recognize the importance of glycemic control in patents with type 2 diabetes, as this often results in improved symptomatology of hyperglycemia, such as thirst, polyuria, and blurred vision. And different studies have associated improvements in glycemic control, as measured by hemoglobin A1c, with a reduction in risk of microvascular complications such as retinopathy and nephropathy.

In the past several years, safety problems associated with certain anti-diabetic drugs have led to suggestions that the risks and benefits of anti-diabetic drugs ought to be evaluated by additional larger studies.

These safety problems do not negate the importance of good glycemic control, nor do they invalidate the use of glycemic control as an efficacy endpoint for drug approval. Indeed, some of the safety concerns seen with anti-diabetic drugs to

bear no relationship to glycemic control, such as troglitazone and hepatic safety, but uncovering a serious safety signal might warrant studies beyond what is necessary to establish blood-glucose control and durability of effectiveness.

More recently, the cardiovascular safety concerns with drugs such as muraglitazar and rosiglitazone have served to focus debate related to the approval standards for anti-diabetic drugs to the question of whether these drugs have any impact, beneficial or detrimental, on cardiovascular risk, and whether long-term cardiovascular studies should be required during the life-cycle of a drug, either before or after approval. The focus on cardiovascular safety of anti-diabetic drugs is further heightened by the realization that patients with type 2 diabetes mellitus have a two- to four-fold greater risk of cardiovascular mortality compared to patients

without diabetes.

This Advisory Committee is being convened to help us decide on the role and nature of cardiovascular risk assessments of drugs and biologics being developed for the chronic treatment of type 2 diabetes.

So the first question, which is on the board, relates to: "Please discuss what change you recommend be made to the current design and conduct of Phase 2 and 3 trials for anti-diabetic therapies that might enhance the Agency's ability to detect the cardiovascular safety signal prior to drug approval. Please include in this discussion the role of: An independent, blinded adjudication committee for CV events; conducting a meta-analysis of safety data from all Phase 2 and 3 trials; and the adequacy of current safety database -- for example, number of patients, duration of exposure -- required for drug approval.

And what I'd like to do, with that

introduction, is start with members of the Committee. And I guess Dr. Holmboe would be the first member -- and feel free to discuss these issues and -- appreciate your comments.

DR. HOLMBOE: Thank you for the opportunity to respond. I think the answer to the first two is yes. And regarding question number three, I think we've learned that the current safety database is not adequate.

So I'd just make a couple additional points. In addition to doing these things, I think one of the themes that I want to highlight is a multi-pronged approach I think is going to be really critical. We've heard a lot of conversation about the need for controlled trial, and I agree with that. However, I would not want to put all our eggs in that single basket.

I think, as Mary pointed out, there are 12 trials out there right now. And they've raised as many questions as they've answered. ACCORD probably being one of the

best examples. And so I think we're going to need to think about this more broadly than just a controlled trial. Clearly, if we had these data from the Phase 2/3 trials, it would be unwise not to use that data and conduct analyses that may identify safety signals. You should do that.

Clearly, having a blind adjudication committee will improve the detection for these events that are certainly important in this particular disease of diabetes.

But again, I'm going to emphasize, I also think that, moving forward, we've got to get out of this passive surveillance mode. In addition to controlled trials, think about other methods such as registries that may pick up other events that controlled trial may not be able to detect.

So thanks.

DR. BURMAN: Thank you.

Dr. Konstam.

DR. KONSTAM: Yes. I do think that we do have to do a better job of cardiovascular safety assessment prior to approval. And I do think that there are going to be a number of components of it. I think that it's very important in all our -- in my view, in our deliberations throughout these questions, to distinguish issues of cardiovascular safety from efficacy, and not to sort of have that issue blurred -- you know, because of the overwhelming compelling point about the value of glycemic control in the prevention of microvascular events.

So I think, to me, the focus really is cardiovascular safety. I do think that cardiovascular safety does need to be assessed through standardization of endpoint definitions, standardization of accrual methodology across the program, and standardization of the adjudication process, which I don't know how you would do that without a blinded adjudication committee.

Particularly if we may consider an approach that sort of creates an integrated cardiovascular safety program across a number of different trials within that program. So I think those points are very important.

The bullet 2 asks about conducting a meta-analysis. I would phrase that differently, because I think -- my short answer to that is yes.

However, I think going into a program a priori, it's not unusual these days at all to think about programs of independent -- of separate trials that then integrate into another trial for another purpose with another endpoint. I think there are many programs in development that are incorporating that approach, and I think an approach like that could happen here. And so that would sort of change the terminology, because it really wouldn't be a meta-analysis, because you'd be having common endpoints, common adjudication process, a

single analytic plan across the program. To me, that then changes the word. It's no longer a meta-analysis; it really is a prospective plan.

And I think from what we've heard, the current safety databases are just not adequate for cardiovascular safety. And I think what we'll probably talk about more, but I think we are going to need more patents -- but I also think that we are going to have to have a healthy contribution by patients with more advanced cardiovascular disease to give us the number of events into the pre-approval program to have a reasonable comfort level around safety.

DR. BURMAN: Thank you very much.

Dr. Lesar.

DR. LESAR: Yes, thank you. I have a couple of concerns related to this question. One is, I agree with the issue related to adjudication, and that certainly is a critical point in terms of determining potential adverse

events.

I think I would like to expand a little bit upon the discussion related to a programmatic approach to development of not only a drug, but also the drug class and the drug -- the treatment strategies is that -- I know there was discussion about trying to reduce requirements for studies, but it seems like we have a lot of answers that are all scattered and haphazard. And whether we can't learn more about not only a drug but drug treatment strategies, as well as issues across drugs by having a greater standardization in some of the methodology that's used in some of these studies, certainly that would help grouping these studies over time, and allow cumulative knowledge to occur and comparison of different therapies, which is really what the clinician is trying to do -- to try to weight the fit into therapy. I think that would help tremendously, really, to define safety

signals that occur by being able to have more similarly-designed studies.

I also am wondering here, while many of the trials have add-on to anti-diabetic drugs, the discussion that diabetes is a cardiovascular disease or they're one and the same -- what are the requirements for at least sub-group analysis of patients who are currently taking statins, ACEs, IRBs, potentially aspirin -- in terms of safety signals that might appear within those sub-groups.

I think that -- the issue relates to the exposure requirements. Are we going to require exposure to specific high-risk groups in these studies early on, or are we allowed to invest the sponsors to determine what are they going to get this approval through a low-risk population or a high-risk population. Certainly because once it is -- if it is marketed, it would certainly be exposed to all types of patients. And I'm

not sure that we can answer those questions in these small trials.

Thanks.

DR. BERMAN: Thank you.

Dr. Proschan.

DR. PROSCHAN: Yeah, I certainly agree that there should be a blinded adjudication committee.

Regarding the second point, I think it would be better -- I mean, I'm not against doing the meta-analysis, but I think it would be better to do something like what Dr. Nissen was proposing. Or my interpretation of what he was proposing, anyway, which would be a fairly large trial compared to what's been done so far for safety -- which would be like a screening trial to rule out certain amount of cardiovascular harm.

I would couch it a little bit differently than he did. Instead of using a 95 percent two-tailed confidence interval, I

would say really since you're looking at safety, you could justify doing this as a one-tail, and if you did that at 90 percent one-tailed, then what you could do is with -- I did some calculations -- with 160 events, you could rule out a hazard ratio of 1-1/2. You could be 90 percent confident ruling out a hazard ratio of 1-1/2, and the point estimate there that would just barely make it is 1.225.

So I would just modify that proposal a little bit, and I think it makes it more acceptable in terms of -- because I don't believe ruling out a hazard ratio 2 is doing very much. So I would require at least to be ruling out a 1-1/2, and I think that's a reasonable way to do it. So I would not rely solely on -- these meta-analyses of safety data from these Phase 2 trials, for example, are short duration.

And I guess that's it.

DR. BURMAN: That's fine. Thank you

very much.

Dr. Flegal.

DR. FLEGAL: Well, I also agree that it would be valuable to have an adjudication committee, because I think part of the problems we're facing is lack of -- some lack of clarity of what are the outcomes we're looking at.

In terms of the meta-analysis, again, there's nothing the matter with a meta-analysis, obviously. But I also feel that maybe something a little more focused, like what the previous speaker suggested might be more valuable in this case instead of compounding some of the confusion that we're facing.

