the last one to think this until just this meeting, which is that, are we hung up excessively on late stent thrombosis? And with Mitch standing there telling us at the beginning of your presentation, unifying these two things, which have been a dialectic for so long, safety and efficacy. But the gestalt that we have to go through to recommend approval or not, I think, again, comes down to the patient or clinical perspective. And, Sharon, many of us have worried about that since day one. But shouldn't we just focus on death MI, and minimize the fact that we're going to make a mistake with counting very low frequency events, but we're sure as hell not going to make a mistake with counting deaths or myocardial infarctions. And within that universe will be a few late stent thromboses, but if there's a higher signal relative to the comparator, which, by the way, is always an issue with the non-inferiority trial, but if there's a higher signal, there's a problem.

And I hate to turn the clock back so far, but is late stent thrombosis just -- are we just perseverating, and really the main things is death MI, as it always has been in this business.

DR. YANCY: Comment well made. Dr. Somberg.

DR. SOMBERG: Well, Dr. Zuckerman brings up a very important question, and I was lumping the numbers together, because that was so disturbing. But if you break it up, and you ask how many finished the pivotal clinical trial for approval in the United States, SPIRIT III, the number is only 35 percent data completions, even more troubling to me. And to make a decision on that is even more difficult.

Now, I understand Dr. Laskey is saying well, you know, gee whiz, the end -- and it's true, the be-all and the end-all is going to be the balance of all these small and major contributors to death and MI in the end,

but I think we should have an adequate sample to be able to judge that, and I don't think it's just on 12 months. You're putting something in that has long-term effects, that can't come out, and that's permanent in patients, so I think you have to have some further follow-up, and some standard should be created, not just a clinical gestalt, or a feeling.

DR. YANCY: I mean, to be fair, SPIRIT III did complete and the endpoint was at 270 days, and we have requested, and the community has requested the additional data for which we only have 35 percent complete acquisition. There are a couple of comments that are pending. I think Dr. Hirshfeld, and then Dr. Krucoff, which we'll get to.

DR. KRUCOFF: I really just have a correction for you guys, Mr. Chair, if you -- which might be pertinent to this.

DR. YANCY: Please. Please.

DR. KRUCOFF: I've been handed

updated information on the time line for completion. And, again, this is not -- the primary endpoints you've got 100 percent from both studies, but the estimated time line to completing the additional 422 XIENCE V patients out to their two-year follow-up is not 18 months, but would be about, at least 8 months, so it's at least 8 months before you would see another 422 XIENCE V patients. And I think in terms of the primary prospective endpoints, both the angiographic and the clinical endpoints that were the co-primary endpoints, you've got 100 percent of the original prospective design. To get to the two-year, which was the question that was asked before, the two-year completed follow-up on what would be an additional 422 XIENCE V patients would be at least 8 months, not 18 months.

DR. YANCY: Thank you. Dr. Hirshfeld.

DR. HIRSHFELD: At the risk of

perseverating on perseverating, I just want to make one more point why I feel that we need to pay a lot of attention to stent thrombosis. And all of us who have dealt with it know what a nightmare it is when it occurs. And it also, if it proves to be an important ongoing problem, it's a specter that hangs over the heads of all of our patients, and it also complicates their management for non-cardiac surgery, and other events down the road. So I think that's the reason that, independently of a more pooled outcome data element, such as death and MI, I think we need to pay particular attention to stent thrombosis.

DR. YANCY: Thank you. Dr. Page.

DR. PAGE: Just briefly. I agree that stent thrombosis is important, but I don't think we can minimize the importance of restenosis, and that's something that is accomplished with a drug-eluting stent.

I think what Dr. Douglas mentioned about this platform being the platform of last

resort needs to be clarified, if I understood you, Doug. And your comment was that when you're stuck, you can use this stent platform in places where you can't otherwise get a stent. Is that correct? And that's what my understanding is from the interventionalists that I work with, so I see a real advantage of having a stent with true technical advantage, independent of the drug-elution, to be available. And when you add to that the option of having drug-elution in the selected, in an appropriately selected patient, I think that represents a real addition to the options that an interventionalist has available to them. So in that way, if, indeed, we see reasonable assurance of effectiveness, which I believe we see, and see reasonable assurance of safety, which we're wrestling with, but I think for the data set we have available is getting there, then I think we need to consider whether it would be appropriate to withhold this technology, and this arrow in

the quiver, if you will, for the interventionalist to have the option of a stent that represents a true advantage in deployment, that also allows drug-elution.

DR. YANCY: Dr. Morrison.

DR. MORRISON: I appreciate those comments. I really didn't want to be misconstrued as implying that, just because we approved one, and it wasn't quite as good, now this one we should approve. But precisely that there's different kind of inference, and that is one of the examples of non-randomized trial data that's before us that I think is extremely important data that's before us, and provides a very powerful inference. The VISION and MINI VISION stents have been available for a long time. We've used them a lot, so if you somehow had the numbers, they've been put in thousands of people. And we know a lot about them. And, similarly, we know a lot about the drug everolimus.

And, finally, the other point is

that it really is difficult, it is going to be difficult even going forward, over and above whether trying to define definite and probable late stent thrombosis. The first thing that happens when you approve anything, as Dr. Zuckerman knows better than all of us put together, is you can't dictate the way people are going to use it. And it's going to be used in settings, and in people that are going to make the rates almost certainly go up.

DR. YANCY: Dr. Normand.

DR. NORMAND: I just want to -- I don't know if I'm following some of the thinking, and so I'm going to tell you what I've been thinking, and that is the following. We're talking about -- we're worried about stent thrombosis. Now if we go back to December, if I recall correctly, the worry was stent thrombosis with bare-metal stents versus drug-eluting stents.

This trial is looking at two drug-eluting stents, so I'm just trying to figure

out, are we looking for a bigger difference in stent thrombosis between the two arms? Is that what we're really talking about here, because this trial is not looking at a bare-metal stent. And, so, I know I keep harping on this, but we really -- I want to make sure I know what we're comparing this to, because in my mind, when I'm talking about data for stent thrombosis, the trial in front of us is looking at stent thrombosis compared to two drug-eluting stents.

Some of the comments I'm hearing right now, I may be incorrect in thinking this, but I feel like it's talking about that relative to bare-metals stents, and so I just want to -- because this is a trial we're asking for more data about stent thrombosis, and this trial is comparing two drug-eluting stents. So, again, I just want to make that clear. And, again, I don't know, Warren, if you're talking about -- your comment about we're worried too much about stent thrombosis.

Again, I'm just wondering, is that stent thrombosis drug-eluting stent versus bare-metal stents, because right now we're talking about two drug-eluting stents, so I just wanted to lay that out, because I'm getting a little bit confused about what we're expecting to find. Do we really expect to find more stent thrombosis in this one drug-eluting stent, relative to another drug-eluting stent?

DR. YANCY: Now, as I see this, and having been involved in these discussions, my sense, and we may all have a different perspective here, but my sense is that we have implicitly accepted the incidence of late stent thrombosis with TAXUS as a reference point. And our intent is to be confident that we don't see a single that is any higher than that. And the concern might be that, with the present database, we simply can't answer that question. So I don't think that we are relating it back to bare-metal stents, because we can't. We don't have that information for

this study, but we have to look at TAXUS as a surrogate of the problem, and compare the XIENCE V to that, for those reasons. But we may have different interpretations around the table.

DR. NORMAND: There's just going to be a lot of references made to the December meeting, where it was relative to bare-metal stents. So I just want to make sure that we're always talking about the same comparison.

DR. YANCY: And I appreciate that. Dr. Laskey, you want to respond?

DR. LASKEY: Well, I -- she just finished my thought. We ought to make it clear from this point on it's DES versus DES. But, again, it's not only versus, we can't do this in a non-inferiority universe. That's the worst way to do this, because of your likelihood of a false positive, in which case you're now approving a stent which is worse. So we ought to be clear about that, for sure,

as we move forward, and let's get off of this non-inferiority thing.

But the rest of it, we all agree that we're talking DES-DES.

DR. YANCY: So we'll hear from Dr. Kato, and then I'll give opportunity to Dr. Yaross, and Karen Rue. And once that's completed, then we'll yield to Dr. Agler.

DR. KATO: And I think that as this discussion has evolved, and I'm still fighting over internally what to do here, but at the end of the day, I think Dr. Laskey and Dr. Yancy are correct, this is a DES versus DES trial, so the question that comes down to our statisticians is, were these trials -- was this trial, I guess specifically SPIRIT III, powered well enough to answer the questions on safety and efficacy. And I'll defer to them.

DR. YANCY: And we'll leave that as an open statement. Dr. Yaross.

DR. YAROSS: I have nothing to add right now.

DR. YANCY: Ms. Rue.

