it's a reasonable assurance of safety and effectiveness of the device for use in a patient.

And certainly the least burdensome paradigm would allow us to consider designs other than a randomized trial if it's realistic that at the end of the day we could develop an appropriate data set that an expert panel like this would feel comfortable reviewing and making a good decision on.

Unfortunately too many times least burdensome can unfortunately be misused such that it becomes the easy way out, such that at the end of the day we don't have the data we need.

That's why in Dr. Ahn's presentation this morning all these alternatives are going to be complex and challenging, but he questioned whether ultimately the least burdensome and best shot for all parties involved might be the randomized trial when you weigh all the potential factors here.

CHAIRMAN YANCY: Dr. Zuckerman, when

you stepped away, at least one panel member indicated that even the best non-randomized control trial would still leave sufficient residual questions that as a panel person they would struggle with the interpretation of that in a de novo application.

Yes, Dr. Yaross.

DR. YAROSS: Yes, I think that is of course important feedback for industry to hear. The only thing I would add to that is, every trial poses risk to the sponsor. And the particular balance of early risk versus late risk and how that risk is mitigated, at some point becomes a decision of that sponsor based on the specific parameters they deal with. And we've talked about many of those already today.

CHAIRMAN YANCY: And certainly in the context of the current ongoing randomized control trials, a sponsor may take a calculated risk that that will be a sufficient database so they can move forward with their non-randomized trial; but understanding that there is risk with that step.

Yes, Dr. Comerota.

DR. COMEROTA: Regardless of design of the trial, and we would like randomization for sure and control, the burning question out there today is, is this intervention for asymptomatic disease, is focused on asymptomatic atherosclerosis, is this intervention better than best medical care?

If the trial - call it a trial, call it a registry, call it whatever you would like to call it - if it is designed adequately enough to answer that question, I think subsequent panelists and the medical profession would embrace it.

But that's the key question that needs to be addressed.

CHAIRMAN YANCY: Point well made.

Dr. Zuckerman, let me summarize for you where we are, so you can help us know what else - how else we should develop this.

I think it's fair to say that the panel shares jointly a sense of ongoing clinical equipoise, and that the only way to resolve that is to actually encourage ongoing

randomized control trials, because proof of concept has not been established, and this is for stenting versus surgery, and especially for the not high risk asymptomatic patient maybe even medical therapy versus carotid revascularization by whatever iteration.

I think that represents the feeling of the panel.

The next thing we discussed is that with regards to randomized control clinical trials, there are several barriers that we've identified and that we've heard expressed today.

We believe that the behavior of the payers is a significant barrier. Physician preference, particularly taking the path of least resistance, is a barrier. There is some statement made that perhaps there may be more off-label use than has been acknowledged.

Patient preference has been stated as another issue. With regard to these barriers, another potential barrier might be the short term endpoints, because it's really the number of events that needs to be

adjudicated, as well as the number of patients.

We've also thought that another barrier has to do with the definition of those events. And so perhaps jointly with those barriers, extending the length of the trials, so we capture more events, and then having events adjudicated by a neurologist may modify some of the barriers.

But the big issues are physician preference, patient preference, the behavior of the payers. Where we are now is trying to say, in the event that we accept the body of information that is being acquired as randomized control trials - that CREST, ACT I and TACIT if it gets established - what are the comments that we can make about an acceptable non-randomized control trial?

And those comments so far have had to do with different kinds of designs, a randomization by institution might require a large sample size. Propensity adjustment, incorporation of a multidisciplinary approach with surgeons and interventionalists, nonsurgical interventionalists, and then again

indicating that these would be trials that would be considered at a lower tier than randomized control trial, and may still reflect some difficulty when one is adjudicating the information for regulatory purposes.

Have I misrepresented what the panel has said so far?

So where are we with regards to what you need, Bram? I mean this is awkward, and you are trying.

DR. ZUCKERMAN: We really appreciate the effort here, because there is no question this is a very difficult and challenging arena, and the panel has done great work today.

But can you just clarify one thing for me? You're saying that at the present time the general consensus is that we need to see some proof of principle, randomized trials for these lower risk patients. Is that the bottom line, Dr. Yancy?

CHAIRMAN YANCY: That is my understanding.

DR. ZUCKERMAN: Okay. Well, that's a very helpful conclusion here, because the

next point I guess is that a - to do that within a reasonable time frame as asked just a minute ago by Dr. Johnston, is going to need continued cooperation by all stakeholders here.

We have an unusual day today in that we have the professional societies, clinicians, regulators, here in the same room, and I think another thing that the agency has heard is that if the professional societies want to continue this discussion for trying to get continued clarity on key points, this is not the only meeting that we're going to engage in. This needs to be a continued development.

So that's point A, because we really need to be flexible and creative here and think out of the box.

Point B is that the panel today has given us a vision that is very consistent with general device development in a way that the agency tries to think, in that as we get more data we try to modify our requirements as they are thought to be - as we can appropriately lessen them.

So again it comes back to, if all

stakeholders are willing to work together, I can envision a time where the concept of a nonrandomized trial design might be a much more tenable one.

And the real question is, how can we get there swiftly, and part of that has to do with just getting all stakeholders really committed to this process right now.

Does that help you, Dr. Yancy?

CHAIRMAN YANCY: I think it helps all of us. Because let me add to that, that I don't think anyone on the panel dismisses a nonrandomized control trial, but I think everyone feels like where this field of medicine is right now still requires some more proof of concept, evidence of - or level one evidence to be confident about the decision making and going forward with new technologies.