And so I think a plan that actually tried to rule out a high level of harm would be advisable as well as a meta-analysis. And that would mean that our current database really needs some additional information to make it really useful.

DR. BURMAN: Thank you.

Dr. Bersot.

DR. BERSOT: Tom Bersot. This is perhaps the easiest question to answer. All of these things are laudable in -- the adjudication committee -- going beyond a meta-analysis. You know, current safety database is inadequate.

The devil here is in the details, and I think we're going to be discussing those a lot with the next two questions. I'll wait to talk about those issues until we get there.

DR. BURMAN: Thank you.

Dr. Henderson.

DR. HENDERSON: I say yes to the first two bulleted items -- that we need an education committee and meta-analysis.

On the third one, I agree with what's been said, that we need to do a better job on having safety data. At the last year's meeting about rosiglitazone, the most frustrating part to me was very obviously, we needed more safety data. But somebody said

sub-group analysis, because it appeared at last year's meeting that there were certain groups that probably had a lot higher risk on that drug than other groups. And so I would on that third bullet emphasize sub-group analysis as well.

DR. BURMAN: Thank you. I agree.

The optimal manager detect cardiovascular events in a Phase 2/Phase 3 pre-approval trial is to have a system that independently examines cardiovascular events including MI death, cardiovascular death, and stroke. A meta-analysis of safety data could also be performed as an adjunct to give further information. Current safety database should be modified to include more patients and improve the confidence intervals, with indication for the hazard ratio that we've partly discussed already.

Dr. Goldfine.

DR. GOLDFINE: I think everybody so far has been in agreement, and I am as well,

that independent committees to review the CVD events are actually really necessary.

Now, there are some subtle statistical differences that Dr. Fleming may advance on about whether or not you pre-specify analysis of pooling of the data from the original trials. And I think that when the data is collected in a very uniform way, this becomes much more feasible and does allow some of the sub-group analysis that become informing as hypotheses for what is safe and what is not safe.

I think the other interesting thing is with all the limitations of the meta-analysis when we move into the forward studies, the risk windows that we see are actually very concordant with each other. And that that actually suggests that while they are limited as an initial approach, that there actually is a lot of validity to them.

I believe that they can be informative on many ways, because when you

look at cardiovascular risk alone, no risk is acceptable for any complication of what we do. Yet you can't look at it in an independent way, because there's also tremendous benefit from the glucose-lowering effects that we are ending up seeing and providing.

And a drug with marginal glucose-lowering effects may be anticipated to have lower benefits from the ability to prevent kidney failure or blindness or other disorders. And therefore, one may have a lower threshold of acceptance of cardiovascular risk in a drug that has a more marginal or lower glucose-lowering potential than one that is able to more profoundly lower blood sugars, especially if it does it without inducing hypoglycemia.

So one may actually want to be able to use these to inform us to toggle the limit of risk that we find acceptable to us, especially in the view of the decrease in

frequency of the cardiovascular events with the concurrent medications that we're using that are so effectively reducing these rates.

And I think that Dr. Fleming may actually want to comment on that a little bit, either at this point or at another point in our discussion.

DR. FLEMING: So looking at the question as -- in essence, what changes need to be made, maybe just specifically briefly to look at what we're doing -- we want reliability. Lack of reliability is generally due to bias in our estimates or variability, lack of precision. And in fact, we have both under the current situation.

If we look at the slide -- very informative slide that Mary Parks presented using rosiglitazone for an example -- and she was trying to give us a sense of the interpretation of the data and what appeared to be excess numbers of events. What you see in that scenario is both lack of adequate

numbers of events to be able to reliably discern whether there is a real signal for excess cardiovascular events, but also significant confounding that exists. So there is lack of adjudication, which as all of my colleagues have said, we have to address.

The sources of information that are being pooled are from very different durations of follow-up. The rosiglitazone patients followed much longer than the controls. Well, you can't compare those unless you're confident that the event rate doesn't change over time. We're pooling non-randomized participants with randomized participants -- they're from different studies that have different randomization fractions. Bottom line is, these can't be interpreted as truly controlled assessments. There's considerable bias that exists because of the confounding in the way this is done.

There's lack of uniform collection

of -- sensitivity and specificity, ensuring that the events that occur are being uniformly captured and properly characterized. And as I mentioned, inadequate duration, inadequate numbers of people -- inadequate duration could be leading to false evidence of concern. Maybe there is some excess early on that doesn't in fact exist later on.

All of these are issues that haunt us in interpreting what is the true cardiovascular risk based on what we're currently doing. So what do we need to do instead? Well, we've heard a great deal about that. An ideal approach would be to have a pre-marketing study. And in the sense of efficiency, where that would be a screening trial, allowing for a less-burdensome undertaking before marketing, then followed up potentially with a post-marketing study as well.

Ideally, for reasons that we'll

talk about when we get to Question No. 2, that should have about 250 events. But it could be as few as 125 events that would be cardiovascular death, strokes, and MIs.

Ideally, from a perspective single trial -- however, great points have been made about the fact that we could instead be doing a pre-specified aggregation of pool-able trials; i.e., you could have a plan where you would get this information from several different trials that would be aggregated. But this should be in a pre-specified way, where each of these sources, each of these trials, would need to be conducted in a manner to meet performance standards that would allow us to pool them, and to address what we want to address. Which is, can we rule out an unacceptable excess risk of cardiovascular events? And to do that, as I tried to point out in my presentation, when you're trying to rule out an excess, you have an even higher standard of quality that has

to be achieved -- in terms of being able to have proper adherence, being able to avoid cross-ins, having uniform capture, having adjudication, et cetera.

So we do need to move to a prospectively specified plan. It could be poolable from multiple trials, where we get rid of the bias that we have that's rampant now in assessing what is truly signaled versus confounding, and where we have sufficient numbers, that we have the precision that we're going to need to be able to rule out what would be an unacceptable excess risk.

And when we get to Question No. 2, I will comment on what I think those numbers might be.

DR. BURMAN: Thank you.

Dr. Felner.

DR. FELNER: I think it's pretty simple. Not to repeat what many others have said, but I would say yes to all three bullets,

and probably have a few more things to say when the next few questions come up.

DR. BURMAN: Thank you.

Dr. Day.

DR. DAY: Well, I agree with Dr. Felner. But I would like to comment, in addition, on standardization of methods.

It's very difficult to look across all the available data and understand what's going on. And sometimes it's talked about in terms of lack of reliability, and it may just be lack of standardization.

On the other hand, if we could -- and point 2 coming up, Question No. 2 -- focus on some core methods but still allow for open -- addition of creative new methods along the way, so that if all trials -- pre-approval, we're talking about now, and then post-approval, whatever we suggest -- agree upon a core set of methods, and then other things can be added in as well. So at least there's more

comparability across all the data sets.

DR. BURMAN: Thank you.

Dr. Rosen.

DR. ROSEN: Thank you. Comment and then response to the question.

So I think what's happened in the last day and a half is that we've seen that there's a cardiovascular issue, and then there's the issue of reducing hemoglobin A1c. And one doesn't diminish the other, so we know we have a cardiovascular issue. That doesn't diminish the importance of lowering blood sugar.

On the other hand -- for microvascular complications -- on the other hand, lowering blood sugar and the benefits of these drugs do not diminish the issue of what is the problem with the cardiovascular changes that occur when we do that. And I think it's very important that these -- although they're separate, they are also integrated.

So in response to the first question, I think we absolutely have to have an independent adjudication committee. And I think Marvin made a point that it should be an integrated program that really is committed to cardiovascular endpoints, not just an independent committee that's going to look at some data, but is really going to oversee a number of the issues.

In terms of the meta-analysis, and I think Dr. Henderson referred to this, the limitations of meta-analysis are the limitations of the individual studies. And if you're trying to pool data in which you have 100 subjects in five different arms and you have minimal -- or very wide confidence intervals, which we saw in the rosiglitazone story, where when you looked at rosiglitazone versus metformin, for example, and your confidence intervals were very huge -- you cannot make -- and the FDA was right in saying that -- they cannot make a judgment

based on that kind of data.

The meta-analysis are good when we have homogenous trials that do exactly the same thing and have pre-set endpoints. But if they don't, that's a real limitation. So I'd be careful about saying let's do meta-analysis unless we have a uniform system of how these are going to be pooled.