MS. RUE: I don't have anything to add right now.

DR. YANCY: So while Dr. Agler is getting the FDA questions, let me remind the panel that at your seat, you have a several-page document that encompasses the different questions. And it's pretty data-intense, so we may want to refer to this often.

I'm just going to make an effort to summarize what I've heard this afternoon, because as we go forward now, all of our discussions will be relevant either to the FDA questions, or to our actual vote deliberation. So what I've heard so far is that the panel believes that we are looking at a second-generation, or maybe second-and-a half generation drug-eluting stent that may be different because of its profile, perhaps because of its drug and the polymer. We have some unresolved and persistent and appropriate questions about antiplatelet therapy that

perhaps merit a different discussion in a different venue.

I think we all agree that, compared to bare-metal stent, and we do have SPIRIT First, this is a dramatically effective stent compared to bare-metal stent, and that is incumbent for all of us to recall.

We've gone through a new dialogue today about looking at surrogacy, and so we've had to identify late loss as the endpoint, and understand what that means clinically. We've talked some about incomplete stent apposition, and have had a healthy discussion about that.

New data have come forward about diabetics. New data have come forward about multiple lesions, and so we are aware of that information. We have wrestled somewhat with the combination of the SPIRIT II and SPIRIT III data. In clinical terms, the patient populations are similar, though statistically, they may not be sufficiently identical for all of the combined analyses, but, nevertheless,

these are the data we have. Our concerns are somewhat muted by a number of number of sensitivity analyses. The imputation analyses have been reassuring, and I think Dr. Hirshfeld really solidified things by indicating where he thought the efficacy endpoint resides.

That leaves us with the final issue of safety, and I think we have wrestled, if I can mention it once more, about late stent thrombosis, but we also understand it's more than just that, it's MACE in all caps, big font. And so those are the things that we've discussed today. And in that context then, we'll begin to deliberate on these questions.

Now the other thing to remember about the questions is that our answers are very important, because the answers to these questions will frame up the way FDA finally adjudicates this. Remember, we are making a recommendation, not a final determination, and so the answers to these questions are

important. They will be captured, and the FDA will be responsive to the kinds of answers that we yield. Heather.

DR. AGLER: Okay. Well, the first question we have for the panel is, "Do the data submitted to-date on the XIENCE V everolimus-eluting coronary stent system provide adequate assurance of safety in the population identified in the proposed indications for use?"

DR. YANCY: The indication, again, is the XIENCE V EECSS is intended to improving coronary luminal diameter in patients with symptomatic heart disease due to the number of coronary artery lesions, length less than 28 millimeters or the same, with reference vessel diameter 2.5 to 4.25. The critical phrase here is "adequate assurance of safety".

DR. LASKEY: So I would suggest that it provides the bare minimum assurance of safety. Throw that out for discussion.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: Yes. I really -- Warren, I really don't know what you mean by "bare minimum." I mean, you have to balance safety versus efficacy, and this specifically asks for adequate. And adequate, this is the smallest sample we have seen, and I don't think that the one to two-year database is adequate. I wouldn't even -- even if they had complete -- 800 patients, complete for SPIRIT III, I would be worried, but to have such a small number completed from one to two years makes it worrisome. And I'll ask the question of why are we racing to try to say that it's barely minimal, when there are other stents available. There is that stent platform for those people who can't have anything else to address that particular revascularization problem. So why can't we obtain that data, and then make a judgment that it is truly adequate?

DR. YANCY: So presently we have a very soft yes, and a firm no. Other inputs?

Dr. Laskey, do you want to respond?

DR. LASKEY: Well, John, you're not being fair here to -- I think we've looked at the metrics. We all see what the point estimates are, the confidence intervals. We're all sophisticated enough to know that it's imprecise. How wildly imprecise, these are adjectives here, adequate, minimal. I mean, we ought to get away from adjectives, as Dr. Normand would urge us to, when we can, but we can't, because we don't have the sample size. But this addresses safety. It doesn't address a gestalt.

I read this question to us as, not the gestalt approval, but for safety indications alone, which to my mind is the TVF story. And there is a point estimate here, and there is some uncertainty, but how egregious is that going to be with 16,000 patients later? So I say this is minimal evidence. It's not no evidence. It is minimal evidence. There's a point estimate

here, which is the best guess we have now.

DR. YANCY: Dr. Page.

DR. PAGE: I think the question we're asked is, do we have a reasonable assurance of safety, and mine is yes. I don't think we're racing. I'm not worried about being held responsible for our decisions. To the contrary, we ought to be held responsible for our decisions, either positive or negative, but I think we have a lot of smart people here who have looked at the data. And I think there are a few of us, anyway, who think that a reasonable assurance of safety has been brought forward to us today.

DR. YANCY: Dr. Hirshfeld.

DR. HIRSHFELD: I'll just add a yes.

DR. YANCY: Dr. Brinker.

DR. BRINKER: I agree.

DR. YANCY: Dr. Morrison?

DR. MORRISON: Yes. I think it's -- I don't think we're perseverating. I think

we're afraid, and I think it's appropriate to be afraid. I think that we have adequate data that this is as safe as TAXUS. And I think we were here a year ago because everybody was scared to death that TAXUS wasn't safe enough. So perspective is enormous here. This is approved in 64 countries. It's going in, and I think that we have the opportunity to go forward and learn more. The data that we have looks like this is at least as safe as the TAXUS stent, and it does have, by inference, a number of advantages. And I think that -- so that's a long yes.

DR. YANCY: Dr. Blackstone.

DR. BLACKSTONE: I would have said that it is an adequate demonstration of safety in the short-term. In the long-term, it is unknown.

DR. YANCY: That's fair enough. Dr. Jeevanandam?

DR. JEEVANANDAM: Yes, I would agree with that. I think, clearly, in the

short-term, it's been shown to be adequately safe, but I don't know about the long-term.

DR. YANCY: Dr. Kato.

DR. KATO: I would share that opinion. I mean, I think that for the study duration that we have, that it is reasonably safe. But as Dr. Somberg has also expressed, I believe that the numbers here are very, very small. We struggled considerably with our decision a couple of months ago on the Endeavor stent, and that was with 1,000 patients over two years, and we had hard data. And so for me to drop the bar, so to speak, down from 1,000 to the 200, I'm very concerned about that.

DR. YANCY: Dr. Zuckerman.

DR. ZUCKERMAN: Okay. I want to go back to a few ground rules here, because as Dr. Yancy has pointed out, the answers in as much detail as we can give to these questions are the most important part of the panel meeting.

Now, some of you have referred to other PMA decisions within the last several years, which is understandable, given that this is a very complex topic, and you're trying to use your best clinical judgment, et cetera. But now we've reached a point where we have to look at what the data is in our present PMA application, and do we have enough data to stand on safety or any of the other questions? And to say that because 1.5 years ago it was adequate to have X number of patients, that that's the rule that FDA follows, is just incorrect.

We have to just look at what we have today here. And, Dr. Yancy, if you could help us define in a little bit more detail the consensus of the panel on this critical topic; would it be fair to say that there's uniform consensus for safety at one year? There may be different view points at two years, and if we can continue the discussion based on the data in the PMA.

DR. YANCY: We're almost there. I just don't have input from one person. Dr. Normand.

DR. NORMAND: I'm just sitting here struggling a bit, so I'm not sure. And part of that relates to I'm trying to figure out what the real safety information that we have in front of us is. And so I'm sort of -- surely, not in the long-term. I mean, they didn't collect the data, so we don't know, so I'm not -- I guess I'm not sure. And this is especially true, given that it's a non-inferiority trial. It makes me a little more nervous. So remind me what you're using as the -- can we just revisit the safety information we have?

DR. ZUCKERMAN: Okay. I would, again, go back to Dr. Yancy's initial comments. Tables 3 through 7 --

DR. NORMAND: Where?

DR. ZUCKERMAN: In your questions are a good composite overlook of 12-month and

two-year data.

DR. NORMAND: So we do have --

DR. YANCY: Dr. Yaross.

DR. YAROSS: What may be somewhat helpful is the perspective that safety, as I believe Dr. Somberg mentioned, is not an absolute, but is in comparison to probable benefits. So whenever these questions are asked for a given application, it's will the probable benefits exceed the probable risks? And that may help narrow the questions of safety and effectiveness.

DR. NORMAND: So I'm looking at TVF, the late loss. I'm discounting, everybody knows, in my mind, but TVF relative to the death, cardiac death and MI. So I guess it shows -- I would then say -- I'm wavering. I'm not 100 percent sure, so that's where I am.

DR. YANCY: But that's fair. So, Dr. Zuckerman, the question that's been posed is whether or not we, as a panel, believe that

there is adequate assurance of safety in the population identified in the proposed indication for use.

