of any study should be to show up this benefit. However, certainly it would be beneficial to the population and their knowledge as a whole if such trial was undertaken, even considering the recent findings.

In terms of hazard ratios, in terms of studies to determine potential risk, and frankly, from my sitting and thinking about risk. Risk ratios of 1.2, 1.3, 1.4, up to 2.0 -- pretty scary, considering the severity of the adverse events and the this large size of the population that could be exposed to the drug. So from a public health standpoint, that risk, that hazard ratio, really how I think about it depends on are we talking about a pre-marketing trial or are we talking about a post-marketing trial?

The reason is in a post-marketing trial the population is exposed to the drug. So how much risk are we willing to place the general population?

The scenario could be that it's a highly effective drug at reducing hyperglycemia: Well-tolerated, easy to take, a large number of patients are taking it. And we are now in the midst of a trial to determine whether its risk ratio -- its haz ratio is 1.2. It seems like a fairly high population risk to take, so I would say that many of my comments will be -- the answer is, it depends.

Hazard ratio would be -- should be much smaller if the population -- the large population is exposed. And if it's submitted to a pre-marketing trial, it could be in the range people have been discussing. And also it would depend on, as mentioned before, absolute risk as opposed to a ratio. Again, what is absolute risk that we're exposing

both out-study subjects as well as the public, too? So given population is important.

In terms of primary endpoints, certainly hard endpoints are important. Well defined, consistent across studies, and, again, perhaps those might vary by the types of populations that are being studied, to improve either sensitivity or to improve sensitivity, or both.

In terms of size, again, five years minimum. I think it's the number of years that should be at least planned, with a plan that if there appears to be separation, or an increased risk starts to appear, but is not statistically significant toward the end of that trial, then it may need to be continued.

Also could be built into that is that if there could be a -- sort of points along those studies which has demonstrated that appears to be very low risk or potentially benefit. That, potentially, the

studies could be stopped. And also that we may need to look at changing knowledge base. That we may learn that we do need to tweak. We need actually study longer or even more populations. Again, so it's going to depend on population and what knowledge basis at that time.

In terms of types of populations, we certainly need to expose the highest risk patients to these drugs and that's who it's going to be exposed to once the drug is marketed. It is, perhaps -- I'll throw something out there -- is that the study initially shows a low-risk potential. Potentially for the lower risk populations, are there alternative methods of monitoring for adverse events, such as post-marketing surveillance, registries, et cetera?

In terms of comparators, I really think in real-life situations, people are going to prepare drug to drug, they're not going to leave a patient without drug, as

mentioned. Again, the important point being controlling as much as possible what drugs are being used and that they are very well documented.

Similar comments related to benchmarks or changes that for -- in terms of glycemic control. Again, it may depend somewhat on the population and initial risk for that patient. So again, there may be some variability. Again, those things can be defined and potentially controlled for.

And finally, certainly we should be treating to establish guidelines. And again, trying to control as much variability as possible.

Thank you.

DR. KONSTAM: Thanks very much. So I actually want to just start with sort of a broad comment and reflecting back on Rob Califf's outstanding presentation yesterday. But I just want to sort of reflect that we have so much to learn about this disease. You know, most

notably, what is the relationship between glycemic control and cardiovascular events in type 2 diabetes, and the metabolic syndrome. And many more questions about the best approaches to glycemic control, but I don't think all the world's problems have to be solved through the regulatory mandate mechanism. I think there are many important questions; we're answering them.

I'll speak on behalf of NHLBI, that clearly, we've shown that diabetes is a major strategic direction for us. And there are many opportunities to go forward with that investigation. And I'm sure I speak for NIDDK as well. And as people have pointed out, there's a tremendous opportunity for the pharmaceutical industry. If, in fact, you can identify that you have a cardiovascular benefit over and above the glycemic control of another agent, man, you're made in the shade.

So you know, I think that

there's -- and I think companies are thinking this way. I think some of the people who've given their talks today -- yesterday -- can help in designing trials that actually could achieve that goal, and I'm not sure that has to be mandated through the regulatory mechanism.

So getting back to the questions, I mean, I guess then as many others have said I feel very clearly that we don't have to establish a bar of cardiovascular efficacy for approval of the next diabetic drug. That would be, I think, unreasonable on a couple of different grounds. One being in my mind, the very clear establishment of glycemic control is an appropriate efficacy endpoint based on its linkage to microvascular events.