And finally, just a final comment. I've been on the Committee two years, and I think the safety analyses are more a responsibility of reporting -- you know, particularly adverse events -- not just adjudication, but how they're reported in the field.

And this is, I think, a global problem. I don't think it's specific for diabetes or for this particular set of clinical trials. We really need a better system of adverse event reporting which really focuses on what happens to the individual subject.

So I'm very much in favor of 1 and 3. Two, I'd be cautious about unless we implement a system that really guarantees that we're going to have data that we can work with.

DR. BURMAN: Thank you.

Ms. Killion.

MS. KILLION: Okay. I agree with Dr. Rosen that when we're talking about micro- and macrovascular issues with respect to diabetics, it should not be viewed as a zero-sum game, so that the more information that we can get with one should not be to the detriment of the other.

To keep things short, I would agree on the bullet points. Number 1, yes. I think that an adjudication committee would only improve the information that we have. The meta-analysis for safety data, I'm a little concerned about, because it has the apple-and-oranges sort of limitations, so we have to get something there so that when we

do these comparisons, we know what we're actually looking at.

And the adequacy of the current safety database -- I agree with the point that Jessica and others have made, that we need to look at sub-groups, because patients -- diabetic patients are a very diverse population, with lots of different levels of risks of different things. And so we have to keep that in mind when we do this kind of analysis as well.

DR. BURMAN: Thank you.

Dr. Savage.

DR. SAVAGE: It's hard to say something new at this stage. But I think that there is one point that was mentioned a couple of times in the last day and a half that needs to be emphasized, and that's that a lot of progress has been made in terms of reducing the complications of diabetes over the last 10 or 20 years.

What that also means, however, is

that we have a narrower range in which to operate in terms of future trials. And also -- certainly in the area of glucose-lowering, because one of the dangers being hypoglycemia, the actual risk may be higher as you push down lower.

Although I should emphasize that the analyses that have been done in the ACCORD trial that were presented at the ADA made the point that they really don't know what was the cause of the excess deaths that occurred.

So there's a need to strike a balance in the pre-approval stage of screening for any major cardiovascular problem and picking it up without undue delay or undue cost of doing it. And I think that I certainly agree with the answers that most people have given. There is a need for an independent adjudication of cases, and there's a need to try and find a way of standardizing data collection so that you're

not combining things that just don't -- really shouldn't be combined.

I was involved with the rosiglitazone discussions last year at this time, and I came away from the meeting really disappointed with the inadequacy of the data that had been put together to give us to look at, because there was just so many different problems, and there were conflicting results and wide error ranges and so forth, and there was no way you could make a definitive assessment from that type of data.

So the current database is inadequate. Can be improved in many ways, some of which would not be unduly burdensome or expensive. The standardization, better adjudication. And I would also like to end by emphasizing something that's just been mentioned a couple of times, but I think is very important, and that's the wide amount of heterogeneity within the syndrome of diabetes -- that if you take someone who has

mild hyperglycemia or is asymptomatic who's just been diagnosed, their risk from intensive glucose control may be minimal, because even if they have some episodes of severe hypoglycemia, the likelihood of the catastrophe is relatively low.

If you have somebody at the other end of the spectrum who's on multiple other drugs who has cardiac ischemia and has a severe hypoglycemic reaction, you don't know what might happen. But it's much more likely to be bad than in the new onset.

So the original analyses do need to take into account the heterogeneity, and it isn't appropriate to just do sort of simple diabetics to get through the first part of the study.

DR. BURMAN: Thank you.

Dr. Fradkin.

DR. FRADKIN: I also agree on the importance of adjudication and developing an approach that will be standardized and allow a

pre-specified plan for aggregation of multiple trials to try to identify cardiac risk.

I guess the point that I would add to all the good points that have already been made is an emphasis on the duration. I think when you look at the ACCORD data, for example, the increased mortality signal really didn't emerge for several years. And it may well be that if you're simply looking at patient years and event rates, that may not be equal -- if you're looking early in the course of exposure to a drug where you may be largely seeing background event rates versus event rates that might be attributable to a therapy. So I think it's going to be important to have an adequate duration of follow-up.

But then, that gets to the complexities that Dr. Joffe described, where for long-term studies, you can't leave people on placebo with inadequate control. And I think that makes for a particular problem

when we don't really know the cardiovascular risk of the comparator drugs. So I mean, if you're looking for a CVD signal, and in your comparator, you might have rosiglitazone or you might have the combination of sulfonylurea and metformin, which Dr. Holman talked about yesterday -- it's a little bit difficult, then, to assume that a drug is safe when you haven't really established the safety of the comparators.

And then I guess, finally, I would just want to say that I think these discussions that we're having really should apply to all long-term chronic therapeutics. And in particular, requiring Phase 2/3 studies to have enough CV events that you can look for a cardiac signal will ensure that people say don't exclude diabetics from trials of other agents in which people with diabetes may well be a substantial part of the population that receives those drugs. And I think that the lessons that we're

hearing here maybe should be applied more broadly.

DR. BURMAN: Thank you.

Dr. Genuth.

DR. GENUTH: Well, at the risk of repetitiveness, I probably will repeat some of the things that have been already said, because I think it's good for the FDA to hear from individuals that a consensus exists.

The first question I think is so obvious. I don't know how we ever did trials without blinded adjudication committees. I've never been engaged in one that we didn't have that way of deciding outcome events, other than those that were continuous measures and done in laboratories.

The second question sort of gets me into a larger issue. I don't really understand how we can define an "acceptable" point estimate or an acceptable upper 95 percent confidence limit on that point estimate. I wrestled with that last night,

and I just don't feel I can say, well, a 26 percent increase in risk if I'm pretty sure that it's no more than 100 percent increase in risk -- I don't know how I can possibly say that.

There are ethical issues, clearly. And political issues, I think. If the FDA made a statement tomorrow that we will accept X percent increase in risk, but it could be as high as Y percent, I think people would be all over you. They probably would want lower numbers, or some people might say, well, for benefit, we have to take big risks.

So the only advice I think I can give is that this is an important enough question, aside from the technique of how you're going to measure the point estimate in the 95 percent confidence intervals -- I think this is an important enough issue that maybe you should convene another meeting and include ethicists at the meeting to provide guidance from the ethical community, or

ethicist community, on what our society considers acceptable risks, or in order to gain certain health benefits. I just can't address it individually.

I'm in favor of the meta-analysis approach, largely because I'm opposed to the construction of a trial whose real purpose -- real purpose -- is safety. No matter how you clothe it, if you construct a trial along the lines that Dr. Nissen suggested as a screening for safety trial, I don't think I could present that to a prospective recruit.

Dr. Nissen feels comfortable he could, but if I really explain the purpose of the trial, it would be very hard, I think, for the potential recruit to see any benefit whatsoever for himself or herself to engage in that trial as a research partner, which the participants really are in a trial.

So that's my first problem with Dr. Nissen's plan. And secondly, I'm dubious

that many IRBs would agree to a trial in which you're trying to rule out harm from a new drug. I think that's another tough ethical issue, and so maybe if you did have an ethical conference in this arena, that would be a second question I would address to the ethicist: Is it okay to even construct a trial in which that's the real purpose, no matter how you clothe it about what we'll learn about benefit, too?

If the real purpose is safety, only, I think that's an issue that needs to be struggled with.

Like everybody else, the meta-analysis approach I think is a better approach than designing a specific trial for safety. And like everybody has emphasized, again, it should be almost a no-brainer that the FDA should create a set of conditions that all drug companies have to follow in designing trials for diabetes drugs.

There should really be a uniform

set of standards in that, because, as others have pointed out, that will clearly make it easier to do a meta-analysis, but more important, to have confidence in the results of the meta-analysis. Because I think we all know they can go wrong.

The third question -- I really can't address. I think that's a question for experts in statistics and trial design. We've all seen numbers on slides, but we've also heard some debate about those numbers. So I can't contribute to that debate.

DR. BURMAN: Thank you very much.

Dr. Veltri.

DR. VELTRI: I don't think one can argue that one will increase the signal-to-noise ratio, and specifically to cardiovascular safety, if you had a blinded adjudication of events -- those clinical event committees typically have specified definitions. They have a charter.