Listening to input from all panel members, I come away with an assessment that at least half the panel has reservations about the safety of this application. Whether or not that safety concern is a modest one, because of some ambiguity, or a definitive one, because of inadequacy of the database, varies amongst the panel members. So I think the one thing that all panel members would accept is that there is, in fact, an adequate assurance of near-term safety at the time of application, and within the first 12 months. But there are sufficient number of people on the panel that would reserve a statement that, beyond 12 months we have adequate assurance of safety pending additional data, particularly the data point set already outstanding.

I think the concerns are that it is an easily applied platform that has

significant clinical utility and works reasonably well, and there's no safety signal for the data that we are provided, but there needs to be additional due diligence on the outstanding data to resolve the issues beyond 12 months.

Did I misrepresent anybody dramatically? Dr. Brinker.

DR. BRINKER: I'd like to maybe add some fuel to the fire here, but I think that there's no reason to suspect that, after 12 months, a stent like this will suddenly turn rogue and have a high incidence. There's no predicate to suggest that something worse happens that's not associated with stopping antiplatelet drugs, which is the real issue that we don't know about any of the stents. But the fact of the matter is that as time goes by, all these stents, get gradually endothelialized and protected against stent thrombosis. That is what we're concerned about. Nobody's just concerned about stent

fracture, or some other unusual kind of unprecedented kind of aneurism formation or something like that with the stent after this amount of time, so I don't think that we could ever be reason -- any really statistically better reassured of actually long-term safety as we have now.

DR. YANCY: That is a very valid comment, and that comment has been captured, that there's no reason to presume that there would be a change, but there is an absence of information. Dr. Morrison.

DR. MORRISON: One thing I want to make very clear is that fairness isn't coming into my thinking at all. What I'm talking about in terms of extrapolating, maybe, would be better exemplified by two brief examples.

It is completely off-label, but if you were having an infarct in your vessels 3.0, and especially you're diabetic, do you want me to put a bare-metal stent or a TAXUS? I can tell you most of the time, I put in a

TAXUS stent. Would I want one on me? Yes. So next week, if I have this stent, and I have a lady with diabetes and a 3.0 vessel with an acute MI completely off-label, so there's just a hell of a lot less data than we have in front of us, would I put a XIENCE in her next week? Probably.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: Well, I must take up your challenge, Dr. Brinker. You said there's no reason to suspect that this would lead to a worse outcome, and I heard your colleague, and I had the same thoughts when I looked at the data, what Dr. Hirshfeld said, is that on one side of the coin is if you have less effect on acute loss, you would -- we have heard the argument that you would have less late stent thrombosis. If you have more effect, you may be causing more damage to the vessel. You may cause more endothelial dysfunction, and you may lead to a later problem. That's hypothesis, and I think it's a very valid one.

And I do animal experiments all the time, and I think it would be a nice thing to carry out.

But deep in my heart, I think this is a good stent, and I think it will turn out to work. And I'm in favor of this seeing the light of day, and that all the interventionalists can use it. I just would like to see the data, and I'd like to see a standard, because otherwise, why should we review 400 patients, 300, 200, 100 in years two to three, because you really don't need the data. We can all base it on up-front: it looks good, and it will behave well.

DR. YANCY: And if you ever get a stent, it really will be deep in your heart.

(Laughter.)

DR. YANCY: John.

DR. HIRSHFELD: I think we need a little bit of historical perspective on this. When Cypher and TAXUS were originally approved, the Agency had the foresight to anticipate that there might be as yet

unforeseen issues that would come up, and they mandated long-term follow-up data, which turned out to be very important in clarifying the stent thrombosis issue when it reared its ugly head. So I think that that is evidence that we cannot hold a sponsor's feet to the fire to prove five-year hazard-free efficacy before their device is approvable.

DR. YANCY: Additional comments? Dr. Blackstone.

DR. BLACKSTONE: This is a unique problem of drug-eluting stents. Given that, have in the December of `06 panel, which I wasn't part of, has anyone come to grips then with the risk-benefit that relates to thrombosis? It gets back to a question that we had earlier, and that is, what are you trading off for thrombosis that would mitigate against this, because I am assuming that the fact that these stents all have a risk of thrombosis, that one isn't going to take every one of these off the market because of that.

Therefore, have we decided how to balance this?

DR. YANCY: I've been advised that I think Dr. Stone has written extensively on the question just posed, assessing the risk balance of thrombosis. And if you wouldn't mind, Dr. Stone, perhaps you can interject a comment.

DR. STONE: We did, actually, a very careful analysis of this question from the TAXUS database, looking at 3,445 patients. We were struck by when we did an independent analysis of that database, we saw -- we identified an increased incidence of late stent thrombosis with TAXUS, compared to bare-metal control. But we saw almost superimposable long-term rates of death and myocardial infarction. And we observed that some prior authors had suggested that restenosis is not benign, and that restenosis can present with death or myocardial infarction, and the procedures that are

required to treat restenosis can lead to death or MI. So we did a very careful blinded analysis going back to the TAXUS database, looking at the incidents of death or myocardial infarction within a week of either a stent thrombosis, or a documented ischemia-related target lesion revascularization unrelated to stent thrombosis to see if there was an offsetting balance in terms of the risk of the hard endpoints of death and myocardial infarction. And we chose a week so just we would isolate any other events that were remote from that. And we published this in Circulation approximately four or five months ago. And what we found was that TAXUS was associated with a slight increased risk of stent thrombosis. However, about 90 percent of those patients had a death or myocardial infarction within the week period, so there were seven excess death or MI events in the TAXUS arm, compared to bare-metal control due to stent thrombosis, not a favorable outcome.

However, TAXUS was markedly effective in preventing ischemic target lesion revascularization. And some of those patients did have death or myocardial infarction. It was approximately 4 percent, a low percentage, but there were hundreds of ischemic target lesion revascularization episodes prevented, which actually led to seven fewer death or myocardial infarctions due to target lesion revascularization from TAXUS compared to bare-metal stents. So at the end of the day, when you added up the death and MIs in both groups, you ended up with the exact same number, which suggested that's why you had no difference. And that's why we think it's very important to look, not at stent thrombosis, because that's only one endpoint, but to look at death and myocardial infarction.

DR. YANCY: Thank you. Dr. Normand.

DR. NORMAND: So, again, I just want to remind myself that when we're looking

at this cost benefit, it's relative to another drug-eluting stent. Right? So we're talking about the sponsor's stent relative to another drug-eluting stent, TAXUS, and to look at that differential stent thrombosis, if that's what we're looking at.

Again, I keep thinking -- I just want to separate the problem, and I know you're saying we know the bare-metal stent problem, but again, this is relative to another drug-eluting stent, so we're talking about a differential there that would have to be -- even a 1 percent differential would need to be large.

It's not a comment on that. I was just reminding that for our deliberations, we need to think about that relative to another drug-eluting stent.

DR. YANCY: Dr. Zuckerman.

DR. ZUCKERMAN: If we could just follow up for a moment on Dr. Blackstone's question, because it's a critical one, what is

safety? It's more than stent thrombosis. Dr. Stone has reminded us for a particular stent, he has an interesting analysis. Can some of the other interventionalists also help us out here? Dr. Laskey, are you familiar with the Cleveland Clinic data that again points to safety as more than stent thrombosis? If we can have that discussion, it will help us here.

DR. LASKEY: I guess that was behind my very quiet tirade about moving off of late stent thrombosis, that it's a larger issue. Looking at the tradeoff, they're different patients, so you can never quite do the tradeoff, but I thought it useful to get Greg up here just so we could all hear the results of that analysis of the tradeoff that we have to go through. There is no way to have a patient die and have ----- you just can't do the experiment that way. But the best data we have would suggest that it is a zero-sum game. And then it becomes an issue

of which -- it's the decision making that goes into doing the procedure in the first place, and all those things that are now called covariates, but bear importantly on the outcome. So we get down to the individual level, as Dr. Brinker was saying. It's really all bets are off, because you can't apply mean data to the individual. But I'm just trying to figure out where you're going with this, that yes, there is a larger issue with the overall safety, that the death MI, we start there, and we keep coming back there. And late stent thrombosis will always be -- I would just say from the way that it looks, it will always be a low frequency event. And death MI is going to approach double digits if we follow this out long enough, so it will be captured. Whether we want to pay enough money and enough attention to capturing a low frequency event, versus another one, which is of much more relevance. I think in terms of the overall safety picture, death myocardial

infarction, to my mind, makes much more sense, but I'm not dismissing the importance of late stent thrombosis. It will occur, but I think it will occur at a very low frequency, and so the detection of low frequency events is the bane of our existence, but we need to move past that when we talk about how safe is the device. And, yes, let's not forget compared to what. I don't know if that's what you -- what button you wanted to push.