And secondly, we have to keep remembering that if we're talking about cardiovascular efficacy, it's versus what? Because presumably there is cardiovascular efficacy of treating hypoglycemia, but nobody

is going to, I think, ethically accept when HbA1c of 12 in a control group over a protracted period of time in order to show that. So that really represents a very difficult bar to hit.

So for those reasons, I think all of the focus should be on risk. And I think the issue of cardiovascular risk is an important one. I'm not sure how to interpret, frankly, the rosiglitazone data, but certainly -- and I think the point was made yesterday -- I don't think there's anything special about diabetes drugs in this regard. I mean, I think you can ask -- raise this question with every drug class. But we are talking about these drugs and I think cardiovascular safety is a reasonable endpoint. And the question then is, how do you get there?

And so you know, getting to this second sub-bullet, I mean, I guess I would start by saying I don't feel that we as a

panel should establish any specific statistical upper boundary. And I'll see if I can explain why, but let me just say that, to me, the most rational approach is a pre-specified safety evaluation program. You know, that begins certainly the early phase -- well, it begins in Phase 1, but certainly early Phase 2. And then goes forward from there with a unified analytic plan and a unified set of methodologies as the best approach.

And I think that -- so what are we really aiming for? I think -- I mean, my own view is the statistics is not a end in itself. It's a means to an end and what you really want is really a clinical assessment of risk, to be informed by particular pieces -- statistical pieces of information. So whatever a statistical bound of a particular trial is, my acceptance of -- my interpretation of that is in fact going to be informed by a lot of other things.

So number one, I think the points have been made. I don't think it's just the upper bound.

I think the number of events that are in the program ought to be taken into consideration. The point estimate, I think, still is important. So statistically, an upper bound of 1.8, you may have a lot of events, and therefore, get an upper bound of 1.5, and have a point estimate that's 1.35 or something, if you have enough events.

So are we happy with that?

So it isn't just the upper bound. I think those other points have to be considered. And the acceptability of a particular upper bound is, I think, further informed by other factors like, are there other signals of concern? I think that is an important question. You know, what else is the drug doing? What else are you seeing in the data set?

I think that the incremental value

of that drug -- you know, so a comment was made yesterday, we need drugs that can achieve better glycemic control with less hypoglycemia. If you really had a drug like that and you clearly were reducing the number of hypoglycemic events, that's a clear incremental efficacy, if you will. Well, incremental value, in a number of regards. So I might be more accepting of a higher upper bound in that setting.

I also think that -- are we talking about a new drug class or another drug of the same class?

I think that's important. I think the points were eloquently made yesterday that every drug is a different drug. But life isn't perfect and certainly the risk of unexpected events is going to be higher if you're going into a new drug class.

I mean, I think that just is a reality, so I think that is another consideration.

I like the points about not sticking to two-tailed, 95 percent confidence interval. I think that -- why not, if it's safety, think about one tailed and think about 90 percent confidence. So you wind up with a certain set of numbers but I like thinking about it, I think, that way. I'm more comfortable with that, too. But the other point I want to -- you know, I also like the idea of potentially a two- step process.

The first step having a more liberal conceptual, if you will, upper bound for safety, to be followed on, if necessary, based on what you see pre-randomization -- well, pre-approval. So I certainly wouldn't say every drug must be mandated to a post-approval trial. I think it depends on what's in the approval data set.

The other thing is that I'd love more discussion about from the statisticians

going in -- as I was thinking going in post the approval you're not starting with no information. You know, you're starting with a prior; right? I mean, if you've done it right you've got a solid base for your statistical data set at the time of approval, so why throw that out? And could there be a Bayesian approach?

You know, if once you've agreed upon -- I mean, if you started at the beginning with a very clear, very well-established approach in terms of endpoint, definitions, and adjudication and an analytic plan, and then you get to the approval time, could you not go forward with a Bayesian approach? If you still have to get that boundary tighter, I just sort of figure a little discussion about that.

In terms of the other questions, the endpoints, I can't disagree with MI, CV death, and stroke as an appropriate safety composite. You know, the size and duration

of the trials, I think we are going to need longer trials. I think some of the answer to this is going to come from the imperatives from the remarks that are being made about what we're trying to achieve for pre-randomization. So I won't go into that further, except that I do think that we're going to need more than we're getting right now.

I think that, by definition, we're going to be stuck -- if you want to say it that way -- enrolling patients with other cardiovascular risks or established coronary disease, if you're going to get the number of events we need for these kinds of safety boundaries. So we're going to wind up moving in that direction and that may have a lot of unintended consequences, including exactly how best to manage glycemic control in those populations. But I don't see any way around that.

