

And when we are looking at device safety and efficacy, to wrap it up into medical therapy I think really confounds it.

It would be beautiful to do it, but I don't know that you're going to, on the backs of the device companies, insist on medical therapy, when what they really want to prove is there is a more effective way or a better way or an alternative way to provide revascularization.

CHAIRMAN YANCY: I guess the question is whether or not proof of concept has been established. Is it best to revascularize it? Or if it's primary prevention, to treat it medically?

DR. CHRISTOPHER WHITE: I agree with you. And I think it's a national health care issue to look at that.

But if the current standard of care is that a surgical procedure is going to be done to revascularize, then the question is, is there a safer easier way to do that.

I agree with you that understanding what the medical therapy would be is another layer in that

question.

CHAIRMAN YANCY: Dr. Rodney White?

DR. ZUCKERMAN: But Dr. Yancy, you've raised a critical question that I hope the panel will discuss among itself when you go to that session.

Dr. White and others are proposing a two step process whereby better devices could potentially be FDA approved because they meet a bar of reasonable assurance of safety and effectiveness. And then the broader public health question could be raised by other parties, or you could do it in one fell swoop.

CHAIRMAN YANCY: Dr. Rodney White.

DR. RODNEY WHITE: Just because Chris and I are identical twins doesn't mean we - no, he's my father.

(Laughter)

Disclosure is part of this, right?

That's actually a very important question, and we went through this in the registry discussions.

One of the reasons to empower the registries, and that would be part of this discussion, is a medical arm could be added, and it doesn't get into this issue,

is a study for a device approval going to have a medical arm that somebody is never going to do because they won't pay for it?

And that's the practicality of the issue. So the science is extremely important. How can the panel empower that? They can empower the registries to collect data and keep a data source. The medical arm then, if it's important, could be added in.

The problem with medical therapy is that it's a moving target. It moves around a lot. The recommendations change, and in fact the patients who take those drugs feel lousy most of the time.

So there are a lot of other issues. The compliance levels aren't good. There are a lot of things to look at. But that is particularly an important question that the registries could look at, and we've considered that.

CHAIRMAN YANCY: Dr. Rosenfeld.

DR. ROSENFELD: Just a quick comment. Ken Rosenfeld again.

The trial, the randomized trials, were not designed to look at the difference between medical

therapy and interventional therapy by whatever means. They were designed to look at two different modalities of revascularization and that's all.

So in order to get into the trials, you first have to be an appropriate candidate for revascularization.

Now that threshold for revascularization, it differs depending upon which institution you come from and what the local standards of practice are.

But the fact is, and so within the trials there is the spectrum. And I'm not saying that the question about the current practice of medical therapy versus revascularization, whether that needs to be looked at.

I do agree, it needs to be looked at. And I think everybody would agree with that. Whether it can be - whether you can stop all the randomized trials and sort of now squeeze in a medical therapy arm I think is not a reasonable strategy.

And I have concerns about whether wrapping all of this up into one big trial is a doable issue. If you think it's difficult to randomize between two

different modalities of revascularization, it's even more difficult to randomize between three different arms.

And that is a little bit of a concern I have with the TACIT trial, although I'm involved in the TACIT trial, I believe that we need to answer the question.

I still think for the time being in order to get to this level one evidence of whether endarterectomy and stenting are equivalent or not, we need to complete the current trials and not sort of hybridize.

So I will be in favor of a two stage process that Dr. Zuckerman was alluding to.

CHAIRMAN YANCY: We have the investigator from TACIT. So maybe you should weigh in on this.

DR. RUNDBACK: First of all I should disclose that Dr. Rosenfeld is actually chair of the site selection committee for TACIT. So I'm sorry to fill this one.

So you know obviously this has been raised, and was raised in our submission to NINDS, whether or not we should do this in a two-step process whereby we wait for the results of CREST, determine the optimal

form of revascularization, and then randomize them through medical therapy.

And while that remains plausible, there is a large number of patients, a large population at risk, in the interim, until CREST is evaluated. And CREST is not all risk asymptomatic patients, which is really the largest population that we need to evaluate.