DR. ZUCKERMAN: No, that's very helpful because safety, as Dr. Yaross reminded us, is on a per-patient basis. I, in no way, want to minimize the culprit called stent thrombosis, which leads to dastardly events, but we also have to incorporate the other key actors, which are death and MI, and to try to come up with a gestalt as to what's happening at one and two years.

DR. YANCY: We've obviously started with the most important question, and I'd like to give the panel members an opportunity to

reaffirm or readdress the original response to Question One, because again, we're running 50-50 in terms of those that clearly believe it's a yes, and those that believe it's something other than a yes. The discussion we've just heard; has that persuaded anyone to be less enthused, or to be more favorable? If it hasn't, then let me restate what our collective response is to Question One.

I believe that we all are of the mind-set that the data submitted for this PMA does provide adequate assurance of safety at the time of application, and over the near-term measured as out to 12 months. Beyond 12 months, at least half the panel believes that there are insufficient data to resolve the totality of the question regarding safety, but it's not to say that we believe that the system is inherently unsafe, that the data just don't exist. Dr. Page.

DR. PAGE: If I may just ask for clarification on that. I think any of us has

some concern about long-term, because there's no way we have long-term data. There are no data beyond two years. But if the -- I'm not sure your summary adequately conveys the answer as to whether we think there's reasonable assurance of safety, as requested by the FDA, regarding approvability.

DR. YANCY: Well, the one thing that we're trying to do is to find some compromise zone, because if we have to make the answer in an absolute term, one would have to look at the polling of the individual members and say that we cannot say that there is adequate assurance of safety. But we can soften that position in support of what appears to be a very effective device, and say we are comfortable that, in a certain context, safety data do exist. And I don't know if we have the license to do that, but certainly within the script of an indication, and within the text that goes into the indications and contraindications, we can incorporate language

that reflects these concerns. Dr. Laskey.

DR. LASKEY: So lest we perseverate on just the stent, there is the obligate antiplatelet therapy for an unknown period of time, which to the investigators' credit, they just picked six months, and it turned out to be a good compromise, good guess, but there is this other piece. There's five years of having a stent of this type, and five years of Plavix. And I would say the risk of bleeding on dual antiplatelet therapy probably exceeds the risk of late stent thrombosis. I don't know that, but I just -- knowing how frequently people bleed after a year, that's an issue.

DR. YANCY: That's Question Three.

DR. LASKEY: Oh. But this is a unit, this is a drug device, this is obligate antiplatelet therapy that must be used. It's just tied at the hip, so that's part of the overall safety of the use of this stent.

DR. YANCY: Additional comments? I

think -- was it Dr. Brinker, or Dr. Somberg?

DR. BRINKER: I think that's -- those comments are very important. And while they labeled their instructions for a minimal of six months, we saw data that two-thirds of them were getting it for the entire duration. I can't remember whether it was 12 months, or 24 months on the slide, but two-thirds were getting double antiplatelet agents. As many of us think now, anyway, longer is better. So I think those are questions -- that goes for any drug-eluting stent, and we don't have the answer to that. And we can't expect someone to now try to work that out in a regulatory trial for a device, I don't think, but it can be worked out in post-market. So I'm okay when it comes to the instructions for use. I think we should substitute what we recommended in December, rather than what they used in their initial instructions.

DR. ZUCKERMAN: Yes. As Dr. Yancy pointed out, we go into infinite detail in

that, on that point on Question Three. Dr. Yancy, sometimes with these questions, the disagreement is good. I think you've captured that there are two viewpoints here, and the FDA is satisfied, if that helps you.

DR. YANCY: So I can skip the question that says, Dr. Zuckerman, is this acceptable? Okay.

In that vein then, I think Question Two becomes a little bit awkward, since we do have a dichotomous opinion. If the answer to Number One is yes, does the application include adequate follow-up? And if not, how much additional follow-up? I think that in all fairness, if someone who believes that we have seen positive response, if you would address that. And if someone believes that there is not safety, if you would address the no part, that would be sufficient.

DR. ZUCKERMAN: And when you do address it, can you pay particular attention to Table 8, which lists the known available

follow-up now, on page 2-4.

DR. YANCY: Table Eight is on 2-4. Heather, perhaps you can just formally state the question so it can be entered into the record.

DR. AGLER: No problem. Question Two -- "If the answer to Number One is yes, does the application include adequate follow-up in a sufficient portion of the patient population? If no, how much additional follow-up, i.e., number of patients or duration of follow-up, is needed prior to approval to confirm a reasonable assurance of safety? Tables Eight and Nine summarize the available long-term follow-up data and important clinical outcomes for patients treated with the XIENCE V stents."

DR. YANCY: Dr. Somberg.

DR. SOMBERG: In some ways, I think it's good to refer back to what -- there were multiple deliberations on this. And if I recall, and I'm asking really as a question,

we were talking about asking for about 1,500 patients for at least a two-year follow-up in prior discussions of this panel, if I recall generally. Am I correct on that, Dr. Zuckerman, or do you remember?

DR. ZUCKERMAN: No, I think you are referring to prior post -- either (a) post-approval study requirements, or (b), requirements for a DES where the FDA designates that we're dealing with a new molecular entity. So, again, for this type of problem, there wouldn't be any defined requirements like that.

DR. SOMBERG: I wasn't talking about defined, but I was talking about a panel suggestion. And I was talking about the panel on stent thrombosis where it was generic. And I must say, and I do take this concept of new molecular entity versus -- I mean, maybe this is just a tangential discussion, but I think when you put something on a stent, and you're putting it on the endothelium, and it has

different release characteristics, unless it's been approved prior to that on another stent, and that it has to be, in my mind, a new -- that's a new molecular entity, because we don't know what happens. Because it was studied and presented in Phase I to III trials for organ rejection, and there's two approvable letters written, to me, doesn't show that that has anything to do with the endothelium and interactions. So, I mean, the science has to be that you -- it's either been studied in that mode, in that concentration, or it hasn't been studied and approved. At least that's my pharmacologic recommendation.

DR. YANCY: So returning to Question Two, for those of you who felt favorable about the safety signal, the first part of the question is, "Does the application include adequate follow-up in a sufficient portion of the patient population?" And I think there were a series of favorable responses to my left, so if one of you might

address that part. And then to my right, were a series of nos, or equivocals, so you can address the second part. Well, let me make a stab. If there was some reluctance because the phraseology may be difficult, but for those who felt uncomfortable about the safety signal, perhaps the response is the attainment of all of the outstanding data might mitigate that concern. I don't want to put words in anyone's mouth, but in the sake of time and clarity, try to come up with some consensus here quickly.

And then for those who believe the data are favorable, then, almost in an obligatory way, you'd have to say that the current application does include sufficient information to justify having said yes. Dr. Jeevanandam.

DR. JEEVANANDAM: Well, I would concur with your first statement, because I was not completely convinced about safety, because I didn't think that the follow-up was

long enough. But I think I would concur that, if the follow-up is complete at two years, then I would be more comfortable. And especially since the comment was made that they could come up with the data in eight months, at that point they would have good two-year complete data. That would, I think, make everybody a little bit more confident about the safety profile.

DR. YANCY: Dr. Blackstone.

DR. BLACKSTONE: Well, I wouldn't to be part of the everybody, because I think with -- either with both of these studies combined, it is hopeless to come up with a signal about thrombosis, so I don't think that completing the study is going to help us very much understand what the hazard function is for thrombosis. So I remain with the idea that I'm convinced of the early safety. And it would be unknown, even eight months from now, what the rate of thrombosis would be; although, that would not particularly sway me

one way or the other in terms of whether it's approvable.

DR. YANCY: Dr. Jeevanandam.

DR. JEEVANANDAM: If we came up with the idea, as Warren said, and take out thrombosis, and if you look at death or myocardial infarction, and realize that thrombosis is a component of that, and it may be superseded by that, and you look at death and just myocardial infarction, would you feel more comfortable?

DR. BLACKSTONE: Do you want me to answer that? Yes. Well, what you have actually -- what the actuarial curves show is that for this study, there's a reduction in early myocardial infarction, in terms of the other elements of MACE, they are the same. And I think that's going to be the same for the next year, whatever.

DR. YANCY: Dr. Normand.

DR. NORMAND: In regard to the first question -- well, in terms of we won't -

- I agree with Dr. Blackstone, we're not going to learn anything about stent thrombosis with the sample size at two years. So if we do stick with the MI or death, then I think, even with that, if you were hypothesizing some mortality rates, or combined rates -- I don't know if we're talking about 12 percent or whatever -- one would have to think about would we still have enough sample size, given what we're looking at, to reach that. And you could play around with calculations, but you may need 2,000 people to do that. So, again, I don't think waiting eight months is going to tell us anything about stent thrombosis.