And I think what has been articulated vis-a-vis the risk of doing the nonrandomized control trial is a statement that says, we certainly don't discourage it, and it will be adjudicated fairly, but at some point in time we have to have the body of evidence

that represents proof of concept for several questions that have been posed by members of the panel.

Now have I misspoken?

So if that's the case we should continue, because we have a few more issues, especially number one, that need to be addressed.

This is choice of control, eligibility criteria, endpoints, and ways to minimize bias and confounding.

And this is in a context of accepting that some amount of randomized control trial data must come forward.

So in a spirit of helping the agency understand what to do with the non-randomized control trials, we said they are permissive with some risk, we should address some of these other issues.

Is this a fair direction to go, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

CHAIRMAN YANCY: Have we developed this enough? If we have, someone can just

summarize it for me, that'll be great.

Dr. Blackstone.

DR. BLACKSTONE: Let me not summarize but make a couple of comments more than on the non-randomized area.

One of the things that discouraged me a little bit about what we saw about, quote, registries - you can fire me, I know that you are in my office now, David - is that there was a paucity of continuous variables. A lot of variables were broken down as categories. If you expect to have really good propensity matching, as many continuous variables as possible need to be in there about the condition of the patient beforehand. The more variables, the better. And these variables should relate especially to these outcomes. Because there is so much focus on whether they're high risk in terms of surgery, but they need to be variables that are related to high risk of stroke, with the kind of details that have been mentioned around here.

The other thing that could help, we have heard that there are some possible semi-

continuous endpoints that I think we should discuss because they could lower the number of patients needed.

Some of those are the psychometrics that were mentioned. Others are, say, the brain MRI, where you might have continuous counts before and after of emboli. Those continuous variables could well provide different efficacy data points that would speed accumulation of data in either randomized or non-randomized situations.

CHAIRMAN YANCY: So we've heard comments about the controlled, using registries that are more carefully designed, and about endpoints using continuous instead of categorical. So those are well put.

Dr. Johnston.

DR. JOHNSTON: I wanted to ask the FDA why the comparison has to be carotid stenting versus endartorectomy? Why not carotid stenting versus maximum medical therapy?

DR. ZUCKERMAN: That's a great question. And I think someone might want to

1 design a trial of carotid stenting versus
2 maximal medical therapy.
3 But as pointed out in the DES
4 discussion yesterday, I think you're really
5 again at the end of the day need to make a
6 reasonable argument of safety and
7 effectiveness.
8 So let's take a scenario where in
9 comparison to the medical therapy carotid
10 stenting shows less strokes at one to two
11 years, but people implicitly assume because of
12 the numbers generated, that carotid
13 endartorectomy is -- probably would have given
14 even lower stroke numbers.
15 So is that an approvable PMA? We
16 would need to really give it some thought as to
17 how much improvement is clinically significant.
18 Sometimes with big numbers, like in a 2,000-
19 patient trial we can generate a magical P value
20 less than .05 with very small differences that
21 are not clinically significant or believable in
22 the eyes of the clinician.
23 So I would just add that caveat.
24 But having that type of trial

design might be one that should be considered.

CHAIRMAN YANCY: Yes, so continue.

DR. JOHNSTON: The reason I ask that is because of the previous comments in the asymptomatic patients. This certainly would be a very sellable randomized prospective design.

In other words you are randomizing patients to relatively noninvasive or minimally invasive therapy. And I believe there is huge clinical equipoise in that question, asymptomatic patients.

DR. ZUCKERMAN: You know I think that's why we needed this panel today. On the face of it that sounds like a very interesting suggestion. But I like how you qualified carotid stenting as minimally invasive.

Hopefully with the technology today as sizes have come down and the technical ability of operators have improved, it's really a 15 minute procedure as opposed to a procedure that in far too many cases causes complications both in the brain and at the femoral artery, et cetera.

But I think if you could - or

people should seriously think about your idea.

CHAIRMAN YANCY: Dr. Somberg.

DR. SOMBERG: A brain CES beats medical therapy is headline. Okay, so you have to read down to the second paragraph, in the Wall Street Journal, and you'd have to ask what was the price you paid for that. And I think - and you know this better than I do - prespecified endpoints in this study, and what would be acceptable for death, MI, stroke, those sort of issues would be terribly important, and that's how you would vote.

But I would say if I was on that panel - and I'll probably be banned after this session and yesterday's - but if I was on that panel I think that would be a very convincing thing that carotid stenting beats medical therapy.

However, what happens if medical therapy and the device are the same? You're left in a problem there, and I think the sponsor has to realize that that might be a risk in that sort of situation, because I love my interventional colleagues, but if I can give

a couple of pills, gee whiz, after we approved that device.

DR. ZUCKERMAN: I think you've said it well. And those are the potential risks with that type of trial. So we will make sure you're on that panel.

CHAIRMAN YANCY: And I think Dr. Good captured the public health implications with all the people at risk.

And so this is a very provocative design. I'm not sure who has the courage to go forward with it. But you know, I wouldn't bet against medical therapy to be honest with you.

Dr. Somberg.

DR. SOMBERG: Just one other thing. The panel, a couple of people on the panel said symptomatic versus asymptomatic in surgically low risk patients, and I just did not know the path of physiology well enough. But is there a path of physiological difference? Or are they just a continuum, and the symptomatics are like the top of the iceberg, and the asymptomatics are that bulk that you're going to sink the Titanic with?

CHAIRMAN YANCY: Well, I think the public speakers showed evidence that even for those people who haven't had a defined event there is subtle cognitive dysfunction. So it sounds like it has a continuous variable.