It would be helpful, actually, if

there was uniformity in those definitions across trials, across various agents. That would be very helpful. You know, defining death, defining the cardiovascular disease and other disease. That would be useful. MI, there's five definitions basically from the World Health Organization. It would be nice to have uniform definitions. And even stroke, hemorrhagic versus ischemic, et cetera.

So I think that kind of is a no-brainer. I think that will increase the amount of information that we have from these trials, specifically in relation to cardiovascular safety.

In regards to specifically a meta-analysis for safety data from Phase 2 Phase 3, I would agree, we typically do integration of various safety in the integration of safety analysis for these development programs. I think it's just too difficult, given, for instance, what

Dr. Joffe presented -- you have different trials of different duration of different risk, different populations.

I don't think you can -- with the current database is really providing meta-analysis, per se -- you can only provide an integration of the safety data and look for signals in that regard, unless somehow you enrich the population who are going to be at higher risk, secondary prevention in patients with diabetes as well.

So I think I don't think we can call that a meta-analysis, and a major change would have to occur in order to really change what we do currently in regards to these events.

Finally, I do think, though, the current safety database -- if one indeed allows the knowledge that if you don't have an adverse effect, some other signal on known cardiovascular independent predictors, and we have the thorough QT to look at proteomic

potential. We have LDL HDL, which you clearly elucidate from these databases. If you don't see a signal going in a wrong direction there. Blood pressure, if you don't see a signal going there. And finally, weight gain.

I think those are very strong signals, independent predictors, of potential harm from a cardiovascular perspective that I think one could allow an approval for an anti-diabetic agent, type 2 diabetes. Because the benefits are undeniable on symptom relief -- and as we discussed the last day and a half, microvascular complications.

That doesn't mean, however, we've completely excluded the possibility of either benefit on the cardiovascular macrovascular assessment or harm. And I think that would lie in the post-marketing approval, where you can adequately attempt to ascertain that information. But I think to do a feasibility

study -- and I think that's the next question coming up -- I think there's just more devils in the details there, and I don't think you're going to get a differentiation of signal to noise. I think there's too many confounders.

DR. BURMAN: Thank you very much, everyone, for their opinions.

Yes, of course. And Dr. Goldfine has a question as well. Either way.

DR. BERSOT: I just want to respond to the ethics issue Dr. Genuth raised.

I'm a vice chair of the IRB at the UCSF, and we ask people to participate in Phase 1 through 3 studies without any promise of benefit to them all the time. And with the issue of safety being one that's being tested. So I don't really see this as being anything different than what we already ask of patients, and particularly if we had the data from the meta-analyses where there's no signal going forward, I think it would be a

reasonable thing on ethical grounds to ask people to participate in these kinds of studies, despite the fact that the endpoint is really a safety endpoint.

And we already do that.

DR. BURMAN: Dr. Goldfine.

DR. GOLDFINE: I actually had the same or similar point to make. And I just want to point out that prior to 1969, the FDA main role was about the safety of what we were administering to people. And it wasn't until the rules changed about that time where it was safety and efficacy, and the mandates were necessary for approval. And I think that they really go hand-in-hand.

But what it's based upon when you're looking at these things is a premise of efficacy. And so at Phase 1, there has to be some premise that this is going to work from our pre-clinical data that makes it justified to do first a human application. And then after that, one begins to build upon

one's repertoire to move it forward into our advance and trial designs.

And always fundamentally under this is the safety of these drugs. And what's different -- and what I think that we're focusing on -- is that it's not completely clear that by lowering blood sugars, which is now what we're discussing for an approved drug to treat type 2 diabetes, that we have to have the premise of cardiovascular benefit. We clearly need neutrality and lack of risk. But that's something that we have to develop as we are building this portfolio from the first in man into a not only an approved drug but one now that we have many years of safety experience with.

And unfortunately, there is -- this is a chronic disease, and we're going to be giving these drugs to people not for 6 months and one year, not even for 5 years, but for 15, 20, 30 years. And there is nothing like five years of experience to know that it's

going to be really beneficial until we cross those thresholds.

So even with approved drugs, we're at 200 people at one year when we're beginning to move them into the clinical arena. So where do they fall in our armamentarium as a clinician, it may not be our first choice for a person. So we may choose to use a drug that we have a longer safety profile on. And then there may be reasons why somebody can or can't take a particular agent, and so we use these newer agents, even when they failed existing therapies. And we really are left with no other alternatives -- or because they're unable to take them. And that's why the wealth of what we're now having available to us is so exciting as a clinician.

But I think that we do need to keep in mind that safety really is the fundamental cornerstone since the inception of the FDA.

DR. BURMAN: Thank you. We have time

for other questions or issues on this.

If it's all right, we'll ask Dr. Holmboe first, and then come to you.

DR. HOLMBOE: I actually just want to pull that last point, because I think Saul's part of something that's really important. I mean, even though we're talking about safety here, I do think there's an ethical issue that if you continue these trials without there at least being the premise of some additional benefit in addition to safety, boy, that's a tough sell for me, too.

I'm really glad, Saul, you brought that up, because again, we're trying to find something that's better than what we have or fill some hole -- to do something that we believe will be better than what we have, or can help patients because the other drugs don't work.

So if there isn't some premise of benefit even going forward as we look at the safety issues, I think Saul's right. I think

that's going to be a real tough sell.

DR. FLEMING: There was an article written in Lancet in 2007 that talked in general about this issue of the ethics of non-inferiority trials. Most often, non-inferiority trials are conducted in a setting where you're trying to rule out that you have unacceptable loss of efficacy. And the authors were saying, is it acceptable to randomize someone to a standard of care against an experimental where you're trying to rule out that the experimental is worse, hoping that it's the same. Why is it to the advantage of patients to be on that trial.

And the bottom line to this has to be, as some of my colleagues have already pointed out, that there are other factors about that intervention that are already established or well-expected to be favorable, such that if you could rule out the loss of efficacy on this measure, then on other measures, you're favorable. So in this

setting, it's if you can rule out that you have an acceptable cardiovascular risk, then other dimensions or aspects of this intervention are really favorable. And that's what's driving the ethics of this. That's what's driving the appropriateness of being able to do this.

It's interesting to say if it's not ethical to randomize you to this experimental arm, then why is it ethical to market this product with uncertainty about the safety issue? So if we can't even ethically randomize you to this experimental arm, being truthful to the patient about not knowing whether there's excess cardiovascular risk, how can we in fact proceed?

And I think the answer to that is, we can because of the knowledge of the presumably benefits in microvascular complications, et cetera, et cetera.

The last point that I make -- and I've always said this -- I've been in

clinical trials for 30 years, 35 years. And I've said, the first time I'm eligible for a trial, I'm going to be on that study. People give enhanced quality of standard of care, enhanced care. People generally seem to do well. We say, why is it that in these trials, the event rates are so low? Well, it's confounded.

It could be selection of favorable patients, but I do sense it's also optimal patient management that's made available by the energies and commitment that people put in and the resources that go into these expensive trials.

So there is, in fact, real benefit to patients both to themselves, but also altruistically to be able to enhance our understanding. So it's a very valid issue. But I think there are some compelling arguments for why it's ethical to do so.

And again, if it's not ethical to randomize due to the experimental arm, why is

it ethical to market the product with the absence of knowledge.

DR. BURMAN: Thank you. Yes, please.

DR. KONSTAM: I want to just continue the discussion and sort of raise the ethical question a little bit differently that may help solve it. And that is the ethics of wasting patients that are participating in clinical trials. And that is to say, if we're imagining that there's an entire Phase 2 Phase 3 "efficacy program," and then a separate entire cardiovascular safety protocol that has the only purpose to ask does it do cardiovascular harm? I mean, there are problems about that from two directions.

You know, one is, do we really imagine sort of wasting the safety signal of the entire population that participated in the entire program? And that would be an ethical problem.

So actually, I think maybe what we have to do is sort of back into this, because

it seems to me that you need standardization of your cardiovascular safety assessment pre-specified as an integrated program as you embark into early Phase 2.

So that every patient enrolled in a trial is participating in the cardiovascular safety assessment in a meaningful way. And if you sort of say, well, we actually have to do that, then I think you come away at the end of that and saying, okay, once we've done that, what else do we have to do. Do we actually have to do another trial or not?

And to me, I think that's the most ethical and efficient way to sort of think about this problem.

DR. BURMAN: Thank you. Any other discussion?

Dr. Temple.