I guess I care a little bit more about -- well, not care, but if we look at death or MI, then there's more hope of getting more reassuring information at two years. But I'm not sure even then, with the sample size that they are using, that you're going to get something sufficiently powered.

DR. YANCY: Additional statements?

Dr. Blackstone.

DR. BLACKSTONE: There's one point that I had forgotten that was presented this morning, which I'm pretty convinced of, and that is, even perhaps with current data, and certainly with the additional data at two years, I think you're going to see that the restenosis rates are going -- and calculate those hazards, they're going to be quite different, because that -- the MI brings down MACE early, but then it's the restenosis that is continuing to separate those curves. And I think that's probably quite important in terms of the late results. We're already seeing that.

DR. YANCY: So -- Dr. Somberg.

DR. SOMBERG: I would just add that, in my mind, we're never going to have -- with this type of study with an individual sponsor, adequate end to make a definitive determination of late stent thrombosis. But if I saw in the data, and you always have the

potential of small numbers here, but if there was very late stent thrombosis, two, three, four in the XIENCE group, and no additional ones in the TAXUS group, one would have to say there's a trend, especially in light of TAXUS II, I mean SPIRIT II study where there was a greater incidence of the stent thrombosis. So it's not -- once again, it's saying there's a point estimate, and there's some sort of signal with a certain amount of data. But with almost very minuscule data, you can't make that determination at all. But I'm not asking for the extreme, either. So I would be a lot more comfortable, to answer the question, with 1,500 patients at the end of two years, or if we can only get eight or nine hundred patients, at least there would be zero. If there was zero-zero from now on, that would be very reassuring to me.

DR. YANCY: Would it be fair to say that in the context of the way we qualified the answer to Question One, that is early

safety and safety out to 12 months, that we would say yes, and that the available follow-up has been sufficient for 12 months?

So I think, Dr. Zuckerman, what I'm hearing from the panel is that even if there were an effort to close the loop and complete the data acquisition for the outstanding data points, there would be no statistically relevant way of resolving any questions about very late stent thrombosis. There might be some reassurance on the very hard endpoints of MI or death, but that that, necessarily, doesn't make any of the panel members feel necessarily more comfortable. And that where we all find a comfort zone is on evidence of safety at the time deployment, and out to 12 months. And there simply needs to be either an ongoing assessment, or some other way of capturing safety issues beyond 12 months. And that would pool the responses to Questions One and Two.

Are there panel members that would

have a concern with that statement? Would that satisfy FDA?

DR. ZUCKERMAN: You use the apt descriptor statistical certainty. What about if you're talking about clinical comfort zone, is there -- as Dr. Somberg was just mentioning, would there be a difference of opinion then?

DR. YANCY: My sense from listening to the very limited opinions of the interventionalists on the panel is that there probably already is a sense of clinical comfort with the use of this application. Am I overstating Drs. Brinker, Hirshfeld, Morrison?

DR. ZUCKERMAN: That's very helpful.

DR. YANCY: Thank you. Heather, let's proceed to Question Three.

DR. AGLER: All right. Question Three: "Do you believe that the language in the proposed XIENCE V stent label adequately

conveys a recommended course of dual antiplatelet therapy following XIENCE V stent implantation? If no, please discuss the appropriate modifications that should be made to the label." Do you want me to read Part B, too?

DR. YANCY: Please.

DR. AGLER: And Part B: "Following the FDA Advisory Panel meeting on DES Thrombosis in December 2006, the labels for the currently approved DES, Cypher and TAXUS, had language added to their labels referencing the ACC, AHA, SCAI consensus statement recommending dual antiplatelet therapy for 12 months following DES implantation in patients who are not at high risk for bleeding. This language has been included in the proposed labeling presented here. Do you agree that this language is appropriate?"

DR. YANCY: If you will turn to page 2-5, you'll see that the verbiage above Question Three reflects what the sponsor has

submitted regarding the use of antiplatelet therapy. And it's too lengthy for Heather or myself to read, but it's before you, and let's look at that very quickly so we can formulate an answer to Question Three. Dr. Kato?

DR. KATO: I would suggest taking out (three months in the SPIRIT First subjects), only because it's confusing to the reader, and that was a small clinical trial.

DR. YANCY: Point made. Dr. Somberg.

DR. SOMBERG: I think there's no data here, so, therefore, they should be a class label based on the Society recommendations, and not based on any particular protocol, new ones.

DR. YANCY: Dr. Page?

DR. PAGE: Yes, I would agree with going with the guidelines. I'd even go further in terms of the labeling. For example, on page 6, "Contraindications to the XIENCE V", if the patients are either

unwilling or unable to pay for, acquire, or take their Plavix, they should be contraindicated for this stent. And it really needs to be very strongly emphasized that they take their medication, their double platelet therapy as recommended. And I think the 12 months at least is what we know right now in terms of a guideline recommendation.

DR. YANCY: Other comments? Dr. Kato?

DR. KATO: Are you suggesting that they take out the five-year comment?

DR. PAGE: Which five-year comment?

DR. KATO: Well, it reads -- again, I would -- I mean, I agree that the American Heart Association, ACC recommendation should stay in there, but the sponsor is stating that they would like to have -- I guess, I assume it's coming from the sponsor, that they wanted to have a statement saying that clopidogrel was continued for five years to reduce thrombosis risk. I mean, is that --

DR. PAGE: That's aspirin.

DR. KATO: Oh, I'm sorry. Okay. Never mind.

DR. BRINKER: That's a good point. I think that suggestion is counter to most everything we've ever done, and that is to maintain some dosage of aspirin indefinitely in patients with stents alone, so even bare-metal stents. So I don't think that five years is --

DR. YANCY: So that should be changed to indefinitely.

DR. BRINKER: It's based on no knowledge, and it's no experience. I don't understand why it's in there.

DR. YANCY: So it should be changed to indefinitely. Is that your suggestion?

DR. BRINKER: Yes, I would say.

DR. YANCY: Okay.

DR. LASKEY: The guideline statement is devoid of evidence. It was just a consensus opinion, best judgment, but it's

devoid of evidence; whereas, this trial does provide evidence up to six months. So let's not lose sight of that.

DR. BRINKER: Well, we're talking about two different things, though. We're talking about aspirin, and we're talking about aspirin and Plavix.

DR. LASKEY: Yes, but to back up to the clopidogrel issue, which the Societal recommendations are for out to one year, that's based on no evidence. But the evidence before us six month data.

DR. BRINKER: But the evidence before us, a good portion of those patients were actually taking the drug for a year, over half according to -- they had split it up different ways, but at least over half. So my feeling is that we should put in the recommendations, also it was a panel recommendation in December that that be there. I'm more interested now, though, in the aspirin. I think the five-year thing comes

out of the blue, and they certainly have no evidence to say that that's something more than what's routine.

DR. YANCY: Dr. Page?

DR. PAGE: With the disclaimer that I'm a representative from the American Heart Association on the ACC/AHA Guideline Task Force, I would take exception to Dr. Laskey's comment that the recommendation is without evidence. To the contrary, that's a panel of experts who convened, and take into account the best evidence as available to them as they qualify as Level A, B, or C, and give their best recommendation.

DR. YANCY: Dr. Morrison.

DR. MORRISON: Well, I would urge that we insist on exactly the same guideline with regard to aspirin and clopidogrel that the Society, that the panel, and that we've recommended for previous drug-eluting stents, not out of fairness, but because what we're talking about in a post-marketing analysis is

gathering registry data where ultimately you're going to be comparing this. And if you only put on here that six months, because that's what the trial, then as we discussed last month, there will be an inevitable temptation to make that into a marketing issue. And then you're going to wind up comparing the five-year results of this stent with the five-year results of other stents in patients where you've just artificially added two more confounders, that we know are important, the aspirin and the Plavix.

DR. ZUCKERMAN: Okay. So, Dr. Morrison, I think that other than the aspirin issue, that was the intent of the sponsor's prose here; the point being that, one, they described in general terms what was done in the clinical trials, but they also added very important recent AHA/ACC guideline recommendations, as well as some specific scenarios below that where one might want to consider not using a DES, because of

concomitant procedures. So what would help us here is whether that general philosophy is a useful one, since it's the same philosophy found in the other two approved DES labels.

DR. YANCY: Thank you. Dr. Normand.

DR. NORMAND: Well, as far as I know, the current study in front of us did not evaluate optimal duration of therapy, so we have no evidence, whatsoever. We didn't look at the data. We didn't look at who complied, and who didn't comply, so we have, in my mind, from a statistical standpoint, not studied that question with the data presented today.