But I think others have made the point that we are dealing with for example people that have had a previous resolved stroke may have a certain lack of symptoms, and those that have never had a stroke but have angiographic disease, don't have active TIA, et cetera, may be classified as asymptomatic.

So it is a matter of definition. So I actually support what you're saying.

DR. SOMBERG: But it's very important, if you have a continuous variable, and I agree with you, then, I would not separate that group, and I think we might be wrong to try to do two separate studies on that.

And the divide might be more divisive than not.

CHAIRMAN YANCY: And I would love to have some of the neurologists and vascular

interventionalists on the panel chime in here. But I think the real issue is respecting the syptomatic group, that is, the patient that has overt symptoms and structural disease and is at risk for future events, with some data that indicate that you can modify that natural history with currently available technologies.

So I think the idea is to keep that group clean and then the question is, what do you do with the group that has a lower symptom burden, whether we call it asymptomatic or not, and I actually think someone already said greater symptoms or lesser symptoms, which might have been a better distinction.

Dr. Good.

DR. GOOD: I think it's pretty clear that symptomatic stenosis is a higher risk than asymptomatic in a general sense. And that's been shown over the years.

And of course the studies that have looked at endartorectomy have clearly separated those because of that.

So but there are all sorts of continuum with the degree of stenosis. Again

that's been well shown in the endartorectomy trials, the higher degree of stenosis, you're very symptomatic the higher the risk.

So I don't know if it quite answered the question.

DR. SOMBERG: But most of the studies are done in terms of, they were symptomatic high surgical risk. And if you take away the high surgical risk, which is not to do with the neurologic but the other concomitance of risk, then you have symptomatic versus asymptomatic. And I'm saying are they a continuum? Or do they have to be studied separately?

CHAIRMAN YANCY: Dr. Haley.

DR. HALEY: I think Dr. Good is correct that in fact they represent a different group clinically in terms of their impending stroke risk.

There is a lot of speculation and some research about differences in plaque characteristics and such between asymptomatic and symptomatic disease. Certainly there is a relationship between degree of stenosis and

subsequent stroke risk by percent stenosis in symptomatic patients, but not so in the asymptomatic patients.

CHAIRMAN YANCY: So if we move this forward, I actually think one of the earlier questions of the day from Dr. Johnston was really about defining what is not high risk. So keeping us focused here, if we go back to addressing what are the features of the nonrandomized control trial, understanding that there is randomized control data that is coming forward, if that's acceptable, good; if that's not, then sponsor, FDA, everyone involved may have to go back and reinvent a way to obtain randomized control data.

But if we are giving the agency advice on the non-randomized control trial, we have to talk about the patient population, what is the risk profile. We've had comments, good comments, about the control group. We've had some good comments about the endpoints.

We haven't talked much about minimizing bias and confounding, although we have talked about propensity issues, and having

at least a rich repository of data in the reference group if it's a registry.

So we are still trying to frame up number one. I think we've addressed most of issue two.

Now are there any other comments about the design of the nonrandomized control trial? Yes, Dr. Good.

DR. GOOD: Just to highlight again the importance of, if you've got a study that is looking at for example endartorectomy versus stenting, whether it's randomized or not, we have to be real careful about the medical treatment so that the current best medical treatment is being applied to both groups.

CHAIRMAN YANCY: So even in this non-randomized control trial comparing two active therapies, you are representing an opinion that there must be really reasonable if not strict control of the medical therapy.

DR. GOOD: That would be my opinion.

CHAIRMAN YANCY: And that's what we're looking for, again, ways to construct this non-randomized control trial.

Other comments in this regard? Yes, Dr. Kindler.

DR. KINDLER: No, I would agree that I think that regardless of whether you are talking about symptomatic or asymptomatic disease, that floor trials need to be very cognizant of medical treatment, and they should be very consistent for medical treatment so we can compare apples to apples as we look at these trials and try to decide if certain procedures are - they should be more broadly amenable to patients.

And I think for the approval process that has to be an important part. Because that alone may be a confounder that neither randomization nor non-randomization will address if we don't appropriately look into that and make recommendations.

CHAIRMAN YANCY: Thank you, Dr. Kindler. Got your name. Got my sheet back.

So I have a sense that we have addressed question one, 2a and 2b. Unless someone has a burning statement to make about equipoise, about the importance of randomized

control trials, about barriers, about overcoming barriers, about the design of a non-randomized control trial, not design as much as just the features, are there other important comments we wanted to make about either one, 2a or 2b? Dr. Yaross?

DR. YAROSS: The last part of the question, the one up there, talks about subject eligibility criteria. And this is where I would just suggest that the guidance to sponsors not be overly prescriptive. As we look at barriers to enrollment, whether it's single armed, randomized, one of the things we've learned in past discussions is that if we cut it too narrowly we just make things harder and harder.

DR. ZUCKERMAN: Right, so that is a good point in again there are general principles, Dr. Yancy, that we've been seeing with all these general clinical trial discussions, whether it's afib or carotid stents. So is there something right now that you're referring to, Dr. Yaross, regarding inclusion-exclusion criteria, or some of the

other panel members could comment on?

CHAIRMAN YANCY: Dr. Johnston.

DR. JOHNSTON: I think we want to keep it very general. And we're really saying that these are conventional patients. And I'm now less confused than I was earlier in the day.

And by that I mean that the patients don't have significant comorbidities, instead of listing them, and that they don't have significant technical challenges for either side of the randomization.

So I would keep it very general and very simple to make them conventional patients.

CHAIRMAN YANCY: Dr. Hirshfeld, did you have your hand up? Okay.

Other comments about who these patients are? Yes, Dr. Blackstone.