So it's unlikely that it will answer the necessary question regarding the best mode of revascularization in the population that most needs to be studied.

So you'd have to start all over, or wait for ACT I and hope that that is a sufficient trial. And it's also not necessarily reasonable from an industry point of view to wait for the results of this single device trial before they would sort of get into the arena to hopefully have a device that is available for approval. So that is a real limitation of that sort of thing.

The other thing I wanted to mention is that we talked about enrollment, difficulty of enrollment in trials. But clearly part of the requirement of FDA,

part of the regulatory requirement generally to do control of interstate commerce, is to ensure the welfare and health of the American public. And in this particular regard I think communication is particularly important, that we communicate to the community; we communicate to lay individuals; we communicate to neurologists and primary care physicians that this is an unanswered question.

Those are the people who see these patients. Those are the people who should be very very involved in sending patients in for randomization, too. So we eliminate some of this sort of economic consideration.

It really should be at the primary care, neurology, and individual patient level that decisions are made, that we don't know the best thing to do, we need to participate in these clinical trials to find out the best alternative and best way to treat that individual, as well as future populations.

CHAIRMAN YANCY: Certainly everyone has an opinion.

Dr. Weinberger.

DR. WEINBERGER: I just wanted to follow upon

a point that was made by Dr. Bacharach.

You mentioned that the surgical results that seem typical of trials like NASCET are not reproducible in the community.

And what concerns me is that if we hope to establish OPC as an alternative pathway, the OPCs are going to be based on reported surgical outcomes. Which are really not what is attained in the community.

Are we going to be comparing apples to apples? Are we going to be comparing revascularization by the best surgeons in the world against revascularization by community endovascular specialists.

So I was wondering if we have some real world ideas of what surgical revascularization complication rates are, and morbidity and mortality at these endpoints, rather than just cherry picked randomized trials.

CHAIRMAN YANCY: Is Dr. Bacharach - I thought he left.

DR. WEINBERGER: I would love to hear from one of the vascular surgeons as well.

CHAIRMAN YANCY: While we are waiting - Dr.

Camerota is a vascular surgeon. Or should we wait?

DR. RODNEY WHITE: That is the criticism of a randomized trial, and we can't get around that. Are the data good, and are they scientific? Yes. The question is, it doesn't translate into day to day surgical outcomes. We're empowered through current registry mechanisms to be able to look. Payments are going to be driven by outcomes. We've tied together those mechanisms. If we want to answer that question this is going to be available. But there is a mismatch between the two.

DR. WEINBERGER: But as a vascular surgeon do you think it's reasonable to tie an OPC to this idealized vascular surgery outcome? Or should the OPC be tied to a real world vascular surgical outcome?

DR. RODNEY WHITE: It should be tied to a real world surgical outcome, always. To make an artificial definition and use that, there is some degree of fantasy involved in that.

DR. WEINBERGER: So my question is, do we have the data today to know what an OPC target should be for real world vascular surgery for asymptomatic low risk

patients like that?

DR. RODNEY WHITE: We have real world numbers that are published in peer review journals. We do not have an audited data set from any of the trials, and the registry data sets will do that.

CHAIRMAN YANCY: Define OPC for us please.

DR. WEINBERGER: As in a threshold or just the acronym?

DR. RODNEY WHITE: This is the target for outcomes. Whatever the outcome standards for.

CHAIRMAN YANCY: Objective performance criteria?

DR. RODNEY WHITE: Objective performance criteria.

DR. ZUCKERMAN: Okay so the methodology has been used by FDA in the field of heart valves where it is felt that there is a great deal of literature such that adverse event rates are well characterized, and one can do one sample testing because the agency after meta-analyzing the literature can come up with absolute performance rates that inserting heart valves, or in this case, carotid stents, would need to come in under a

four adverse event rates, and for performance goals such as you know freedom from death and MI.

CHAIRMAN YANCY: Dr. Zwolak.

DR. ZWOLAK: Thank you.

The question was posed a couple of minutes ago about actual endarterectomy data, and I have two citations both published in peer review journals in 2006.