DR. YANCY: So, Dr. Zuckerman, if I can summarize the panel's commentary on Question Three: "Do you believe that the language in the stent label adequately conveys a recommended course of dual antiplatelet therapy following stent implantation?" The answer is actually no, and that would address A, and the modification would be to be as

compliant with the accepted ACC/AHA statement. Obviously, in other places within a label, one can comment specifically on the duration of use within the trial, but for this particular section, I think I hear my peers suggesting that we be consistent, and that we respect the guideline statement. Sufficient nods say that that's -- is that acceptable to you?

DR. ZUCKERMAN: Yes.

DR. YANCY: Thanks. Question Four, please.

DR. AGLER: Question Four: "The SPIRIT First study, the XIENCE V, Everolimus-eluting coronary stent system was demonstrated to be superior to the bare-metal VISION stent with respect to in-stent late loss, along with reduced rates of TVF and percent volume obstruction. In the SPIRIT II and SPIRIT III trials, XIENCE V was found to be non-inferior to TAXUS with respect to 180-day in-stent late loss for SPIRIT II, and 240-day in-segment

late loss for SPIRIT III.

Additionally, since each study found that XIENCE V was non-inferior to TAXUS, a superiority analysis was performed, and XIENCE V was found to be superior to TAXUS in terms of in-segment late loss. Do the data represented on XIENCE V provide a reasonable assurance of effectiveness?"

DR. YANCY: I'm going to be bold enough to say that this panel believes that the answer is yes. Is that acceptable, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

DR. YANCY: Question Five, please.

DR. AGLER: Okay. Question Five deals with the labeling. 5A is: "Please comment on indications for use section as to whether it identifies the appropriate patient populations for treatment with this device."

DR. JEEVANANDAM: Could I just ask a question?

DR. YANCY: Yes.

DR. JEEVANANDAM: Question Four, we believe it's as effective, but are we saying it's superior, as well? Because there's a thing that says a superiority analysis was performed, and XIENCE was found to be superior to TAXUS.

DR. YANCY: But we're not saying that. We're just answering the question: "Do the data presented on the XIENCE V EECSS provide a reasonable assurance of effectiveness."

DR. JEEVANANDAM: Okay.

DR. YANCY: And the answer is yes.

DR. JEEVANANDAM: Yes.

DR. YANCY: Without any hesitancy. But thanks for brining that issue up.

So we need to defer to Section 9 in Volume I for the indications for use. And Dr. Page has already prompted us by pointing out a very important contraindication that was seemingly omitted. 5A is indications, 5B is contraindications, C is warnings, D is

operator instructions, and E and F are as they are presented. Any comments about indications for use?

If you look at on page 6 of 58, in Section 9A, Volume I, 2.0, the indications, the statements that you've heard - this is a statement you've heard several times today. Are there any disagreements with that statement? It's page 6 of 58, Section 9A, Entry 2.0.

DR. ZUCKERMAN: Okay. For ease of reference, this is the standard type of FDA indication for DES.

DR. YANCY: Dr. Page.

DR. PAGE: The only thing I would comment on is that we've looked at data for 4 millimeter stents that were non-randomized, and the rest were randomized. I personally am comfortable combining that, but I think we just need to make note that we're acknowledging that the randomized data go to a smaller diameter.

DR. YANCY: I think that Dr. Normand helped us get clarity on the 4.0 data set. You thought that that was a relevant data set with regards to way it was acquired.

DR. NORMAND: Yes, but I didn't say I would necessarily combine it with the randomized arm.

DR. YANCY: Okay.

DR. NORMAND: But I believe they wrote 4.25 in the description earlier. Right? I think they mean 4.25. That's what they had said. I read that earlier in terms of the inclusion criteria.

DR. AGLER: For the reference vessel diameter.

DR. NORMAND: Yes. I mean, that was what they used in their inclusion criteria. Right?

DR. YANCY: So is the answer that we are comfortable with indications? 5A is no additions, no modifications. Is that acceptable, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

DR. YANCY: 5B is contraindications. Dr. Page has already made one adjustment to this with regards to whether or not a patient has access to antiplatelet therapy.

DR. PAGE: Access to, and compliance with.

DR. YANCY: Point made. Other comments about contraindications? Hearing none, is that acceptable to the FDA?

DR. ZUCKERMAN: Yes.

DR. YANCY: 5C, warnings and precaution. This is Section 4.0, and Section 5.0, again on page 6 of 58.

DR. LASKEY: Perhaps a warning about the use, that there is no information on the use of this particular stent in a patient who may receive other types of drug-eluting stents, or has received other drug-eluting stents. We have no information.

DR. YANCY: Would that be a

warning, or a precaution, or does it matter?

DR. LASKEY: One of the two.

DR. YANCY: One of the two. Any other statements? From an interventionalist's perspective, John, do you have any other comments on this section?

DR. HIRSHFELD: The only thing is that if you look at one of the bullet points under - where is it - 5.1, I guess this means that Abbott is going to refuse to sell this stent to any laboratories that do angioplasty without free on-site cardiac surgery.

DR. YANCY: So that's bullet point two.

DR. HIRSHFELD: Yes. I don't think it's relevant to what we're saying here, but it is interesting what's in their labeling.

DR. BRINKER: Well, they say hospitals in which surgery is accessible, so that can be transported to a --

dR. YANCY: Very loose definition.

DR. BRINKER: And most of those

hospitals have some quid pro quo, so I don't -- I wouldn't stumble over that.

DR. YANCY: John, do you have any opinion on that?

DR. JEEVANANDAM: There are a lot of places that do stenting without a cardiac surgeon, and they're accessible to helicoptering.

DR. YANCY: So my sense is that for 5C, we feel comfortable in the proposed language. Dr. Zuckerman?

DR. ZUCKERMAN: Good.

DR. YANCY: 5D, comment on the operator instructions. As close as I can, the relevant section looks like it's Section 5.131 and 5.132, starting with page 11 of 58. My sense is that these are fairly intuitive statements. And I'd be concerned about anybody who wants to study this first before they apply the stent.

DR. ZUCKERMAN: That's good.

DR. YANCY: 5E and F. This is

Section 5.8, 5.9, and 5.10 that have to do with drug interactions, which relates to the information in 5E. Separately, they're sections on pregnancy and lactation, 5.6. My sense is that the panel feels that the proposed labeling is acceptable.

DR. ZUCKERMAN: Thank you.

DR. YANCY: Let's move on to Question Six, please. This relates to the post-approval study. Heather.

DR. AGLER: "The post-approval study has been designed to evaluate clinical outcomes in a cohort of real world patients receiving the XIENCE V stent system during commercial use by various physicians with a range of coronary stenting experience. Evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications, determine clinical device and procedural success during commercial use, evaluate patient health status by the Seattle Angina Questionnaire."

6A is: "Are the objectives identified above appropriate, and should additional objectives be considered?"

DR. YANCY: Read them all, please.

DR. AGLER: Okay. "Does the plan provided by the sponsor adequately address these objectives? If not, how should the sponsor's plan be modified?"

DR. YANCY: This is a fairly important topic of discussion.

DR. ZUCKERMAN: In trying to answer the full breadth of this important section, also if the panel could look at Slides 132 and 133, especially, from the FDA presentation this morning.

DR. NORMAND: Okay. So my first comment is, we definitely need to have some sort of comparison group; otherwise, the information that we will obtain won't be very interpretable. And, so, using historical data, I don't think is going to help us at all, so we need some concurrent comparative

group to collect information on. So I'll start with that comment.

DR. YANCY: The sponsor might want us to suggest what kind of comparator group. Do you have any initial thoughts about that? Either Dr. Normand or Dr. Somberg?

DR. SOMBERG: Well, Sharon passed it to me, and contemporaneous patients who are entered in laboratories that are acquiring the information on the XIENCE stent, and I think it might be useful to acquire data for not just TAXUS, because it seems to be a simply TAXUS, TAXUS, TAXUS comparison. But I would look at other drug-eluting stents, as well. And I would make it a comparator to drug-eluting stents. But what I'd also do is try to keep it simple.

And I think, as I look at it, the study was a little bit more complex. There was quality of life indicators, there was some things looking at performance at different sites, a whole host of things. And I think

for the company, if this is on the market, it would be very useful to have follow-up, and to look at death, Q-wave myocardial infarction, non-Q-wave myocardial infarction and late stent thrombosis, and very late stent thrombosis. And I would try to keep it as simple as possible, because when registries get more complex, they get -- they often don't get completed, or the information, there's so much omission that we will have a special session on imputation, and tipping and non-tipping. Anyway, my recommendation is to keep it simple, and have a control group, as well.

DR. YANCY: Let me just pose a question to Drs. Normand and Somberg referable to the planned trials that the sponsor brought forward earlier today. The SPIRIT IV is a randomized control trial of the XIENCE V versus TAXUS, with 2-1 randomization, 3,690 patients. And then the SPIRIT I is a randomized control trial versus Cypher, outside U.S., and then the SPIRIT India.