You know, the comparator, it's an

interesting question. I mean, I think that in thinking about it again from the perspective of a safety analysis and understanding that we are going to treat hypoglycemia, I mean, I wonder whether we're not simply talking about basically documenting that we are, whatever boundary we're talking about, no worse than other established therapies.

Now, that assumes that those other established therapies don't carry excess risk, but as a first approximation, that would be my shorthand answer to that. I think it is -- and I think that thinking about a program, if you are going to accept the program approach then it's going to be a mix and match.

So there's going to be -- wind up having to be an analysis of all drug patients versus all comparative patients because there may be different ones. And I would accept that.

Let's see, I won't -- you know, I think the glycemic control, I won't -- you know, I'll just sort of defer to my endochronological colleagues. I will say that one thing the ACCORD study says to me is, we've got an awful lot to learn. I mean, my own belief is, it's not the target per se, but it's how we got there or the population that was suddenly thrust into a much more tight glycemic control. So you know, I think this is a tough question that I think I'll leave to others.

I will say a word about the management of other -- the final bullet, management of other blood pressure and lipids. And so I think it's a very important point and I disagree a little bit with some of my colleagues. I do think that it's reasonable to go into it with a standardized approach or background therapy. I'd be a little bit careful about mandating post-randomization, mandating that certain

targets continue to be achieved. And when you're asking the question of what is the effect of the drug as opposed to a strategy trial, because if Pioglitazone reduces cardiovascular risks and it does so partly by reducing LDL cholesterol -- if it does that -- or reducing blood pressure -- if it does that -- so what? Why is that a problem?

If the question is, what is the effect of this drug? And so I guess, my quick answer would be, I would probably go into it with sort of an approach and make sure that patients are on guideline driven treatments, but I don't think I would say you need to then force people to treat the certain targets in order to balance those. That's very important if we do a trial that specifically asks the question, what is the isolated effect of glycemic control? As the ACCORD study was.

But if we're asking, what is the effect of the drug? What we're asking is the

integrated effect via all mechanisms. So I'm not sure that I would do more than that.

DR. BURMAN: Thank you.

Dr. Holmboe, we're looking forward to your comments, and then we'll open it up for a discussion.

DR. HOLMBOE: So I agree with everything that's been said.

I'll try and make this quick. So I think there's been a lot of conversation, but the first one, already I agree that you don't need a trial to necessarily show cardiovascular benefit. That you would clearly want to look at the cardiovascular risk, however I'm not comfortable with the idea that you'd randomize harm. Rather, the frame should be in the context of a non-inferiority trial.

And given that we've all pretty much agreed that you need a comparator, I think that's very doable. So I don't think that would be problematic.

I also agree, particularly around the risk issue -- I don't think you can just take a limit -- particularly, I agree with Tim, I had the same things written down. It's a population risk issue.

We need to look at the absolute risk and it really has to weigh the other benefits that we've been talking about and that is not an easy calculus. And I believe that you're going to have to use judgment through some sort of consensus process to determine what that is.

And it would probably require other types of individuals that are not here today to help make that sort of judgment. That's just were we are. I won't say any more about that.

I agree the composite clinical endpoint, but also is certainly struck by the mortality endpoint in the ACCORD trials. I don't think we should lose sight of that. But as people pointed out, the FDA does it

already. Clearly, you need long-term trials. You know, these things tend to cross.

I'm particularly struck by the estrogen trials. You know, everybody said, oh, this just proves our CTs show the population data's not any good. And yet those trials cross, and guess what? You follow along enough, actually the population data looks pretty good for what the randomized control trial data showed later. So you're looking at least three to five years.

What type of patients? I think, from a practical point of view, it's got to be high-risk if this is the safety signal we're trying to find. I'm cognizant of the other populations, but it's probably not practical to enroll the number of patients over the period of time required to see an event signal around safety, so I think I agree with you, Marv, this is kind of where we are.

I've already talked about the fact that this needs to be a comparator. I think, given that if you're going to pick a high-risk population who, by definition, probably has diabetes that has been present for some period of time. I can't see using a placebo. So I really think you're going to have to use the drug.

I agree with the deteriorating glycemic control -- obviously ethically, you got to handle that.

How best to handle that, I think, is where there's a little bit of difference on the panel. I was -- I certainly am empathetic to Tom's comment that you want to mirror the real world as best as you can, so again, I think that's a judgment call, whether you make this algorithmic or try to quote near the real world. And that's the balance between efficacy and effectiveness. And that's always a tough one.