DR. TEMPLE: The later questions refer to the definitive trial. But I just want to be clear on what you're all saying about the -- I don't want to mark it as Steve's proposal, but

it's got that element to it. The proposal as I understood it was sure, he's in favor of a trial after marketing to pin things down. Let's say it's a combined efficacy and safety trial. So we duck the ethical issue. And he didn't really say specifically what the -- oh, the sort of rule out something over the threshold trial should be in Phase 2 and 3.

And it I guess could be a pooled analysis of multiple trials, whether we call it a meta-analysis or not. It could also I guess be a sort of medium-sized cardiovascular trial. But I'm not sure I quite heard whether people liked that general idea, that there should be a more-assiduous attempt to put an upper limit on the risk in the development program in Phase 2 and 3, even if you then do something else after marketing.

Was their general view that that was a good idea? Which would involve, as he said, putting more people with higher risks,

making sure there's some long-term follow-up, and of course, as people have pointed out, you can't have only one group have the long-term follow-up, you've got to have both groups have long-term follow-up. And that kind of stuff -- was there a general agreement with that thought? The comments about meta-analysis were here and there. And I couldn't tell. And that seems an important part of the advice we're asking for.

DR. BURMAN: Anybody want to respond to Dr. Temple?

DR. FLEMING: Bob, can you clarify -- you're specifically saying, is there general agreement about what?

DR. TEMPLE: Well, what I understood Steve's proposal to be saying -- exactly how to do it remains in question -- is that more than we now do, we should put some threshold on risk. This is not entirely original thought, Dr. Hyatt and Lipicky proposed this for all cardiovascular drugs, you should allow an upper limit of

1.5 -- was that generally what people thought was a reasonable thing in the course of this meta-analysis? You could argue about what the upper limit should be --

DR. FLEMING: Right, right.

DR. TEMPLE: And whether there should be a point estimate as well as an upper bound. But was there general enthusiasm for that?

DR. FLEMING: In response is to the first question, we were really giving an answer to what are we currently doing and what are some of the changes that need to be done? Your specific question now about the upper limit I see as the answers to the first three bullet points of Question 2. So we're going to -- at least I for one am attempting to answer your question --

DR. TEMPLE: Okay.

DR. FLEMING: As we answer the first three bullet points of Question 2.

DR. BURMAN: Marvin, did you have any further comments?

DR. KONSTAM: I had the same thought. I mean, if you want to wait, or we could get to it now, but --

DR. TEMPLE: Never mind, then.

DR. BURMAN: Good. Then let me summarize Question 1, and thank you all for your thoughtful consideration of it.

This is -- trying to derive a consensus, obviously, isn't exactly a perfect process. But it seems that the majority of people -- and let me know if someone violently disagrees -- but the majority of people thought that a uniform, balanced, reliable, pre-specified, standard adjudicated approach with pre-defined numbers of patients and durations seemed an appropriate approach in the pre-approval process.

There should be a detailed reporting system for a variety of specified and multiple adverse effects, including cardiovascular events and others. Some members agreed that a meta-analysis was

appropriate and others didn't. But the term "meta-analysis" may be somewhat misleading and probably most agreed that some sort of integrated analysis seemed reasonable, although it had certain potential certain flaws.

The ethical issues were of course discussed, and this is all in the background of -- in decreasing mortality of diabetes over the last 20 or 30 years, increasing benefit of treating microvascular disease. And we're focusing on the macrovascular relative and absolute adverse events at the present time.

Does anyone want to disagree with that sort of consensus or add to it or modify it? All right.

Thank you very much. So let's then move on to Question 2.

Please discuss the following aspects of design and conduct of a long-term cardiovascular trial with an anti-diabetic

therapy.

Should the trial's objective be to show cardiovascular benefit of a new drug or to rule out an unacceptable increase in cardiovascular risk? An objective to show cardiovascular benefit should be discussed in the context of the fact that conclusive evidence of cardiovascular benefit has not been demonstrated for any of the currently available therapies for type 2 diabetes mellitus, despite the fact that several large, long-term trials have been conducted with this objective.

If the objective is to rule out a pre-specified increase in cardiovascular risk, such as a non-inferiority trial, what magnitude of additional risk should be excluded? Is a relative risk or hazard ratio of 1.2 to 1.4, observed in several recently designed cardiovascular safety trials an acceptable non-inferiority margin?

What should the primary endpoints

be, for example, total mortality or composite clinical endpoints such as non-fatal MI, CV death, and stroke?

Please comment on the size and duration of the size and duration of these long-term cardiovascular trials.

What type of patient population should be enrolled? For example, pre-diabetes, non-diabetics, high-risk diabetics for cardiovascular events such as patients with acute coronary syndrome?

And lastly, as it is unlikely that such a study will be able to randomize study participants to the placebo only, please discuss the possible comparative groups. For example, drug X versus drug Y, or alternatively, drug X added to standard of care versus placebo added to standard of care, or drug X added to standard of care versus drug Y added to standard of care. For add-on to standard therapy trials, how should standard therapy be defined?

On the next page, how should deteriorating glycemic control be defined and handled. Include a discussion of escape criteria and how to include patients who have been withdrawn due to worsening diabetes in the efficacy analysis.

And lastly, should investigators be encouraged to manage blood pressure, lipid profiles, aspirin use, and other cardiovascular factors to current guidelines, which will not necessarily ensure comparability across treatment groups, or should algorithms be used post-randomization to ensure that these risk factors are equalized against treatment groups?

Dr. Veltri, you have the auspicious duty of being the first to answer these.

DR. VELTRI: First of all --

DR. BURMAN: Please take it in part so we can understand each aspect.

DR. VELTRI: I think a cardiovascular trial in the post-marketing arena would be

adequate, given the knowledge gap we have. And I think such a trial would need to answer both efficacy and safety.

I think there's a huge gap here. We don't understand whether it's because the agents may have benefit on microvascular disease and we haven't followed them long enough. There's a latency period. I think there's confounders there among the various agents, as well as the groups that are studied. And I think that that long-term clinical cardiovascular trial needs to be enriched for patients who are going to have events.

I think there -- I'm a believer in a simple trial, so I think that all other standards of care to target the evidence-based levels, LDL, blood pressure, et cetera, should be taken into account. I don't believe in an algorithmic approach where it would be pre-stated what drug or what level. Just basically on top of

standard of care.

I think the biggest difficulty is what's the comparator. And many of these folks are going to require more than one, maybe two or three other anti-diabetic agents. And I think that could be a major confounder. But I think that some way, shape, or form, that needs to be controlled for, in perhaps somewhat of a stratified approach or sub-group analyses thereof.

I have a real problem, however, in a pre-marketing study as a basis of approval to exclude a harm alone -- in that I think it's admirable and I think it's meritorious if one can do that, so there's an opportunity there to narrow the gap in knowledge. But I think the devils are in the details, and I think it would be very difficult to try to control for all of those confounders as part of that trial.

I also have a problem in trying to identify a particular point estimate or upper

confidence -- 95 percent confidence interval bound to go by, for many of the same reasons that were previously mentioned. And I think, as was said before, I think if even one targets 127 or 87 or whatever that number is, you have to assume a certain percent patient year annual risk to get to that number. So you have to accrue the full 4,000 or whatever before you know -- because you don't know -- what that actual point estimate's going to be.

But I would agree, obviously, if the odd ratio is 1, you don't need as many. But you don't know that going in. So that automatically requires you to somewhat have a certain sample size for a given annualized risk. So I think I have difficulty there. And it also doesn't answer the question, I think, ultimately. Because all of the confounders about maybe there is a latency. Maybe there is things we don't understand yet about diabetes and macrovascular risk.

I think that would potentially -- not paralyze, but delay drug discovery, drug development, and innovation in this area. And despite all the inroads that have been made with symptoms of microvascular disease, I think there's room to go.

So I think that it's certainly appropriate to do a post-marketing cardiovascular trial, adequately powered to try to answer both efficacy and safety, given that these patients are CHD-equivalent and we need to know that information.

But I think designing that trial has a number of issues.

I don't think, though, a harm trial -- trying to exclude a certain level of harm, though, is needed pre-approval. I think one can label around that, as was said before.

DR. BURMAN: Thank you. There's some other issues there. You can go down the list.

For example, what do you think should be the primary endpoints?