The first one appropriate because we are in Maryland: 23,237 carotid endarterectomies performed in Maryland. All the carotid endarterectomies in the Medicare database over a decade.

The in-hospital death rate was 0.5 percent, and the in-hospital stroke rate was 0.7 percent for a total of 1.2 percent.

Now those data are criticized because those are in hospital, and certainly some number of patients leave the hospital and have a complication two or three days later, although that number is probably relatively small.

At any rate, strokes, .73 percent; deaths, .5 percent. That represents I think a mix of about 80

percent asymptomatic, and about 20 percent symptomatic patients.

The other data published in 2006 is in the NSQID, the National Surgical Quality Improvement Database. These data are independently analyzed and entered by a nurse who is employed by the facility. This is a combination of VA data and private data. 13,622 endarterectomies performed over five years. The stroke plus death rate was 3.4 percent at 30 days; primarily VA data, but I think about a mix of 80-20 VA-private data.

So 3.4 percent total, and again, a mix of symptomatic and asymptomatic patients.

So those are the ranges, the Maryland data, 1.2 percent total in hospital, and NSQID data, 3.4 percent at 30 days.

Thank you.

DR. WEINBERGER: And these involve a neurologist examining the patient post op?

DR. ZWOLAK: Neither of these would - the NSQID data are all entered by an independent nurse at the facility. So if the patient had sufficient symptoms

to merit an evaluation. If anyone says anything in the recorded data about stroke, then that is recorded as a stroke by the nurse.

The endarterectomy data in Maryland has been criticized for that exact purpose. These are clinical data, and so you have to think of the clinical sequence that occurs in the hospital.

And the point that is made in response to that, yes, for sure, there are probably some subtle findings that go unnoticed or unaccounted for.

But the hospitals are now pretty aggressive about recording complications because of course they get paid for complications and comorbidities, so in that sense it's probably relatively complete.

CHAIRMAN YANCY: Very brief comments please.

DR. CHRISTOPHER WHITE: I do not wish - I mean what Dr. Zwolak just said is absolutely true, and that's fine.

But we know that from audited trials and carotid stents where we are watched very closely that the neurologist detects minor stroke very often. In fact minor stroke are always the majority of our

complications, and these are strokes that in fact leave no telltale sign in 24 hours.

So that unless you have - we have to compare apples and oranges here, and that is, that these very seriously done trials, with neurology before and after examination, have to be looked at in a different context than population based studies.

And I just think the numbers are just not comparable in this form, they are not comparable.

CHAIRMAN YANCY: It's a point well made.

DR. ZUCKERMAN: Dr. White, before you leave, before getting into a tit for tat, you've made a key point that I want the panel to focus on this afternoon.

You know our primary endpoint is stroke. The majority of these strokes are minor as opposed to major. So do you have any suggestions for better assessing what is clinically significant?

DR. CHRISTOPHER WHITE: It's great, because when I listened to the neurology recommendation their primary endpoint would be total stroke. And that's not what I would care about. Because at the end of a week I cannot measure the effect of a minor stroke.

So I want to know about disabling stroke. That is what I'm trying to prevent, and that's what I care about.

So my major endpoint would be death and disabling stroke for both - any revascularization strategy as well as medical therapy.

People left TIAs with every balloon inflation. Do we count those? It's a therapeutically induced TIA. I don't think that's important. I think what's important is disability, lifestyle changes and mortality for any therapeutic modality.

CHAIRMAN YANCY: Just one second. I want to be certain that all the panel members have had a chance to become involved in this discussion.

Does anyone have a comment about anything we've discussed over the last 30 minutes that hasn't been vetted or addressed?

Dr. Good.

DR. GOOD: I'd just like to comment about complications. And I agree completely that a neurologist should be examining these patients, and that needs to be an important part of the outcome.

I also agree that there should be somewhat severity adjusted. And I think that was what the Academy of Neurology said as well. So I don't think there is any argument on that.

But I think to blithely say that minor stroke is of no consequence is also probably incorrect. There are ways of monitoring strokes. I mean use the NIH stroke scale, monitor right away severity immediately. And so neurologist can do that.