And then, likewise, for the last

question. You're going to have to have some degree of management because we know these things are important. The question then becomes, how stringent are you going to be as a co-intervention over a period of time.

And I think again, it depends on what your goal is. If it's really mostly about efficacy of this specific drug, you're going to probably be more stringent in trying to mirror real world activities, maybe from a safety perspective, than you would be a little bit more lenient in how those things change over time.

DR. BURMAN: Thank you very much and thanks to all the participants. And just to go over the schedule again, I think it very important that we hear individual comments that we just did, but also that we have an active interplay of discussion that -- I have about 1:55, almost. So what I'd like to do is do this and have an open discussion among the panelists and bring out a lot of issues until around 2:30.

And go to Question No. 3 at 2:30 and we'll vote on that from 2:30 to about 3:30, because everyone will explain their vote. And then from 3:30 to, hopefully, 4:00 or 4:15, go to Question No. 4.

But I'd like -- if that plan meets with everyone and I do want to try to get out on time, for sure and maybe even earlier since people have flights. But also I think this is a great opportunity now to open the Question No. 2, open for discussion and interaction. And if anyone has any questions of other panelists or want to raise any issues in general, please feel free.

Dr. Temple, I see your --

DR. TEMPLE: I just wanted to state one thing about the second bullet. Those figures, 1.2 and 1.4, were intended to represent the upper bound of a confidence interval, not the point estimate. There's been some back and forth on that and I wasn't sure that was clear, so --

MR. LESAR: You said there could be some comments related to how the scenario plays out. There's a safety signal enough to require -- agrees there should be a follow-up study. I'd say it started pre-marketing. Three, four years later, or five years, the study is done and they suggest a hazard ratio of 1.25, but it includes one, what occurs? What happens then?

Well, it doesn't demonstrate harm, it still suggests that harm that we saw initially might still be there, in fact, maybe makes this feel like it's a stronger signal than we thought.

DR. BURMAN: Was that directed at anyone in particular, or is it just a comment?

MR. LESAR: My concern was what happens follow-up. If we still see a safety signal into marketing, after these are done, what -- how would that play out as opposed to taken as any safety -- seen by -- this is a drug guide, if we knew that this was the safety

problem -- 1.25, 1.3, 1.4 -- would we have approved it for marketing? Now, years later, we find out that that is actually what the harm appears to be.

DR. JENKINS: Well, that's obviously some of the risk you have to take in making approval decisions. And I think that was inherent in some of the phased approaches that we've been hearing. Obviously, if you complete that post-marketing study -- if that's the goal of the program -- and you still have a worrisome safety signal, that may mean that the drug comes off the market at that point. It may mean that it gets restricted to a third or fourth line use to try and improve the benefit and limit the risk.

So you know, it would be all the usual regulatory options at that time, but I think it's important to emphasize that there's always a risk involved in making an approval decision and then following it up with a confirmatory trial. There's always a

risk that that first decision will prove not to be borne out as the pathway you might have wished you had taken. But that's part of the way the system works because you can't know everything at the time of approval.

I think even Dr. Nissen acknowledged that in his two-step proposal. You know, if you do the trial after marketing and you find harm, that may lead to drug withdrawal. And I think we need to understand that could be part of the system, not necessarily that it was a mistake, but that's part of the system that you can't know everything before approval. You may learn things after approval that will lead to the drug needing to be withdrawn. If that's viewed as a mistake, then it makes it very hard for regulators to take that initial risk to approve the drug in the first place. Because, if it comes back that something you could have anticipated, leads to a drug withdrawal after approval and that's viewed

as a mistake, then that's something that we as regulators have to factor into our decision-making. How certain do we have to be?

How much risk are we in society willing to take for the possibility that on rare occasions something will need to be removed from the market because of something we learned after approval.

DR. KONSTAM: Ken, can I make a suggestion? I wonder whether it would be worth picking up on Ruth's cognitive advice and maybe ask you to maybe go over those groups of points and state where -- basically taking in everything that everybody said and sort of restate to what extent do you feel like we have consensus? To what extent do you feel like there's uncertainty?

DR. BURMAN: Sure, I'll be happy to. Dr. Temple, do you want to make your comment first or do you want me to go ahead?