DR. BLACKSTONE: I think that excluding comorbidities, why would you want to do that? I think as we heard the risk is coming down and so on. That makes it so easy to get rid of patients, and yet they are patients that are going to be done once the

devices are approved. Why would we want to get rid of high risk patients?

CHAIRMAN YANCY: Dr. Johnston.

DR. JOHNSTON: Apologies, I misspoke myself. In the high risk patients they were defined as people who included one of for example congestive failure and so on.

And what I was trying to say is that we can include all patients. So we're on the same page, and I misspoke myself.

CHAIRMAN YANCY: So your statement is consistent with Dr. Yaross then being less prescriptive and more broad?

DR. JOHNSTON: Yes.

CHAIRMAN YANCY: At least with regards to comorbidities?

DR. JOHNSTON: Yes.

CHAIRMAN YANCY: Does that reflect a feeling that others have?

DR. ZUCKERMAN: So that's an interesting concept that I'd like the panel to explore a bit. Because number one, for some companies that already have the higher risk indication they want - might want to be more

1 proscriptive and just enroll lower risk
2 patients.
3 But there are other carotid stent
4 companies out there that don't have any
5 indication, might want to do a more general
6 trial. Or what if a company that has previously
7 done a higher risk registry just wants to bite
8 the bullet and do a randomized trial enrolling
9 patients across the risk spectrum and compare
10 it to CEA for more rapid enrollment.
11 Can people comment on that?
12 CHAIRMAN YANCY: Dr. Yaross.
13 DR. YAROSS: Yes, my intent was to
14 say that the Guidant - the guidance should not
15 overspecify that. That doesn't mean the
16 individual sponsor who saw a reason to do such
17 a trial should not be free to propose a more
18 narrow eligibility criterion if that's
19 appropriate.
20 CHAIRMAN YANCY: Other comments?
21 Certainly if the sponsor was coming
22 forward with a randomized control trial with a
23 broader patient population, I would hope the
24 comments we've made about the randomized

control trial would be incorporated, particularly attention being paid to the medical treatment strategies.

Dr. Zuckerman, do you need us to address 1, 2a, 2b further before we go on to question 3?

DR. ZUCKERMAN: Are there any other panel comments? The discussion has been quite useful.

Dr. Cavanaugh, do you have any other questions?

DR. CAVANAUGH: Just to specifically address question 2b, which I think we covered through the other questions, discussing how to facilitate enrollment in the randomized control trials.

I think we touched on some of that, so if no one has anything else to offer, we can move on to that question with the others. It was specifically mentioned, that's why I brought it up.

CHAIRMAN YANCY: And also, Dr. Buckles, are you satisfied with what you've heard about 1, 2a and 2b?

DR. BUCKLES: I am.

CHAIRMAN YANCY: Thank you.

Did someone want to make specific comments in response to Dr. Cavanaugh? Dr. Blackstone?

DR. BLACKSTONE: Specifically one other piece of information we haven't heard about that could tie in to either one of these designs is, have we learned, or has the FDA learned anything from the post-market cohorts that we haven't actually heard anything about.

CHAIRMAN YANCY: We did hear that the data were being collected.

DR. BLACKSTONE: We heard it was collected. We heard it was consistent. We heard nothing about whether it might modify some of our opinions.

DR. ZUCKERMAN: I think that the post-market trials have in general, one, indicated that more operators can be trained in carotid stenting adequately; two, that results seen in the higher risk preapproval registries can be extrapolated to a broader universe.

But thinking how those results

could be extrapolated down to lower risk populations to decrease burden I don't think we learned that, or that the registries were designed with that purpose.

CHAIRMAN YANCY: Yes, please.

DR. BLACKSTONE: Let me tell you what I was hoping to hear. What I was hoping to hear is that the stents have been used in broader populations that perhaps in the original studies, and that one could look at those patients and simulate say pseudorandomized trials in each of these areas to get more insight into how you might design better the trials, or even better sample size, estimates, and so on.

DR. ZUCKERMAN: The registries were generally enrolling patients that were indicated, meaning on label. And so that data isn't there.

CHAIRMAN YANCY: I really wanted to be certain that we entertain any other comments about these first - these are the major questions as I see it, about randomized control trials and their importance; the nonrandomized

control trial design; and the context of whatever randomized control trial data may come forward, issues of barriers to enrollment and ways to address that.

Are there any other comments? Have we allowed everyone to address their opinion?

Dr. Naftel.

DR. NAFTEL: I'm sorry, just got to make sure I'm clear.

So the first thing that we answered was, does there need to be randomized control in trials in this group of patients? And we said, yes. And then the second question was, however, if there are not going to be randomized control trials in the future, then here's how we do it.

Is that what just happened?

CHAIRMAN YANCY: No my thinking is, we said we need randomized control trials because most of us believe that there is residual clinical equipoise in several domains.

But to extend this further and to make it practical and useful for the agency, we said in the context of the randomized control

trials that are coming forward - so we came back as if they aren't being done, and may not yield reasonable information - were a non-randomized control trial database to come forward, what should it look like? What would be the features that would be reasonable?

DR. NAFTEL: And that seems reasonable to me. Just the logic sounds a little bit strange. You're saying do a randomized control trial, but if you don't do one here's how we think you should do it.

CHAIRMAN YANCY: No, actually that's not correct. There are randomized control trials being done, period. We can't tell anyone to wait, and I think we used the word, risk. You can go forward with a non-randomized trial understanding that there is some exposure there. If we don't have the body of knowledge that establishes the proof of concept, the level one evidence, then somebody may have to go back and do that all over again.