DR. VELTRI: I think the primary endpoint should be CV disease, stroke, and MI, adjudicated, of course, by a CEC. I think the size and duration of these long-term trials has to be adequate to identify a certain benefit. I think we heard yesterday that a meaningful clinical benefit is somewhere between 10 and 15 percent on top of standard of care, and the reduction of those events, and therefore, depending on the population one goes after -- and I would think it would be a higher-risk diabetic type 2 diabetes population -- maybe some atherosclerotic (?) demonstration already whether it be sub-clinical or clinical, post-MI or demonstration of arthrosclerosis would be appropriate.

And again, it has to be a high-risk patient population. Again, I would --

DR. BURMAN: And your thoughts on compared --

DR. VELTRI: I think this would be an add-on trial, the standard therapy. However that's defined, provided that the background therapy does allow adjustment for glycemic control based on current standards.

I think going below current standards have some hazard to it. And just as a commentary, I mean, hypercholesterolemia, hyperglycemia and hypertension all have the word "hyper" in it. Okay? High cholesterol, high glucose, high blood pressure. We know you lower cholesterol and probably not get to a hazard. But if you drop blood pressure and if you drop glucose, two essential ingredients for survival, I think you end up with patients on the floor. So I think we do have some understanding, potentially, of mechanisms of harm. Either too aggressive or too early aggressive reduction in glucose, or blood pressure, for that matter.

So therefore, I think the standard

should be to current standards as depicted either by NCEP, ADA, AHA, ACC. Again, simple trial design. I think that you can't mandate or give algorithms. I think you would assume you're going to control all the other risk factors as best you can with whatever agents are appropriate.

DR. BURMAN: Thank you very much.

Dr. Genuth.

DR. GENUTH: It would help me to put the Question 1 up so I can follow it. Yeah.

DR. BURMAN: This is the first part of Question 2.

DR. GENUTH: I think there should be a post-marketing trial for cardiovascular disease outcomes. It should be primarily to look for benefit. Obviously, we will learn if there was an unsuspected risk. But I think it should be designed on the premise that there might be, still, cardiovascular disease benefit in lowering glucose as an independent risk factor, despite the failure thus far of trials to show

that. There may be defects in all of the trials that we heard about yesterday. Unintended, obviously, but nonetheless, they don't allow us to conclude definitively that lowering glucose cannot have a cardiovascular disease benefit.

Also, as was brought up by speakers yesterday, a drug may by chance have a cardiovascular disease benefit other than through lowering glucose. And if in fact we eventually decide, as the cardiologists now appear to believe, that type 2 diabetes and cardiovascular disease are virtually synonymous, and then a drug might attack a pathway, and that both lowers glucose and by some other mechanism decreases the risk of cardiovascular disease.

So for those reasons, I think more trials are still appropriate. But I think it should be post-marketing.

DR. BURMAN: Your thoughts on the hazard ratios, if any?

DR. GENUTH: I think I've already said

that. I can't decide what's an appropriate negative hazard ratio; that is, how much risk I should accept for how much benefit or potential benefit. I'd like to hear more discussion of that here, more specific discussion about why we should accept a particular safety risk for a particular benefit in some quantitative equation of risk benefit. I just don't know how to do that.

I think the primary endpoint should certainly be stroke, MI, cardiovascular disease death. And as I made notes, I was tempted to add a fourth equivalent outcome, mainly revascularization, coronary revascularization -- particularly coronary artery bypass surgery. A little bit less certain about adding stents, with or without drug allusion, et cetera, because I think there's more potential for bias entering into the decision or the judgment on whether to revascularize in the course of coronary angiography. But I think there's less risk

of bias when the recommendation is made for bypass surgery.

So I think I would add that as a fourth event.

DR. BURMAN: Dr. Genuth, can I ask a point of clarification? Are your thoughts that you'd like a composite endpoint of all three?

DR. GENUTH: Composite, yes.

DR. BURMAN: Okay.

DR. GENUTH: I'm sorry. Obviously, though, each element in the composite has a secondary outcome that needs to be assessed. Because it's conceivable there'd be differences. Five years seems like a reasonable, practical duration of the trial. But I don't know that five years will always answer the question. It's already been pointed out there could be very long-term benefits or risks that aren't apparent in five years, but I don't see any way out of that except to make a practical decision about how much effort we can do, how much cost we can incur to answer these questions.

As a side comment, I've heard the word "burdensome" mentioned several times in the last couple days, that the FDA cannot make burdensome requirements on pharmaceutical companies. I don't quite see that. I think it's reasonable to make requirements burdensome if that's what it takes to satisfy us that a drug should be on the market.

I would enroll people with diabetes, not people with so-called pre-diabetes. Although that's an arbitrary decision, I don't believe there is such a thing as pre-diabetes by glucose levels. I think what we now call pre-diabetes has impaired glucose tolerance -- impaired fasting glucose is just an early stage of diabetes. But I think it's reasonable to conduct trials primarily in the people who pass the test -- current glucose tests of diabetes, we might want to someday move to earlier stages of diabetes for trials. But

it's been pointed out over and over again that the event rates can be expected to be much lower, requiring larger numbers of subjects or longer trial durations.

I would much prefer drug versus drug trials to add-on trials. I really want a new drug to be more beneficial, if possible, than any current drugs in lowering glucose levels. So I much prefer drug -- new drug versus standard drug. But I recognize what Allison has pointed out, that -- as well as her patient representative -- I apologize I don't remember your name -- that patients are different, and there may be two drugs with equal glucose-lowering benefit, where one of them is more appropriate for patient A, and the other is more appropriate for patient B.

But we already have 10 drug classes now to make those choices from. And so I would much prefer that any new drug actually lower glucose more than standard drugs so

that we can come closer to reducing or eliminating microvascular complications.

Is there something else I have to address?

DR. BURMAN: Yes, the question about glycemic control.

DR. GENUTH: Oh, yes. I'm not in a quandary about that like I am about some of the other issues. I really think that other risk factors should be controlled as equally as possible by protocol in trials, in order to get the purest possible answer as to whether the drug we're testing has a cardiovascular disease benefit or not -- independent of or because of glucose-lowering. If we don't do that, then we will always have the risk of confounding. And we've seen that in the other trials -- the PROactive trial is probably the best example we have right now.

And so I'm for protocol mandating control of the other risk factors. And it can be done. I can tell you from one trial

I'm participating in now.

DR. BURMAN: How -- briefly, how would you like to suggest handling deteriorating glucose control in these trials?

DR. GENUTH: Well, you said "briefly." That's a challenge. It's very difficult without introducing confounding of drugs. You end up, instead of having a pure test of drug X versus drug Y or drug X as an add-on versus placebo as an add-on -- as soon as you start adding standard drugs of one sort or another to equalize, or to sort of rescue people from glucose levels that have drifted up too high, you introduce confounding. But I think we have to live with that, because we cannot allow patients in a trial to have undue microvascular risk in order to decide if we have a better new drug.

So I don't see any way to avoid that, you just have to add other drugs, and maybe insulin is the best other drug to add in those situations, since we sort of know

the most about it.

DR. BURMAN: Just to ask you a question on that, if I might. I was thinking about this as well, in that if you add-on another drug to someone who's hyperglycemic and is failing -- whether it's placebo every other agent, then obviously that confounds the variables over the short and longer term.

And if I'm thinking correctly, over in the classic -- is it popular now the intent to treat analyses, you would include everybody into the analysis at the end regardless of what add-on therapy you had. But in diabetes, with the hyperglycemia, if you brought their glucose down and the hemoglobin A1c down with another agent that you added on because they failed the study, is it really proper to include them in the final intent to analysis?

DR. GENUTH: Yes, I think intention to treat analysis should always be the first analysis.

And when that's done, I think the investigators and their statistician colleagues have to decide whether it's appropriate to do secondary analyses to try to untangle or unravel the confounding they produced by following the strategy that you point out. And it's essential strategy, and we can't let people go for four or five years with hemoglobin A1cs above -- you name the number. I would say 8 percent for sure. But now maybe that number's got to come down.

DR. BURMAN: Thank you. It certainly confounds the long-term analysis. And I think the last question I think you answered that you would -- already answered, that you would manage them to optimal levels to the other -- with the other parameters; correct? Yes.

Thank you very much.

Dr. Fradkin.