I will say that the complication rate of endarterectomy is dropping for a lot of reasons. You heard some good papers here that suggest that's true. It was also pointed out that from a hospital credentialing point of view, hospitals are just not going to allow surgeons who have a poor outcome and pay for performance going forward. It just isn't going to happen.

So I don't think that that is going to be - I think it's going to be less of a problem going forward.

CHAIRMAN YANCY: Along that line, in regards to the question Dr. Weinberger raised about different thresholds for surgeons in trial and in the community,

Dr. Comerato or Dr. Johnston, did you want to follow up on these issues about surgical expertise and outcomes?

DR. JOHNSTON: The only data that I can quote is data from Toronto published in the Journal of Vascular Surgery, and data from Ontario. It may be different. But in Toronto it was an audited, not neurologist assessed, data, for all the surgeons in Toronto. Those morbidity mortality criteria met NASCIP, the CAS criteria.

Second is the population of surgeons in Ontario was audited but not on site; it was through a sort of database. And again it met the same criteria.

So in our province a large number of people, surgeons, we did not see a difference between academic centers defined by Toronto -

CHAIRMAN YANCY: So you're meeting the same threshold basically? Other comments from the panel on these issues? Yes, Dr. Naftel.

DR. NAFTEL: Just for a moment if I could go in a different direction. So two of the speakers alluded to or just flat said perhaps their registries could help. So I want to make sure I understand the

groundrules and see if people agree with me.

Many times when there is a discussion of randomized clinical trial versus nonrandomized, when people criticize it, they'll say, well, there's rigor in a randomized control trial, and there is lack of rigor in a nonrandomized.

And I want to make sure that we understand, or that I understand, that that's not what we're talking about here; that whichever way we suggest these studies get designed, most of the components would be identical, and that is, there'd be a DS&B clinical events committee, follow up, IRBs involved, precise endpoint descriptions.

In fact, nine-tenths of the description of the study you wouldn't know which one you were in. So I'm assuming that's what we're talking about.

So that brings me to registries. And under full disclosure we run three registries at UAB, two heart transplant, and then Intermax. And so I'm very much a registry person.

But not today I'm not. The only role that I see for registries in this context is if a CRO like NIRA

uses a registry platform to collect data within the structure that we're talking about.

So I wanted to bring that up to see if the panel agrees, but also the two people who said, hey, maybe you can use my registry, give them a chance to -

CHAIRMAN YANCY: But not everyone on the panel may be fully facile with the structure you described vis-a-vis NIRI collecting, using it as a tool

DR. NAFTEL: Yes, so not NIRI, but whatever trial design a company goes with there will almost always be a CRO, a clinical research organization, either within their company or they'll hire it out, in a way a mere detail is how you collect the data, paper forms or web-based data entry.

If an existing registry out there says, hey, why don't you use my system to collect data, that's fine. But that is totally different from saying, let's use a registry mechanism for the study.

So I think in the discussions today, I think we are not - I don't think any of us are to the point of proposing registry studies for a PMA. We're still talking about a structured FDA study that's very

structured and has all the definitions and not a registry.

CHAIRMAN YANCY: Dr. Somberg, this seems like a point worthy to discuss.

DR. SOMBERG: I just - didn't have that - maybe I'm misinterpreting things. But my interpretation was, the presentation of the registries was to use them as a control group and a comparator for approval purposes.

And that's what I'm hearing from the speakers out there. And I'd like to, if I may, get back to what I was saying a couple of hours ago is what I think the question is, why we're here today is, how do you prove efficacy and safety of an interventional device for carotid artery stenting? And I've heard randomized control trial, they're going forward. I've heard about the possibility of concomitant non-randomized control trials.

I've also heard the proposal, as you were talking about a minute ago, and by the way data collection could be through those registry mechanisms that you mentioned, but then I heard that they wanted to

have a single armed control study with some sort of performance maybe like a graph or something like that, using the 6 and 3 percent, rather than symptomatic or asymptomatic patients, or use it compared to a registry.

And I think you know we should get to the quick. And maybe talk about where the panel is, what should we do first? Which is like going around and around a circle here, and it would be forever, or would could tie the knot.

CHAIRMAN YANCY: Dr. Comerota.