But as you're going forward with the non-randomized control trial, because we made it very clear, that's the level one

evidence that the panel thinks is still required. But if you go forward with the non-randomized control trial, these are the features that it should entail.

Am I pushing this too far? Is that representative?

DR. NAFTEL: I guess, I'm sorry, but I'm still a little confused. If I'm a company sitting out there about to plan a trial. So do I do a randomized trial? Or can I do something a little innovative based on what I've heard?

CHAIRMAN YANCY: If you feel lucky, and you think that what's out there right now is sufficient to answer the proof of concept question and generate the level one evidence, then you do a non-randomized control trial.

If you don't feel that the data that are coming forward will be suitable for this panel, then you should rethink your approach.

Now that is just one man's opinion.

DR. NAFTEL: Well, then, if that's what we're doing, I'm glad my red light's on, then the non-randomized trials, the question

one, we really just kind of danced around the edges. We didn't say, okay if you're going to do this, should it be concurrent controls, or should it be in an OPC? I mean we really haven't answered anything except some details around the edges, endpoints and all that.

CHAIRMAN YANCY: That's why the pause and prompting more discussion to be certain to get to it. So continue.

DR. NAFTEL: Okay, so I propose OPCs.

CHAIRMAN YANCY: So Dr. Kato.

DR. KATO: Well, I mean if you just say OPCs, then which ones? At what numbers are you going to use them and why?

DR. NAFTEL: I don't really have a good answer.

DR. KATO: I think that's the problem with getting into the non-randomized control trials. The same thing getting into the specifics about this is leading down the path of doing the job of what the sponsor is supposed to do.

The job of the sponsor is to, as

Dr. Yancy I believe stated, is to make that decision about what their goals are, how they want to market their device. It is not up to us to tell them how to market their device. That's the thing that they figure out what to do, and then they bring it before the panel for a vote.

DR. NAFTEL: And I'm all for that. I just want to make sure that we're clear on what we've done and what we haven't done.

So what we've done is, we've opened the door and said it's possible to do a non-randomized control trial, and at the moment what we're saying, the details are left to you, that's your job, to plan it all. You've heard some possibilities.

But I don't want a company to leave here thinking they have clear direction, because they don't, not yet.

CHAIRMAN YANCY: Please?

DR. SOMBERG: I think we just went off some place where we weren't at. I thought we had a clear discussion of non-randomized trials, and I didn't hear OPCs before this. I

heard about that there was a need for concurrent groups. We had several proposals made. There was propensity adjustment. There was real time adjustments. Then later on we mentioned some clustering which you mentioned the penalty is very large studies and all this.

But I mean I don't hear anybody saying a single arm study based on - and I sort of been paying - I haven't fallen asleep in the past six hours. So I think there are some good guidances here.

CHAIRMAN YANCY: I would support Dr. Somberg. I think we have outlined some features, but I appreciate pressing the issue. Because this really is why we're here, and I am sensitive to the fact that there are people in the audience, virtual and real, that want to hear what it is we have to say about the non-randomized control trial.

And you bring up a point, and it's being vetted now, and that's appropriate.

DR. ZUCKERMAN: Okay, David, to put your comment in context, and you and Dr. Blackstone are the real experts on OPCs, but

from the FDA perspective these single point estimates in this day and age need to be based on real good quality data.

In fact our general recommendation for development of OPCs is that a sponsor should have access to the line data to develop point estimates with variance; should share their calculations with FDA, et cetera, for an independent check et cetera.

So in the scheme of things, OPCs are usually the third stage in development when the technology matures. So we go from randomized proof of principle trials, to lesser non-randomized trials with concurrent controls; to real maturation of technology with OPC development.

And from what you've heard today, how could you make this giant leap to OPCs without data?

DR. NAFTEL: If I may, I said OPCs just so the companies out there would thank me for forcing you to say what you just said.

So I totally agree with the steps you outlined, and I only made the motion for

OPCs for the discussion, not because I was for the motion.

CHAIRMAN YANCY: And even beyond that, I mean what the panel has told you is that we're still at step one, requiring randomized control trials to establish proof of concept. And we're suggesting that should a sponsor come forward with a non-randomized control trial, it's in the context of whatever comes out of the effort for step one, which may be sufficient, and it may not.

So that's where we are. Dr. Abrams

DR. ABRAMS: We heard two proposals for non-randomized control trials this morning.

CHAIRMAN YANCY: Which we cannot discuss.

DR. ABRAMS: So even in a general sense we shouldn't be making any comments about it?

CHAIRMAN YANCY: We cannot discuss what we heard this morning. But thank you for being careful with that.

Dr. Weinberger.

DR. WEINBERGER: Just to add one

more dot to this, I don't think that we could ever agree on OPCs, given that we can't agree on what event rates you're looking at. Because even among the surgeons, whether you have a neurologist there or not, you get wildly different numbers. So OPCs, my opinion, don't exist.

CHAIRMAN YANCY: Let's move on to question 3.

DR. CAVANAUGH: If the proof of concept of carotid stenting in non-high risk patients is successfully demonstrated, would your study design recommendations change? If so in what way? For example would you recommend a non-inferiority randomized control trial comparing two carotid stent systems?

CHAIRMAN YANCY: While everyone is mulling that over, I think stealing a word from Dr. Zuckerman, maturation of a paradigm probably drives most of this. If you ever get to a point where the field has sufficient information, then you could very much envision yourself in a scenario like we are with other technologies, where we are comparing already

established systems with new systems.

But there is a certain body of evidence that has to come forward before that.

But others please comment on this.

DR. SOMBERG: I think yes.