DR. FRADKIN: I think we heard convincing presentations yesterday that a drug doesn't need to show cardiovascular benefit to

be approved for treatment of diabetes, that clearly, the cardiovascular benefits of glycemic control, and also the quality of life benefits of glycemic at certain A1c levels and above are well-established. And so I would say what we're talking about here is studies that are designed to assure that we're not doing harm as far as cardiovascular disease goes.

I'm a little confused about which studies we're talking about right now, because I think this question was developed before we sort of had the paradigm that Dr. Nissen presented yesterday of a pre-approval Phase 2/3 and then a post-marketing study. And so then I think some people are answering this in terms of a post-marketing study, but then when Dr. Temple asked his questions, I guess there still is some discussion to be had with regard to a pre-marketing study. So which context should we be answering this question in?

DR. BURMAN: My opinion -- and I'd love, Dr. Parks, or anybody else in the FDA to comment -- is that this question was devised to allow you latitude in which way you -- to answer whether you'd like it pre- or post-approval. And as you know, in question 3, when we actually ask a question, it then divides it up into what studies you want pre- and post-approval.

Dr. Parks, or anybody have any further comments?

DR. JENKINS: I'll take that. Yes, that's true. This question is really about, independent of when the study is done, how do you think a large cardiovascular study should be done? A long-term study. So this is purposefully put before question No. 3 to allow you to explore all the issues that need to go into designing and conducting these trials.

If you're in the camp that thinks that the screening trial that was proposed should be an independent -- Dr. Temple termed it an intermediate-sized cardiovascular

trial -- these factors still come into play about how do you design the trial, what are the endpoints, what do you control for. So this is really kind of a stand-alone question of what are the design features of a long-term cardiovascular trial, whether it's a pre-approval trial or a post-approval trial.

DR. FRADKIN: So if I -- So I think --

DR. BURMAN: Do you have any thoughts on that?

DR. FRADKIN: I think I've sort of answered these two bullets, have I not?

DR. BURMAN: Well, the first part. The second part is, do you have any thoughts on the relative risk to hazard ratio?

DR. FRADKIN: You mean, what the level to be excluded is? I guess that would -- I guess I would sort of tend to favor the approach that Dr. Nissen talked about, with potentially defining some level that would be okay to take you forward into an approval process. But I

think if you didn't see any signal, if you really had a point estimate that was close to 1 and you had enough events in the pre-marketing aggregated studies, I think it might be an issue as to whether -- that the FDA might then decide whether a post-marketing study was really required or not -- on the basis of the signal that was seen in a pre-marketing study.

So I guess if I saw a risk that was certainly approaching a 25 or a 30 percent increase potentially in a somewhat under-powered pre-marketing study, then I think you clearly would want to define that more carefully in a post-marketing study.

On the other hand, if you had pretty good confidence intervals based on your number of events and no signal of increased risk, I think I might be comfortable not recommending a subsequent study.

I'm not sure if that really answers the question or not.

DR. BURMAN: It does, and is relevant to -- for the questions as well.

DR. FRADKIN: Then I agree that the primary endpoint should clearly be clinical events and not CVD surrogates, and that it should be a composite, but with the individual events looked at as secondary outcomes.

As I said before, I think that the duration is particularly important, and I think you would want to have sizeable numbers of patients who were in fact treated for several years, because I think -- again, based on the ACCORD time course of events, the signal really didn't emerge for a couple of years.

In terms of the patients, I think it should clearly be people with diabetes rather than pre-diabetes, because I don't think you would be moving drugs from diabetes to pre-diabetes until you had seen some benefit in patients with diabetes. And I think you would want to enroll a range of CVD

risk profiles within the diabetic population, including people who have established cardiovascular disease, and people who just have presumptive cardiovascular disease.

I think that I would like to see people controlled to comparable A1c levels in the trial, so I think there would have to be active comparators. I think this is one of the hardest aspects of the question, and I guess what -- I would hope the trial would be designed -- it would partly depend on the way the drug is going to be used. I mean, if you're talking about an oral agent that's likely to be an add-on to current oral agents prior to people getting insulin, then I think probably what you would want to do would be to have people who are on some baseline of therapy -- say, metformin -- and then the randomization was to your new drug versus one of the other established drugs, with then additional therapy being added in the future, as Dr. Genuth recommended, with all the

potential confounding of that.

But I think you would have to control glycemia in the long-term. So things would have to continue to be added.

And I think I've answered these.

DR. BURMAN: The glycemic control?

DR. FRADKIN: I think I talked about glycemic control. So you would want to add additional agents as needed. And that might be additional oral agents or it might be insulin, depending on the patient's situation.

And I agree that we should be managing blood pressure and lipid and aspirin to the current recommended guidelines. I think it would be important to ascertain what drug therapy people needed to take to get to those guidelines. So if in fact your drug had favorable effects on needs for statins or needs for additional blood pressure drugs versus increased requirements -- but I think the levels of blood pressure and cholesterol should be equalized so that that wouldn't be

what's driving the outcome.

DR. BURMAN: Thank you very much.

Dr. Savage?

DR. SAVAGE: I think I'd start by saying that I like many of the suggestions that Dr. Nissen has made about some type of a pre-approval trial. I think the devil is in the details, however, because the magnitude of that trial, I think we might disagree upon.

But provided that something was done that was a smaller number, shorter duration, prior to approval, the question arises as to the need for a long-term trial.

I'm sort of struggling with two facts. One is that a long-term trial is expensive, time-consuming, burdensome on the patients. On the other hand, there is this history in terms of medications used to treat diabetics of a potential adverse cardiovascular effects, as was shown in some of the talks yesterday. And I wonder if we shouldn't, at least for a while, try to get

more long-term data as a new drug is introduced, and maybe after 5 or 10 years reassess the situation. But there is this problem of several drugs over the years being associated with potential cardiovascular toxicity.

As far as the first question about conclusive evidence of cardiovascular benefit, my opinion, after hearing the presentations of the three trials at the ADA and the presentations yesterday and the results of the other trials going back to the UKPDS is that we should really be satisfied with something that doesn't do harm. I don't think it's likely that given the current tools that we have available, it would be easy to show or likely possible to show a significant cardiovascular benefit for a new drug being introduced unless it had some really unique characteristics -- if that's being introduced in the setting of people being treated for their other CBD risk

factors with very potent and effective agents that lower the risk associated with hypertension and dyslipidemia.

So I think that just doing no harm is sufficient, because we know that a drug that helps to control glucose is likely to have the benefit in terms of the microvascular complications.

As far as the ratio is concerned, again, I suspect we all have a different sense of what might be acceptable. I think it also depends upon what type of event you see. If you -- you know it was mentioned by Dr. Gerstein yesterday that in ACCORD, there was a -- the primary event was tending in a positive direction, but there were the excess cardiovascular deaths. And obviously, excess cardiovascular deaths are much less tolerable, even at a lower ratio of excess, than some of the milder symptoms associated with cardiovascular disease.

As far as primary endpoints, I

agree with Dr. Genuth and Dr. Fradkin that you want hard cardiovascular disease endpoints. I think -- I was going to comment later upon subsets of patients, and one of the questions that comes up is, is there any sub-clinical disease assessments that could be used in these trials? And I think at the present time, the answer is no, because we don't fully understand what causes the excess cardiovascular risk in patients with diabetes. Clearly it affects lipids, it affects blood pressure. But it also affects the coagulation system. It may in some ways make people prone to fatal arrhythmias. So I don't think anything that looks at just sub-clinical disease would be sufficient for any of the trials, which has major implications in terms of costs, obviously.

Size and duration of the trial? Provided that a pre-approval trial was relatively short, there is the need to look at whether there's anything that develops

after a period of time. And the slide that was shown yesterday by Dr. Gerstein showed that the excess deaths in ACCORD started to develop, I think, about two years out.

And despite the fact there have been some comments made in editorials and so forth about hypoglycemia and rapid lowering of glucose in ACCORD, the rapid lowering took place in the first four to six or eight months, and there was a fairly long period before the problem started to appear. So I'm not at all sure that the hypothesis that some people have put forward is the explanation of what happened.

I think it's quite plausible -- particularly if you take people with recent onset of diabetes -- that a five-year duration may not be sufficient. And on the other hand, that is a practical time limit. If you find out that you either do or don't get a benefit at the end of five years, that's something that can be done.

Going out much beyond that, as any type of a mandatory trial, seems hard to justify.