Would any of those represent a reasonable data set as the comparator, so that the registry can go forward as a single arm initiative?

DR. NORMAND: Again, I think if the purpose of the registry is to look at real world experience, using a clinical trial population doesn't do that, so that's one thing. And then the other thing, the one study is focusing on certain subgroups, and that's not necessarily going to be used as the comparison group, so I continue to feel very strongly that if you're going to answer the question on how these things perform in the real world, then don't use a clinical trial population. You use a real world population, and then you also need a comparison group.

DR. SOMBERG: May I add something?

DR. YANCY: Please.

DR. SOMBERG: And the last thing is, I think it's the greatest piece of insurance the sponsors buys, is to have the comparator group from the same population

you're drawing the information on your own product because let's say things were terrible for the registry, but if you have a comparator group, most likely things will look as terrible, or even more terrible, and that's very, very important. So I think obtaining data from India, or data from an OUS population just doesn't cut it.

DR. YANCY: Just so there can be more than one opinion, and with an incredible amount of respect for the opinions that have already been expressed, this panel went to great lengths on multiple occasions to identify the right way to constitute an objective performance criterion, and with a whole aggregate of contemporaneously acquired registry data, and additional randomized control data. I think that working with the Office of Post-Approval Studies, it might be possible to be able to design such a study utilizing data that, although maybe not in the same opportunity as the registry, or at least

reasonably contemporary. I mean, as someone who does these things, it is especially onerous if you have to recruit now twice as many patients, and have to account for the other variables. So I recognize that in the pure sense having a contemporaneous comparator is great, but this panel over the last year has really made a statement that we would accept OPC. And I would like to see us try to find a way to make that possible.

DR. NORMAND: I think the thing about the OPC, though, we can -- first of all, I don't remember 100 percent consensus on that, but who recalls? I'm sure somebody will read the transcript back, but the thing about the OPC is, of course, you need the patient -- to do it properly. You need the patient level data, and so it's not very sensible to compare it to one number. You actually need the covariates because in the real world, the population changes, and so the OPC can be done, but I would say it's done correctly very

few times. And, so, I just caution that recommendation. Obviously, we can have more than one opinion. I'm not doing that, but we definitely need to in the real world. We know that it will be used in other patients, and an OPC typically does not move beyond the patients in the clinical trial, and that is where the trouble lies.

DR. YANCY: Dr. Hirshfeld.

DR. HIRSHFELD: Yes. I'd just like to agree with the Chairman. I think at this year's TCT, there were at least 10 large observational series from large practice groups presented that characterized observationally long-term outcomes of TAXUS and Cypher stents. And, so, I think that there is an increasingly large volume of data out there, which are relatively internally consistent in terms of complications rates and stent thrombosis rates, and so I think that this is going to be good enough to serve as a comparator to similarly acquired data in

registry format here, that I think asking the sponsor to continue to conduct large randomized trials is going to be overly burdensome, and not necessary.

DR. YANCY: Dr. Page.

DR. PAGE: I would agree with you, as well, but two other issues on the post-approval study. I agree with Dr. Somberg that Bullet Four, "Evaluate health status", I don't think that would be useful, and I think that's extra work. I would like to expand on Bullet Two, "Evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications." And I would actually encourage the sponsor to really look at this, and find out any relationship. Over five years, you're going to see just people fatiguing from taking Plavix, and I don't know whether this stent -- first of all, I don't know how long we should have patients taking Plavix in the approved stents. I think it's possible this one may be different from them.

And in that way, whatever information we can glean, even in a non-randomized observational way in terms of relationship of duration of Plavix continuation, and any temporal relationship with cardiovascular events related to discontinuation could be very valuable.

DR. YANCY: Additional comments about the design of a post-marketing study? Dr. Blackstone.

DR. BLACKSTONE: This morning the FDA noted that they wanted for sure that this study be long-term, that it go at least to five years, and so I'd echo that. What I disagreed with is the idea that one would determine rates at certain points, and then there would be some kind of correction for looking multiple times. What we want to know is what is the hazard function for this continuous across time, and that we could get from a reasonable number of patients without any of this fishy little things of looking at

some specific time points. We ought to be trying to get what is the curve for this.

DR. YANCY: Yes, Dr. Somberg.

DR. SOMBERG: I think I can speak for Dr. Normand, as well, on this one, is that neither of us recommended that it had to be randomized, or it had to be one-to-one, the control group.

DR. YANCY: So, Dr. Zuckerman, I think what you've heard from the panel is that there are probably several ways to design a post-approval study. And we would advise the sponsor to work with our office that has been formulated to specifically view this. And if it something other than a concurrent comparator group, then it needs to be done very correctly, very precisely, or a novel way to have a comparator group that is least burdensome would be a recommendation.

You've heard comments, as well, about what we think the appropriate objectives are, and about the duration of follow-up.

DR. ZUCKERMAN: Okay. And those comments regarding design are extremely helpful, but I think the biggest point of disagreement right now between the sponsor and FDA concerns the key primary endpoints. And that, consequently, I would like the panel members to look at FDA Slide 133. Dr. Duggirala this morning suggested that these should be the two primary endpoints. Do people agree, disagree, would they like to hear further from her for explanatory purposes?

DR. BRINKER: Well, I would want to know why you made the co-primary endpoints of death and MI, which we've had echoed here as being very important only obtained at one year, since that may be a better judge of real problem than trying to figure out stent thrombosis, and more reasonable on a smaller, relatively speaking, population.

DR. AGLER: So you want FDA to comment? I would ask Dr. Duggirala to come

up, since she's our post-approval study expert.

DR. DUGGIRALA: Well, we certainly take that recommendation back to the sponsor, but the study would have to be powered to detect that out to five years. But you believe that it shouldn't be a problem in terms of the sample size.

DR. BRINKER: Well, if you're interested, you have a bigger problem in trying to estimate stent thrombosis, as has been said here with the power that you have. It's much easier to do, and as long as you're getting all this data up to five years, I think it would be nice to have more distal data than one year for death and MI, which are real important endpoints.

DR. YANCY: Other comments? Dr. Blackstone.

DR. BLACKSTONE: Also, if we're talking about this tradeoff that I mentioned earlier, we should be talking also about need

for repeat revascularization, especially target vessel revascularization as the possible tradeoff for this, rather than just looking at death, MI, and thrombosis.

DR. YANCY: So what we're hearing then is that with regards to endpoints, target vessel revascularization needs to be written into this language, death, MI more than just one year, and accepting the five years. Does that reflect the concern interest? Yes?

DR. PAGE: I agree it ought to be followed to five years, but I'm still concerned as to the primary endpoint being stent thrombosis. What matters to me is have they had a heart attack, and are they alive? And there's tradeoff. There might be higher stent thrombosis, but due to the fact that there hasn't been repeat revascularization and other issues going on, that would be a more important clinical endpoint, and harder endpoint, in my mind.

DR. YANCY: So would you prefer

target vessel failure that incorporates that?

DR. PAGE: I think that would be preferable.

DR. BRINKER: Well, the problem with target vessel failure is that over time, there's more lesions, new lesions that develop. And these patients are already prone to disease, so target, as Greg said, even for the one-year study there's a lot of noise in target vessel failure, it becomes more at five years.

The issue about stent thrombosis, though, I think it -- we want to know, in addition to MI and death, I think just to gather the data, and also to correlate it with antiplatelet therapy, which, as you pointed out, already is still an unknown.

DR. YANCY: Dr. Normand.

DR. NORMAND: I agree. First of all, even with a sample size of 5,000, as we've heard earlier, is not going to be powered enough to find a difference in stent

thrombosis, so why is that going to be a primary endpoint at five years? That's the first question.

The second question is, I'm not sure we need to stick to the usual 80 percent power and Type I error .05. Why do we keep doing that? If we're looking maybe for safety, maybe we can afford to have more of a Type I error, so I urge maybe us to think about that in doing these sample size calculations. We're fixated on .05, and 80 percent or 90 percent power, but to detect a safety problem, I think we might be willing to make more of a Type I, that type of error. And, so, I think that I agree with moving up MI and death.

Now in terms of the last comment, the noise issue, that's the one I don't understand. I mean, I understand it's noisier. You're saying there's some noise in there, but if you have two groups, unless you think it's systematically biased in one group

than the other, then there's no reason to worry about the noise, because we're taking a difference. So it may be -- and this is the point of not hanging your hat on one number. You need a difference between the two, because if they're comparable, if the noise is comparable and evenly distributed, which I guess there should be no reason to be, unless I hear otherwise from people, then that's a non-issue, at least statistically speaking.

DR. YANCY: So there is a suggestion on the floor of actually suggesting that the primary endpoint be death or MI.