CHAIRMAN YANCY: The answer is yes from Dr. Somberg. Can you develop that further please.

DR. SOMBERG: I'm not sure I want to.

CHAIRMAN YANCY: There is no need.

Other comments? Dr. Good?

DR. GOOD: Just a question. I'm not sure what FDA policy is with other devices. I'm assuming once proof of principle has been established that this is the general modus operandi. Is that correct?

DR. ZUCKERMAN: I'm not quite clear that I understand your question. But the key thing to recognize is that, let's do a hypothetical, if the CREST trial is completed, and there is a positive approval decision for that particular company, then that company gets on the market and they might own those data.

So for a competing sponsor, one realistic possibility is to do a non-inferiority randomized control trial versus that approved device, because it would be recognized as an acceptable standard of care.

Is that your general drift?

DR. GOOD: Yes, and that seems appropriate to me.

CHAIRMAN YANCY: So we have two opinions that are consistent, Dr. Somberg and Dr. Good. Dr. Milan?

DR. MILAN: I agree.

CHAIRMAN YANCY: So three opinions, great. Dr. Blackstone.

DR. BLACKSTONE: Do you think people would really want to do that? In other words, let's say that now device X, and so now I'm going to have to buy Abbott devices as part of the randomization?

I had problems with this when we were discussing heart valves, if you remember, although I was a proponent of randomized trials there.

But I think the -

DR. SOMBERG: The device is approved. The CREST study is over. The device is approved. And then are they going to do a clinical - I mean is that like yesterday? I didn't ask them, but I don't think Medtronic was buying J&J cypher stents, or Boston Scientific Taxus. If there were no wonder those guys were still happy at the end of the day.

But I really think it's just the way we see things done is that you would go out there, you would get a few bucks for your entering some patients and all that, but otherwise you're getting clinical billings for that sort of stuff.

CHAIRMAN YANCY: So getting back, Dr. Comerota.

DR. COMEROTA: To answer Dr. Zuckerman's question. If the results - and we'll take them in symptomatic versus asymptomatic patients, if the results in asymptomatic patients were equivalent and respectably low, for the two procedures, then a subsequent trial comparing the stent used in CREST versus another stent would certainly be

appropriate.

If however the results in asymptomatic patients were suspiciously higher, the adverse event outcome was suspiciously higher in both carotid endartorectomy and the stent trial, then subsequent trials comparing that stent to another one I think would still be open to question.

And that's where a proof of concept needs to come in. I hate to keep getting back to that, Bram, but I think it's critically important, unless our treatments for both, carotid endartorectomy and stenting, ratchets down.

And hopefully they will.

DR. ZUCKERMAN: Okay, and you just pointed out a key problem with non-inferiority trials that perhaps Dr. Naftel and Blackstone can sort of comment on, which is, non-inferiority drift or creep and always looking at the absolute rates and imputing the true control, et cetera.

That's why as you point out these trials have to be carefully examined with all

1 those factors in mind, but if a sponsor were to
2 show that there was a significant non-
3 inferiority creep by going through those
4 arguments, certainly that RCT design would be a
5 winner in the end.
6 DR. SOMBERG: Can I just interject
7 something?
8 CHAIRMAN YANCY: Please.
9 DR. SOMBERG: If the trial was
10 completed, and it led to an approval of a
11 product, then a subsequent company has every
12 right to do a non-inferiority trial. If you
13 don't like the results of that trial, but it
14 led to approval, that's a regulatory basis of
15 comparison.
16 Am I right, Dr. Zuckerman?
17 DR. ZUCKERMAN: That's the paradigm
18 that has largely driven for example the
19 widespread use of the bare metal stents and
20 subsequently drug eluting stents. As you point
21 out, it's the paradigm we discussed yesterday.
22 And I think that Dr. Comerota
23 doesn't have a problem with that, so much that
24 sometimes with non-inferiority trials again you

can get the magical P value, but if the absolute rate is a very high alarming rate, even though you've shown non-inferiority you have to further examine the trial data, and what have you shown non-inferiority to?

CHAIRMAN YANCY: Well put. Any other comments specifically about question three? I'm sorry, yes, Dr. Blackstone.

DR. BLACKSTONE: Okay, so let me reopen the issue as it relates to what has just been said. And that is, let us say that the first device gets approved because of a trial. Let's just say against endartorectomy. And now you have a device that is approved.

And let us say that that comes in under 3 percent better. So now I have a 3 percent rate in one, 6 percent in the other, and we decided to improve it.

Now when you talk about non-inferiority with respect to the next one, are you going to raise it from 3 to 6? Isn't that what you were sort of implying would happen? And then now it's 3 percent above that, and so now we're up to 9.

CHAIRMAN YANCY: And so that really relates back to the components of the non-randomized control trial back in question 1 that we should respect fairly tight margins.

DR. BLACKSTONE: Exactly.

CHAIRMAN YANCY: And I support that.

Are there other comments about question 3? If not we can proceed forward.

Dr. Zuckerman, is this discussion adequate for question 3?

DR. ZUCKERMAN: Yes.

CHAIRMAN YANCY: Question 4, please.

DR. CAVANAUGH: What other recommendations do you have that may facilitate initiation and enrollment completion and interpretability of clinical trials for this indication, the non-high risk indication?

CHAIRMAN YANCY: Dr. Najarian.