DR. TEMPLE: No, I only wanted

to -- this may be obvious to everybody, but what the proposal of discussion here is -- it says, well, yes. There's still a risk of putting a drug out and then deciding later that you didn't want to, but it guarantees that a certain kind of information that is never available spontaneously as the results of a large controlled trial will be available in a scheduled way. You know, you don't find risks of 1.2 epidemiologically. You certainly don't get it from AERS. The only way to know about these things, the only way is to plan a big large trial. And that's the point John's making. It might come out in a way you didn't like, but it might be hepatatoxic, too.

DR. BURMAN: Good.

DR. PROSCHAN: One thing that I just wanted to add that the problem of finding out that you approved a drug that's harmful. And that's all the more reason that you want to make sure that you have a number of events before you approve it and, you know -- so that's why I'm

really reluctant to say, well, if the results are better based on only 20 events, then maybe you still approve it. I mean, I think you need some minimal number of events before you can feel fairly confident.

DR. BURMAN: Dr. Day?

DR. DAY: If we're going to move with the suggestion just made, I would recommend that you would summarize each chunk and then throw it open for discussion. And then do that sequence later.

DR. BURMAN: Sure, I'd be happy to. This is a daunting task to try and summarize all of this.

DR. DAY: Oh, no. You're very good at that. We can disagree with you.

DR. BURMAN: For sure, but I think this is an important point and thank you for bringing it up.

And I was going to do this at the end of this session, but I think it is very appropriate to do it now. And I appreciate

the suggestion because we do want to try to figure out a consensus because we give advice to the FDA.

So Question No. 1 -- which is this part of the question of part 2 -- discuss the following aspects of design. So the first part is easy. I think there is consensus that there should be a large trial with a pre-specified endpoints, including cardiovascular events, should be performed either before or after approval of anti-diabetic agents, I guess, is my thoughts on the first part.

DR. KONSTAM: When do we get to disagree?

DR. BURMAN: Well, I think now. So we're going to do it in turns, so --

DR. KONSTAM: So I mean, I just come back to the thing I've been raising about whether -- you know, if the question is safety -- whether it be -- whatever point it is and let's talk about the point of approval.

Again, I'm not sure that you need to have a single, large, cardiovascular trial to get there. I think that -- I'm going to propose that you could get there with a safety program that is very well laid out and pre-specified.

DR. BURMAN: I agree, a large trial or set of trials, and analysis of data.

DR. KONSTAM: Okay.

DR. BURMAN: And that the -- on the same issue, the endpoint should not be cardiovascular benefit, it should be lack of harm. People have --

DR. BERSOT: I would just say that I agree with you if the duration issue is dealt with -- the duration of therapy issue is dealt with.

DR. KONSTAM: So there might be -- you know, so right now, I guess they have a certain number of patients that they mandate have exposure for a year. I mean, I think you can tackle it. We haven't really gotten into this, but you can tackle it concretely by saying

within this program that you need a certain mandated median exposure time across the program, and/or a certain number of patients with a year of exposure, and a certain number of patients.

Maybe a year's too short. Maybe it needs be a certain number, two years. So I think you could have parameters built in over an above the raw statistics of the result.

DR. BURMAN: Any other comments on that first --

DR. FLEGAL: I think there is some flexibility, Marv, as you're talking about, but I would call it some flexibility. I mean, it should still be a prospective plan that's laid out -- and it may well be laid out to aggregate what I call poolable trials, where each of these trials would need to be done with proper performance standards to allow us to interpret the data from the perspective of being able to rule out excess cardiovascular risk. And where it makes sense, in terms of numbers of patients,

numbers of events, duration of follow- up. So we're getting into some fine-tuning here, and I don't know if time allows, but my sense of what you're saying is consistent with the general approach to, say, you would need to have the ability to have a source of information that would reliably allow you to address the level of excess cardiovascular risk.

DR. BURMAN: Let me answer Dr. Fleming -- at Dr. Rosen's request -- did get some figures written down on a slide that I'd like to put, when we're done with this part of the discussion, I want to go to the easier parts in the end and then come back to the hazard ratios, if that's okay? Anybody else have any other comments on the first part? Yes?

DR. HOLMBOE: I think that what we're really arguing here is that we need to change the pre-approval process. You know, that right now we don't have sufficient data to be able to let the kind of risk we've already got. So whether that's a single, larger trial or, Tom,

as you pointed out, poolable, I think that's the issue.

And I think there may be some flexibility that your point, Marv, about how to get sufficient data to pick up a safety signal that would then make a determination of what you do post-marketing, whether you need this post-marketing trial, or maybe it could move into perspective surveillance systems, and not necessarily be another large randomized clinical trial. But I think that's what we're kind of struggling with here.