DR. JEEVANANDAM: I want to bring up the concept of target vessel revascularization. I mean, what I'm hearing is that this is the same vessel distal to where the stent is, and as a surgeon, we often see stents that go in proximally, and then distally you start seeing a proliferation of tissue, and you see a much thicker vessel that you're bypassing if you do have stenosis.

That may be a small group of patients, but I think that's something that may be affected by the stent, the stent design, whatever is on the stent, so I think if it is that same vessel, it is something that needs to be followed.

DR. YANCY: Dr. Laskey.

DR. LASKEY: So hence, TVF. We keep going back to TVF because it captures that universe. There's nothing else --

DR. JEEVANANDAM: Absolutely. I think there was a comment made that TVF has a lot of noise in it, but some of that noise may actually be important noise.

DR. LASKEY: Important noise, and important to understand how it behaves differentially or not, so with the control arm, that's how you do it.

DR. YANCY: Other comments? Dr. Somberg.

DR. SOMBERG: Well, I think Dr. Yancy was right when he said it should be --

the primary endpoint should be death and MI. And then you look at secondary endpoints, which is total target vessel revascularization. Thank you, it's getting late here. And also, late stent thrombosis. Because, as Dr. Normand says, we're not going to power the study to do 11 to 21,000 patients, I think, is the estimate to really make it powered for the endpoint of late stent thrombosis.

DR. YANCY: Mitch, very brief, please.

DR. KRUCOFF: Mr. Chair, just a point of clarification from the, as was indicated on the slide in our presentation. The sponsor and the Pis for the post-market study actually are interested in advancing death and MI to a primary endpoint for this study. It's simply been the timing with regard to this panel has not allowed us to formally discuss that with the FDA yet, but we're on board with that.

DR. YANCY: Appreciate that. So, Dr. Zuckerman, what you've heard is that based on what we've been provided, we would suggest a very different post-approval study that would put clinical endpoints that were fairly comprehensive as the primary goal, and the size would still be considerable, that is 5,000, and the follow-up would still be out to five years. And the rest of the details we would trust the Office of Post-Approval Studies to work out with the sponsor.

DR. ZUCKERMAN: Thank you.

DR. YANCY: We will exhale. It is 5 p.m., and we will lose a critical mass here within an hour, so we will take just about a five-minute break for essentials, and we'll set the panel up for our vote and deliberation. But I would very much like to start no later than 10 minutes after 5.

(Whereupon, the proceedings went off the record at 5:04:03 p.m., and went back on the record at 5:12:11 p.m.)

DR. YANCY: It's imperative that we start as soon as possible. This is for the panel members, as well. We will now resume the meeting. Is there any further comment or clarification from the FDA, Dr. Agler or Dr. Zuckerman?

DR. ZUCKERMAN: No, we're fine.

DR. YANCY: Heather, is there any additional input from the FDA?

DR. AGLER: No.

DR. YANCY: I know that the sponsor wants to make specific comment, and I will respect that request. We have to create an opportunity for a second open discussion. If there is anyone who has a need to speak to the issues of today, this is the last opportunity. There's no one that has signed up. I've not been made aware that anyone was waiting, and I see no one coming to the panel, so the second open public hearing is closed.

The sponsor has requested permission to make a presentation. The

critical mass of our panel will begin to dissipate within the hour, so I would ask the sponsor to be very sensitive to time, and truncate it to as short a presentation as possible. Please begin.

DR. POCOCK: I'll go straight to the point. This is about the long-term safety data, and we fully understand the need of the large post-approval studies, and that's fine. I wanted to comment on the issue of what you would gain in the extra two-year data, if you went out to complete the full SPIRIT II and III data.

I think the perception is that you wouldn't gain very much, like you've got two stent thromboses after one-year at the moment. So if you double the size of the data, a little more than double the size of the data, you might get an other two or three, or you might get zero or five by random chance. And, therefore, I think one wouldn't gain much more insight quantitatively. The real issue of

these longer term safety issue flies in the large studies in the post-approval issue, and that's the point I wanted to make. Thank you.

DR. YANCY: Thank you. Is there any other comment from the sponsor?

DR. KRUCOFF: Thank you, Mr. Chairman. Just briefly, from a clinical perspective, I think given the discussion in a phrase used frequently in this arena, I think it's important as clinicians that we take a half a step back, and recognize that the notion that good light loss is somehow bad for safety is a result of the past, but solving that, and resolving that we could get better endothelial channels, and better endothelial healing is actually the goal of design improvements in the future. And there, as have been elucidated, a number of design aspects, even just the thinner struts of this particular platform to potentially support that.

The theme that has been repeated,

as well, that is very crucial to this decision is compared to what? And as has been noted, this is compared to the TAXUS stent, this is a comparison that shows at least as good or beneficial superior efficacy with every indication and all data available that safety is roughly equivalent. So while I think we can recognize in the legacy of this pipeline, drug-eluting stents that at one year have had this kind of consistent findings, have not turned rogue, to take Dr. Brinker's term, in later years. It's a linear hazard, that there's no expectation for rogue behavior, that there is a need for vigilance, and we are absolutely committed to that vigilance.

DR. YANCY: Thank you.

Dr. Stone.

DR. STONE: Thank you. And I'll give you one last perspective about safety, which actually, interestingly, came to me while this excellent discussion was going on this afternoon. If you actually look at where

we are right now, at one year and two year, with these hard endpoints that we've talked about, cardiac death and myocardial infarction, at one year, we're actually 4.5 percent with TAXUS, and 2.7 percent with XIENCE. In the two-year data set with all available follow-up data, we're 6.3 percent with TAXUS, and 4.7 percent with XIENCE. So we're actually not starting numerically equal, but we're actually favoring XIENCE.

Now there is, I think, a real chance that that is real, that that's not just statistics, and that's a chance finding, because we've heard about this tradeoff between stent thrombosis and restenosis. We've seen identical stent thrombosis rates to-date, .8 percent in both stents at one year, but we've seen two things. We've seen reduction in peri-procedural myocardial infarctions, and that's not chance. There's a mechanistic explanation for that based on the design characteristics of the thinner stent

struts, and we've seen a reduction in ischemic target lesion revascularization, and some of those events we've now published do cause death and myocardial infarction. So I am hopeful that we are actually on the verge of having a stent that will improve outcomes. And, of course, we need much more follow-up data, but it looks like it is going to be safe, potentially even safer than the other devices we have on the market.

DR. YANCY: Thank you. Are there any other comments from the sponsor? Thank you very much for your brevity and clarity.

We're now ready to vote on the panel's recommendation to the FDA for this PMA. Let me remind you that at your place there is a multi-colored sheet, which outlines the instructions for voting. We will respect that instruction sheet.

Let me also remind you that we've had all day to discuss this, and hopefully you have formulated in your mind a very clear

feeling about what it is you're interested in, and the way you want to express yourselves. If we can respect the same issues of clarity and directness, I think we can be fair, and be appropriate, and also be expedient.

Having said that, then I will turn our attention to Mr. Swink, and we'll ask him to read the panel recommendation options for pre-market approval applications. Mr. Swink.

MR. SWINK: The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990 allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications that are filed with the Agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application, or by applicable publicly available information. The definitions of

safety, effectiveness, and valid scientific evidence are as follows.

Safety is defined in 21 CFR Section 860.7, "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to the health from the use of this device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use outweigh any probable risk.

Effectiveness, as defined in 21 CFR Section 860.7(e)1, "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use, and warnings against unsafe use will provide clinically significant results."

Valid scientific evidence, as

defined in 21 CFR Section 860.7-(c)2, "Is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without mass controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is a reasonable assurance of safety and effectiveness of a device under its conditions of use.

Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness."

Your recommendation options for the vote are as follows. Number one is approval. This is when there are no conditions attached. Number two is approvable with

conditions. The panel may recommend that the PMA be found approvable subject to specific specified conditions, such as physician or patient education, labeling changes, or further analysis of existing data. Prior to voting, all of the conditions should be discussed by the panel. Number three is not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or the data do not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each panel member to present a brief statement outlining the reasons for his or her vote.

DR. YANCY: Are there any questions from the panel about these voting options before I ask for a main motion for this PMA?

DR. PAGE: Is the post-approval study a condition?

DR. YANCY: It was a condition. Are there any other questions of clarification?

DR. KATO: I'm sorry. The question was, again? Would you ask, I'm sorry, Dr. Page.

DR. YANCY: Is a post-approval study a condition? The answer is yes.

DR. KATO: It is. Okay.

DR. YANCY: Yes. Any other questions? That having been said, is there a motion for either approval, approvable with conditions, or non-approvable from the panel? Dr. Morrison.

DR. MORRISON: Mr. Chairman, I move for approvable with conditions to include, but not limited to a post-marketing study, and labeling with regard to duration of antiplatelet therapy.

DR. YANCY: There are no conditions