DR. NAJARIAN: I've been relatively quiet. I just have one question regarding the problem with a control study as we've all said takes awhile to perform. And if we look at endartorectomy, and I'm not a surgeon, but the same procedure has been done for 30 years. I

1 don't think there have been any major
2 developments in endartorectomy. Maybe the
3 approach might be different, whether shunting,
4 non-shunting.
5 And all day long we've been
6 comparing endartorectomy with stenting. And
7 stenting, it's a protean process. We've had
8 people who have been doing it, including
9 myself, since 1994. But carotid stenting in
10 1994 is totally different than carotid stenting
11 in 2007.
12 And I suspect it's going to be
13 totally different in 2009. And as we progress.
14 And not only do people get better at what
15 they're doing, but I think mostly it's the
16 technology. And as the devices become smaller,
17 and as the protection devices get better, it's
18 going to become a better procedure.
19 I have no doubt, and you may see me
20 in 10 years, but that carotid stenting will
21 become one of the chosen, preferred methods of
22 treating carotid disease, not that carotid
23 endartorectomy is a bad procedure.
24 So what we're doing is comparing a

technology that is rapidly changing with one that hasn't changed at all. So I just think that as far as interpretation of results of any randomized study that is performed, that I guess new - that has to be kept in mind because the stents, if you look at the TACIT study, the stents that are used are the ones that are available today, but there could be another one that is developed three years from now, let's say when the TACIT results come out, that are much better.

So there has got be a way to incorporate the newer technology in an ongoing fashion with the study.

CHAIRMAN YANCY: So your response to question four is, without knowing exactly how to they should at least be significant sensitivity to technological improvements. And that's reasonable.

Other comments on question 4? Just, Dr. Good.

DR. GOOD: This probably really isn't question 4, but coming down to - it may be related to interpretability - when we talk

about inferiority or non-inferiority do we ever decide what a reasonable delta would be? We had talked about that as being important. I'm not sure we ever really discussed that.

CHAIRMAN YANCY: No, and Dr. Blackstone kind of brought this back on task for us. And it's out there, whether it's a 3 percent margin or less, or a higher margin.

But I certainly think there is a qualitative statement that the margins should be reasonably tight, particularly because of this concern of creep.

But certainly others can chime in. Dr. Hirshfeld, you've been frowning for the last hour, and you're my friend. So what's the problem?

DR. HIRSHFELD: No, I'm not frowning. I agree that the delta for non-inferiority should be very tight because my sense is for the asymptomatic patients we're dealing with very small event rates, and I think what will be a challenge for the sponsors is that I think if they want to pursue this that a long follow up is needed in order to

demonstrate efficacy.

And one of the things about the ACTS trial that was - we talked about before is that the revascularization strategy was actually behind best medical therapy for the first two years, and it didn't achieve equivalence until two years of follow up, and then after that revascularization became superior to medical therapy.

So a one-year observation may not be adequate to demonstrate what people want to demonstrate.

CHAIRMAN YANCY: So what we've heard so far in response to question four is accommodate new technology; have a sufficient follow up period; and a tight margin.

Other comments about question four?

DR. ZUCKERMAN: Okay, I'd like to add one question so that people can comment on it, like yesterday's discussion, there is no requirement that all the data be obtained from U.S. patients.

I heard a lot today about difficulties with U.S. enrollment. It

1 certainly is not unique to this particular
2 field.
3 So if a sponsor were to do more of
4 a global trial, including outside U.S.
5 patients, would panel members have problems
6 with extrapability of the OUS data, or are the
7 key features just picking good sites that can
8 execute the protocol per the way the protocol
9 is written.
10 CHAIRMAN YANCY: Dr. Somberg.
11 DR. SOMBERG: Exactly what you said.
12 You have to follow the protocol very carefully.
13 You have to have a population that represents
14 the broad American population if you will where
15 it will be used. And you have to have a
16 pharmacologic therapy that is similar if not
17 identical.
18 And those latter two things are
19 problematic, and they have to be looked at very
20 carefully.
21 I just want to draw attention to
22 one of the things in the stent discussion was
23 clopidogrel. It's generic in Europe, and there
24 were 15. And there's a pharmacologic article,

1 or there is an article in a pharmacologic
2 journal in Belgium that states that some of the
3 generics are not comparable in terms of
4 activity. And I don't know if it's true or
5 not, I'm not advertising it. I'm just saying,
6 that could be a phenomenal confounder between
7 the European late stent thrombosis problems or
8 not.
9 And you can have a similar thing
10 here. So be very cautious. And we also have
11 to be - every one says standardized medical
12 therapy. But that is - it takes a lot of
13 thought. Because whether you should add beta
14 blockers because of sheer stress, or ACE
15 inhibitors. What about A2 antagonists, which
16 may be more efficacious? And what about lipid
17 therapy? Lipid therapy is from lipostatin to
18 cerivastatin, which is a tremendous difference
19 in potency, and that really changes efficacy.
20 So I think that there are almost as
21 many unanswered questions we haven't talked
22 about as we have. But you have to be
23 consistent.
24 CHAIRMAN YANCY: Just for the

benefit of those who didn't have the privilege of being involved in yesterday's deliberations, one of the central pieces of data came from a study that was done entirely outside the U.S., and it was central in our deliberations. And so that's the reason for Dr. Zuckerman's question.

And more other comments about outside U.S. data?

You've heard Dr. Somberg's perspective. Any other comments?

I realize my task is to remain objective. But I have to register a fairly strong statement of disfavor or displeasure with that approach.

I've had too much experience in clinical trials where you are dealing with a chronic medical condition. And I see atherosclerosis as that, where the standard of care, and I don't mean this in a disparaging way, it's just different; not lower, it's just different.

And I think it would be terrific if there was a way that you could ensure the

adequacy of medical therapy, but there have just been too many clinical trials in which I've participated where there have been very real differences between OUS and the U.S. experiences.