DR. COMEROTA: I just wanted to address two questions. The one is about the outcome measures and why prior randomized control trials of carotid endarterectomy did not meet community standards in subsequent reports.

When those reports, when those community reports were generated, I think it's fair to say there was a large volume of general surgeons doing carotid endarterectomies, and I think that evolution has changed.

Most of those surgeons are retired. And today the individuals who are performing carotid

endarterectomies are either vascular surgeons or vascular trained neurosurgeons.

So there is a real decrease in operative related complication rates, which I think is reflected by current studies and reflected by the randomized trial that we saw, the EAV-3S and so forth.

The second point is that minor strokes, or let's say asymptomatic diffusion weighted infarcts, which we know occur at a reasonable percentage after carotid angioplasty and stenting, and to a lesser percentage after carotid endarterectomy occur. They're asymptomatic. When you test these patients, test the people for neurocognitive function and dementia, there is significantly accelerated neurocognitive dysfunction, and significantly accelerated dementia in individuals who have new infarcts from baseline to follow up. And this was not - published not long ago in the New England Journal from a very large, over 1,000 patient sample, from the Netherlands.

And I think it's a point that we need to appreciate, and we can't dismiss a minor stroke, even though we surgeons have been accused of that. But we

can't dismiss it because it does become important.

CHAIRMAN YANCY: It is approximately 2:30, and I wanted to continue this discussion until 3:00.

Again for the purposes of clarity what I've heard as we've been reviewing comments from the speakers that volunteer information was respect for the ongoing randomized control trials. I heard almost unanimity with allowing some iteration of a nonrandomized control trial.

We had I think a reasonable discussion about at least the theoretical benefit of understanding medical therapy. We have had a limited discussion about the definition of what is not high risk, and what is high risk. We have had a reasonable discussion about barriers to enrollment. And we've just entertained I think an important discussion about endpoints vis-a-vis stroke, and what is the definition that is clinically meaningful. And we've actually heard polarized opinions almost, which is fine.

So in the next 30 minutes, before we take our break and then come back and specifically deliberate on our four questions, are there other areas that we want

to explore so that we have the body of information addressed in order to answer the FDA questions?

Dr. Zuckerman.

DR. ZUCKERMAN: Yes, I just want to get back to Dr. Naftel's critical point if it isn't clear. The discussion today has been randomized trial design versus nonrandomized trial design.

And Dr. Naftel has said regardless there - given that this is a procedure that carries significant mortality and morbidity; that certain design elements need to be in these trials. Internally that's the FDA position before granting additional approval for any IDE.

And I think Dr. White may want to comment also, because a specific CRO was mentioned, New England Research Institute, or NERI, which I think ran CARESS. And we're not here to advertise any particular CRO as opposed to just underlining what are the key elements as outlined by Dr. Naftel.

But Dr. White, did you have thirty seconds?

DR. RODNEY WHITE: Yes, that's a very relevant point. And in fact the registries that we proposed do

need what would be the FDA standard, and we have had discussions with Bram separately about how that could be translated to an IDE.

So the forms are the same. The reporting, the automated reporting, the level of auditing, the neurological assessment; it's not by a neurologist, but it's by a neurology trained person; so that all those components are there. They're assessed, and it's chart verification by a CIO that does a lot of this. So it is built to do that because it needs a lot of things that are going to be needed for the surgeons' outcome requirements for what's coming down the line in terms of outcomes and reporting, at least the CMS stuff, and it's also been designed to potentially do what we're discussing here, to be a level of evidence equivalent to what would occur in a clinical study if it were to occur during an IDE and be assigned to a CRO, which would be sort of an investigator-IDE model than it would easily accommodate all those other things you're talking about including low DSMBs and the rest.

So it's built to do that. I guess the registry then is maybe not the right term.

DR. NAFTEL: We really need another word, even though we have three registries, if anybody in my office says the word registry, I fire them.

DR. RODNEY WHITE: Well, I don't work for you so I don't care. But it is then on some other level. It is a clinical study that has the same equivalence. We're calling it a registry because that - well, it's an outcome assessment tool, how's that?