DR. BURMAN: Cliff?

DR. ROSEN: I think Eric summarized it appropriately. I think the real question on the table is, are we modifying the pre-approval process and how are we going to do that?

DR. BURMAN: Oh, I'm sorry. Again, I didn't see your hand. Thank you.

DR. VELTRI: I think if I understand this, you really are in a process of considering

a paradigm shift in the approval process, but also in how drug development is, on an internal basis, an industry. And from a sponsor's perspective, it's going to be looked upon.

I think we look at diabetes as a CHD equivalent. And there's a huge residual risk there. There's no anti-diabetic therapies as we've discussed yet that have had an impact on mass macrovascular disease. So if from a sponsor's perspective, perhaps, if one is to embark upon a large clinical trial to exclude harm, one would also want to make sure that one potentially has the opportunity -- if one's a believer, like myself -- the glass is half full, actually, rather than half empty. To be able to conduct such a trial where you optimize your chance of showing a benefit.

And there maybe a newer, innovative therapies for diabetes, other aspects, because it's going to have to be drug specific because there could be changes in

LDL, HDL besides the HbA1c, which could actually impact upon the benefit side in the risk.

And let's face it, whether it's 10,000 or 25,000 followed for five years, and again it's an event trial. And the good thing about events is it gives you an opportunity to look for a good outcome. You see, if you take a low-risk patient population you're going to take longer and you may not see the signal you want in the highest risk patients.

So I think, when you look at the time and the resource that's required, if a sponsor's going to want to do that, they're going to want to look at both sides, that's number one.

Number two, from the other aspect, again, looking at it internally looking out, obviously there's a regulatory issue here but if we see no signal in the pre-clinical database and the usual

biomarkers -- independent predictors -- and yet we see in a limited database, whether it's integrated or otherwise a signal which isn't necessarily a precise signal. There may be some noise there. Internally, there could be a decision made that says, we don't want to go forward. You know, there's some risk there, as opposed to maybe another developing program, maybe within the same category.

So I think this is changing the paradigm. It's changing the paradigm not only from a clinical perspective and a regulatory perspective, but also what goes on internally is perhaps many sponsor's the way they look at things.

DR. BURMAN: Thank you. Other questions or comments on this particular --

DR. KONSTAM: Can I just react to that? Because I think I understand what you're saying, but, I mean, I think we've all sort of settled on cardiovascular safety as the thing

we're talking to the FDA. And so that's what we're sort of giving them advice on now. If you come along and think you don't really want to develop another hypoglycemic agent unless you're going to be leading the market. And the only way you're going to get there is by showing incremental clinical efficacy, and that's the way you want to design your program, you're free to do that.

And I'm sure that you can do that in the context of also satisfying the safety requirements that we're talking about.

But --

DR. VELTRI: What I'm saying -- I'm not saying we should be satisfied with where we are, even with glycemic control and microvascular disease. I'm not saying that at all because there may be trade-offs. Different patients -- and I think it is an individualized therapy. But there may be new innovative therapy which may not have any impact at all on microvascular disease, but obviously that's a

huge opportunity. You know, no one's going to argue about not trying to reduce risk -- cardiovascular risk in diabetics. So I just think that we shouldn't be throwing the baby out with the bathwater here. I think we still want to develop better anti-diabetic therapy for areas where we know we can have impact. And perhaps, even better impact. So I'm not throwing out symptoms in microvascular disease, but clearly the big win, I think, is microvascular.

DR. BURMAN: Thank you.

Dr. Temple?

DR. TEMPLE: If I heard the discussions before, for the large study now, whenever it's conducted, there's general agreement that you have to match both groups with respect to glycemic control, lipids, and blood pressure. Maybe other things, too. If that's the case, then you're studying what were called yesterday, off target effects of the drug. Because you can't win on those by doing

the usual things because they're all going to be matched up. Everybody thinks it's unethical not to. So you're really only looking at off target things.

Now, I just want to be sure everybody thinks that's so. That in long-term trials, especially, you can't leave people inadequately treated. I mean, if you were testing specifically what the best level of HbA1c to get to, then you could. But for these things we're talking about, for the safety studies that are required, we're talking about groups that are going to be matched in every respect possible. I just want to be sure that we understand that, if that's what you meant, or that you tell us if you didn't. Because that's one kind of trial. That's not an add-on study where you take people, get them to the best control and compare drug and placebo. That would be unbalanced with respect to hypoglycemic control. Nobody thinks that's acceptable