And for something like this that involves not only a procedural intervention but management of a chronic disease, I would have some problems. But that's just one vote.

Dr. Lindenfeld.

DR. LINDENFELD: Just a brief statement. I know that you don't have the power to do this. But this is an area where clinical trials network would be enormously valuable.

You know we have it some other areas where it's really improved enrollment in trials. And I think in some specific subsets of heart failure for instance they are developing them.

And if there were any way for the FDA CMS to help that process along or make it happen, it just seems that that would facilitate getting rid of some of these

political issues that we have seen, and perhaps with the clinical trials network that some other insurers would get on the same page to say it might be important to fund these.

So if there were any way to encourage that kind of application to this specific problem, I think it would help enormously to improve enrollment.

CHAIRMAN YANCY: Dr. Hirshfeld.

DR. HIRSHFELD: I was just going to observe that we heard from the sponsors about the difficulties in enrolling patients. And this may be a challenge for the professional societies to help everybody get on board.

And I think it's important to remind people that we also heard that there are 130,000 carotid endartorectomies performed a year in the United States. And we ought to be able to capture a couple thousand of those patients for clinical trials.

CHAIRMAN YANCY: Completely agree.

Dr. Yaross.

DR. YAROSS: I think the comments you made about the challenges with OUS data are

of course very valid, but you know, I just need to remind the panel that should a sponsor be able to address those challenges, we would expect the agency and the panel to look at that favorably.

CHAIRMAN YANCY: And such would be done, particularly if they were cognizant of our sensitivities.

Any other comments about question four? There is no question five; there were only four questions. It was 2a, 2b.

Dr. Blackstone.

DR. BLACKSTONE: Okay, so could I raise question 5, because it's related to comments on question 4. I had suggested that there be a trans-sponsor study. We've heard from Joanne about the network study two. So let me put out another scenario that I think FDA should think about.

And that is, let's say that all that is rejected, and it turns out that we have six trials of six devices all done at once, and each one comes in with values that although are within the delta that is acceptable to us, one

of the sobering things is the article that just came out from Europe and seven such trials that shows in aggregate the carotid stenting has higher risk that does carotid endartorectomy.

And that could happen with each individual one of them being within specs, but as an aggregate group they are not. In which case I think somehow the idea that out in the future someone needs to be looking at the aggregate of what's going on, because we are trying to protect safety of patients after all, and sometimes these smaller studies don't get at that.

CHAIRMAN YANCY: It's actually a good point. Dr. Abrams, did you need to comment on that?

At the risk of trying to envision that we have completed, our task, let me just summarize for Dr. Zuckerman and Dr. Buckles what I think the panel has said, and see if we can make this make some sense.

We'll start with 2a and indicate that the panel believes that there is sufficient equipoise and that randomized

control trials are still needed, and that there is insufficient level one evidence. And that really takes primacy in this whole discussion.

We have acknowledged that there are barriers to enrollment, and we have listed those barriers. Briefly, the payers, MD preference, patient preference, short term follow up, definition of events, length of trial overall.

We've indicated that there may be some strategies to overcome some of this by lengthening trials, by having multidisciplinary approaches, having neurologists more deeply embedded in the studies.

We have identified that we are amenable to the non-randomized control trial design, because we do respect the fact that it is difficult to do this.

But it has to be in the context of establishing a reasonable data base, especially for patients with a non-high risk lesions or asymptomatic.

When those non-randomized controls come forward comparing carotid artery stenting

with endartorectomy, there are several components that we think are necessary.

There has to be a very well defined control group. We think the registry might have some benefit, but it has to capture a sufficient number of patient characteristics.

We believe the definition of symptomatic and asymptomatic are not entirely clear, but we think the symptomatic group has a sufficiently different natural history that those that are not in that group would reflect the kinds of patients that should be in those non-randomized control trials.

The endpoints again we believe should carry out longer than one year. The endpoints should be stroke, MI, and death.

We think that there are ways that you can address bias and confounders, especially with propensity scoring and propensity analysis.

But we also believe that there will be a residual amount of bias that will make the interpretation somewhat more limited, and again it gets back to the necessity to have the

randomized control trial as the primary data source.

We believe that if in fact proof of concept exists for carotid stenting in non-high risk patients, we have to be very careful in future study designs that we don't allow creep to occur. So we believe that tight margins have to be respected.

We believe that in that scenario, where there is adequate proof of concept in the non-high risk patients, that a non-inferiority randomized control trial could be done.

We've heard a number of recommendations or strategies to go forward. For example we've heard medical therapy versus stenting for non-high risk asymptomatic patients.

We have heard of clinical trial networks. We have heard of using strategies to accommodate iterative development of new technologies.

We have heard comments again about longer follow up in the new studies.

We have heard a request that as the

new studies come forward that we continue to provide appropriate supervision of the aggregate data, again to be certain that we are not realizing a change in the events.

But I think the statement of the day that probably needs to go forward at the end is that this panel believes that the level one evidence does not yet exist, and randomized control data are still requested and desired, and really represent the first step, using your paradigm, to allow us to move forward with trials that are non-randomized, with control populations, and then getting into OPCs.

There are sufficient head nods that I think that reflects what we have done today.

Do you or Dr. Buckles or Dr. Cavanaugh have any additional questions for us?

DR. ZUCKERMAN: I think this has been an excellent's day's work, and I want to thank everyone on this advisory panel for their due diligence today.

CHAIRMAN YANCY: We're adjourned.

(Whereupon, the above-entitled matter adjourned at 5:12 p.m.)

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