The type of patient population? I agree that pre-diabetics are not a good group to study. The excess CVD event rates in them are -- it's only a small excess, and it would take a long time to develop a large number of hard cases. There's another group of people at the end of the spectrum with advanced cardiovascular disease. I'm not really sure that we would need to study that subset of people, because their life expectancy may be relatively short anyway.

The three trials that have just been reported looked at a group of people with relatively high-risk of cardiovascular disease, either a previous event or risk factors that make them high-risk. One of the groups that needs to be considered, particularly for oral agents that would be used early in the disease, would be people that were relatively recent onset patients.

It is possible -- and it's just speculation -- but it is possible that treating the disease earlier could have a different effect than treating people that are already high risk.

To compare the groups, again I think it depends upon what agent I think that you're going to have to use in almost just about any of the patients -- if you're talking about any patient group of type 2 diabetics -- if you're talking about a five-year trial, you're going to have to add some type of an agent. Metformin seems to be a relatively benign one to start with as a basic agent, and then add something to it.

I don't think placebo trials are likely to be very feasible if you want to keep the glucose under control in a substantial number of people.

How should deteriorating glycemic control be handled? I think the current environment would suggest that you shouldn't

let the glucose rise very far before you add another agent. One of the questions then is what to add and how to do it. There are big clinical trials like ALLHAT where there was sort of a structured addition of agents.

There are others such as the three trials that were presented at the ADA, ACCORD, ADVANCE, and the VA study, where the practitioners were allowed to use the agents that they felt would be most appropriate for that patient. And you can argue the pros and cons of either approach. The one advantage of a stepwise approach if you're trying to look at -- as a defined stepwise approach of adding drugs would be, you might have a little bit better chance of determining whether or not something caused a problem when you added it to the regimen if you then saw some type of a spike in events later on.

And the last question, should investigators be encouraged to manage blood pressure, lipids, and so forth to current

guidelines? I think that given the evidence that exists from the blood pressure trials and the cholesterol-lowering trials, those are the most potent ways we can reduce the risks associated with the lipid and blood pressure abnormality. So I think we're pretty much confined to having to try and use the current guidelines as long as we don't think there's a safety concern in a particular patient.

So I think that's it.

DR. BURMAN: Good. Thank you very much.

Ms. Killion.

MS. KILLION: My answer will be much briefer because I'm not qualified to address 97 percent of this question. So if it's acceptable to the panel, I'll just touch on those portions of the question I feel I can answer, and avoid embarrassing myself by repeating, "I have no idea, I have no idea."

So I'll just go through it in

order. With respect to benefit and risk, I don't think -- I agree with others that the trial should not be required to show benefit, because the drugs we're studying here are designed to treat diabetes and not CVD. So I don't think that we are under any obligation to show that we also treat heart disease.

With respect to the risk, I think that some element of the trial should be designed to assess an increase in risk for CVD. Because this would be valuable information for many diabetics to process when they're considering the treatment options.

With respect to the pre-specified increase in cardiovascular risk, I don't know how to assess this because the risks are so variable over time and over the population of patients. So I just don't have any way to give an answer on that.

Going back down, now. Skipping down to the type of patient population. I

think that the study should strive to involve diabetics that are at an elevated risk for CVD, although I think that presents a lot of challenges with respect to the consent form. But I think that there probably are significant portions of the diabetic population that based on -- would give informed consent.

Skipping over the comparators. How should deteriorating glycemic control be defined and handled? I'm not sure how it should be defined, but as far as being handled I don't think that we can allow diabetics to lose glycemic control because it might confound the study of the cardiovascular disease risks. So I think that that has to be a primary point that regardless of what -- if it may confound or not, we have to make sure that diabetics involved in these studies, the primary objective is to maintain their glycemic control at an acceptable rate.

Should the investigators be encouraged to manage blood pressure, lipids, et cetera? As long as you have these people in a trial, I think that this can only benefit participating diabetics. Even if it confounds to some degree. I hope that, at some point, I have faith in the statisticians that they'll be able to sort this out eventually. But if what we're thinking about patient health and patient benefit, this could only be of benefit to them. So that's what I would encourage.

So I'm done.

DR. BURMAN: Thank you very much.

Dr. Rosen.

DR. ROSEN: Thank you. So first I just want to emphasize, again, as Peter summarized, we do have an issue with cardiovascular risk with our treatments. And that's what this is all about. So we're going to have to deal with it, and although it might be a little more burdensome, if that's the right

word, we need longer studies. We need long-term, well-controlled studies. And I think Peter made that point again.

And we've learned it from a number of different trials and we've seen graphs over the last two days where there are changes acutely that then come together and then go away, or others that appear as benefit later in the course of the trial.

So I'm in favor of longer-term trials, and I think we have to address the issue of cardiovascular risk.

So the question is how to do it. And I'm very much in favor of Dr. Nissen's proposal for pre-approval evaluation. And I think the reason is, is that we really have to get at the issue of cardiovascular risk. I'm not saying that there couldn't be possible benefit, and I think Steve made this point in his talk several times that although we're worried about cardiovascular risk, it's not out of the question that these drugs

could have cardiovascular benefit. And that's only addressable in a longer-term study.

We know from the UKPDS that metformin -- at least in a sub-study -- appeared to have nearly significant effects in reducing cardiovascular risk. And we also have some data, however it is, on pioglitazone. So I don't think we can exclude that possibility. And that brings me to the issue of discussing the hazard ratio, or whatever the relative risk is. So I'm going to drop down to that and then come back to the cardiovascular benefit, or risk.

And just remind people that I think when we try to talk about a hazard ratio, the key question is not the ratio number but the confidence intervals. Particularly the upper confidence interval. And of course the lower one. And I think this was come back to several times during the presentations, and

Dr. Temple alluded to it several times as well, that if you have a hazard ratio of 1, and you have confidence intervals that are equal, that gives you very strong confidence that this drug probably doesn't have risk.

But if you have a confidence -- a hazard ratio of 1.23 and your confidence intervals span both a 60 percent reduction and an 80 percent increase, those are the kind of issues that have to be addressed in a pre-approval study.

And I think that's why this proposal makes some sense. And so I'd like to emphasize the importance of looking at confidence intervals rather than a point estimate per se. Although that's obviously very important.

Also I think it's critical that we recruit high-risk patients because the numbers needed for this kind of evaluation, as you can see from the handout from Dr. Nissen as well as others really depend on

what the MACE annual event rate is. And if it's 3 percent, then those numbers match up a little better with what Dr. Parks was suggesting in terms of studies. If it's 2 percent or 1 percent, obviously these are going to be large, extensive studies.

And I think it really behooves us, because the problem is -- and Peter's alluded to it just previously -- the problem is, the younger diabetics are much more heterogeneous -- younger being in terms of onset of disease -- than those that already have cardiovascular risk, have established disease, and could have significant problems with hypoglycemia.

So in response to Question No. 2, I do think a pre-approval process is indicated. I think risk is the most important, but I think looking at confidence intervals, it's not out of the question that a new drug may have benefit in addressing that in a standardized, randomized, controlled trial

isn't a critical issue.

I think that we should consider the 1.8 upper 95 percent confidence interval as one that would be acceptable, although of course nothing is acceptable in terms of risk. And people have made that point clear. But as others have suggested, and it's very important as I've made that point previously, you can't dissect out the positive benefits from the hypoglycemic effects of these drugs from the negative risks. So there are positive benefits, of course, and we're looking for risk that may be inherent.

I would suggest that we look at composite endpoints, and that these be very well-defined. And that the trials at least be of three years duration and particularly if we're having a 3 percent MACE annual event rate. And at least 1,500 subjects in the trials for this kind of pre-approval program.

But again, I think it's really important that we consider looking at

higher-risk individuals rather than the low risk subjects. And so in answer to the type of patient population, I would say smaller studies are indicated for the pre-diabetic or early diabetic patients, but I'd like to see higher-risk individuals included in a pre-approval study. Because I think that's the only way we're going to get to this factor of what is risk or what isn't.

And it's interesting how reminiscent -- I hate to go back to bone, but it's a little more reminiscent of what we see with fractures, in that we're recruiting high-risk individuals in osteoporosis trials because those are the only subjects that you're going to be able to see fracture risk reduction. You have to quadruple or tenfold the number of subjects in order to see fracture benefit in individuals that have osteopenia, but do not have fractures. So in a very similar way in order for us to get at these individuals -- and that's the question