DR. BLACKSTONE: I believe there is one piece that is missing from your list that you just summarized, that at least I heard I believe. And that is the idea of having studies that cross devices, that cross companies, and so that you have a pool data model from which then either there are subset of that information used for a given device, or at least that pool data establishes the performance criteria, what have you.

Isn't that another idea that came up.

CHAIRMAN YANCY: I do think that was a statement.

Are there other directions we need to go?
Yes, Dr. Good.

DR. GOOD: I just want to come to this safety

and efficacy issue, and FDA's role in looking at devices. And I have a little concern trying to compare this with some other devices that the FDA may have looked at in the past. For example, comparing this to AAAs, and again, I am not opposed to other trial designs other than randomized clinical trials, but you have to think about, this is a huge public health issue; it involves thousands and thousands of patients; there's huge cost ramifications with national health care; and you are comparing it to something that has level one evidence.

So I think you have to be careful in just saying, well, safety and efficacy, we can compare it to everything else the FDA has looked at. Because I look at this as a special issue.

Plus the stakes are high. If somebody has a bad disabling stroke, it's a huge public health as well as personal issue.

So I think we have to be a little - I'm respectful of what you said, but I think we have to be careful in this situation. And I think randomized clinical trials, at least for proof of concept, are

probably going to be important.

CHAIRMAN YANCY: Well, this is exactly why we're here. It's one of the reasons I raised the question of proof of concept in tandem with Dr. Hirshfeld's point, because it's exactly that kind of input which FDA requests from us, and which you heard before is just a laundry list of what we've been addressing. And I think that is an appropriate entry on this list, that the randomized control trial is still necessary to establish level one evidence. And that opinion is very much requested.

Other panel members, input? Dr. Abrams?

DR. ABRAMS: The comment was made by one of the speakers about, you know, that obviously the primary responsibility of the FDA is to protect the public health. We have - I'm wrestling with two questions here. There's the issue of whether CAS versus CEA, which one is better. And that's one issue.

And then there is the second question, second issue that Dr. Hirshfeld alluded to, what about the asymptomatic patient in which we really don't know whether either of these is really an appropriate

treatment for? I would like some of the - given the fact that we have this dilemma here, it would seem that by making alternative trials and alternative ways to get stenting more available sooner, we're actually perhaps facilitating the introduction of more treatment for conditions that really should not be treated by these particular methodologies, whether it be CEA or CAS alone.

And I was just wondering if some of the public speakers would comment on that. Why would the FDA want to be facilitating perhaps the spread of use of these procedures, whether it be - particular CAS which is obviously the thing we're focusing on.

Why should the FDA want to facilitate the greater use of these devices, given the fact that we do have a randomized control trial that is in progress, and that we will have data from that within the next year or two?

CHAIRMAN YANCY: Please proceed. Dr. White.

DR. RODNEY WHITE: Actually, I don't think the point about the registries is in fact to facilitate use. What it is, is a way at a very high level to look at

outcomes from clinical centers across the country and compare the two modalities.

And it's built in the outcome model, but everybody is now accepting should be the standard for not only device approval but recertification at local levels and even payment.

So my presentation here is not to say any of these should be used, or actually would address the question of treating asymptomatic carotid endarterectomies, and what are the outcomes at local level hospitals, which again today you've heard a lot of opinions about. Does NASA actually reflect that in clinical practice? What you've heard today is that it does not, and yet we quote that as level one evidence. That's why I don't like level one evidence. It does not reflect clinical practice, and that is what I would tell the patient in an informed consent.

CHAIRMAN YANCY: Dr. Yaross.

DR. YAROSS: Yes, as we try to tackle this I think we're looking at a couple of things. In terms of the issue about whether or not it's important for FDA to expand use, I think the issue is more of getting data in

front of the FDA so it can adjudicate safety and effectiveness.

And as we talk through this, to the extent we are able to tease apart the regulatory safety and effectiveness question on a given device, versus these broader and very important public health questions, that's really what I think the task is that this panel has to do.

CHAIRMAN YANCY: Dr. Milan.

DR. MILAN: I just want to see if I'm right about this, is that I understand the trials that are ongoing are not to determine what the best therapy is for revascularization, but whether or not stenting is non-inferior to carotid endarterectomy. And I think it gets back to my point before, which is, you have to establish some inferiority of margin when you do these non-inferiority trials.

And if for asymptomatic patients we are cutting it so fine that you need to treat 18 patients already to prevent one stroke, how much inferior are we comfortable with for this new therapy, for asymptomatic patients?

CHAIRMAN YANCY: I think your point is very well made.

Additional dialogue in that? Dr. Comerota?

DR. COMEROTA: Is that the case? Is our charge just to compare CEA with carotid angioplasty and stent in asymptomatic good risk patients?

CHAIRMAN YANCY: No, our charge actually is to give the FDA input on what we think would represent an appropriate clinical trial design for PMAs to come forward with carotid artery stenting.

And we may decide that the only trial design that is reasonable, particularly in an asymptomatic patient, is a trial design that includes an arm, whether it's registry or prescribed in the clinical trial, that has a medical treatment arm, so we can answer that again proof of concept question.

We may decide that that's outside of the purview of what it is the FDA's charged to do. And we would tell the FDA to be certain that the trial demonstrates clear evidence of non-inferiority compared to carotid endarterectomy done at the level of the recommendations that we're seeing less than 3 percent,

et cetera, if that can be attained in clinical practice.

You're assertion, which I respect, is that it can be. We just heard Dr. Rodney White say that it isn't always. So that still seems to be a question.

So that's the input that they're looking for. We are charged with the responsibility to let the FDA know what kind of clinical trial design. We have a number of things on the plate. A strict randomized control trial, a non-randomized control trial, a single arm study with objective performance criteria, registry data with propensity analysis and covariate adjustment, all going into a three arm trial that can tell us - that contains a medical treatment strategy.

So we have a number of options to consider, and that's part of the reason for having this deliberate discussion, so that when a question is posed, we can crystallize our thoughts.

Dr. Somberg.

DR. SOMBERG: Just to follow up on both your comments there is that I can conceive of a study where you are comparing a device for carotid stenting versus medical therapy given the data we have with

endartorectomy in the background there, the device beats medical therapy significantly, and it's large enough to give a point estimate on both effectiveness and safety.

The question then would be, okay, so it beats medical therapy, but how different is it that endartorectomy? And remember, endartorectomy requires surgery and all the problems that that may ensue. And I can conceive of having an inferior therapy that may be better for some population, and that will be decided by clinical practice and clinical decision making.

So we don't always do what is proof positive of best clinical practice. We do what is a reasonable practice for that particular patient set.

So I think there is an alternative of stenting versus endartorectomy as a regulatory trial. And I think I said that twice, and I'm not sure anyone else agrees with me.

DR. ZUCKERMAN: From the FDA perspective I would agree with Dr. Somberg. Again, I think he's crystallized a key point. While one approach is to do everything in one fell swoop, and answer every question under the sun, another is in a more careful stepped

approach as outlined by Dr. Somberg, which is to establish a reasonable assurance of safety and effectiveness in comparison to a legitimate control, which all the appropriate caveats.

And sometimes, as Dr. Somberg indicates, secondary - if you're going to accept a hefty non-inferiority margin, which is the case here, some of the secondary benefits that can be established, such as percutaneous treatment rather than endovascular - rather than surgical treatment, et cetera, are important components.

It's not an easy decision to weigh the results at the end of the trial, and I don't mean in anyway to diminish the key concepts brought out by the neurologists on this panel who are continually reminding us that these data would need to be extremely carefully looked at to make sure that we can establish an appropriate risk-benefit profile.

CHAIRMAN YANCY: Comments?

Looks like a number of our public speakers have additional comments. I don't know who is first, Dr. Zwolak, you can proceed.

DR. ZWOLAK: Just a very brief comment. I think that I'd hate to leave here with the thought that the definition of a stroke is a political definition.

But seriously, though, when you think about the definition of a stroke, we've seen recent literature that suggests a stroke may not be in fact an imaging-based diagnosis; it may be a clinical diagnosis. And the definition of the trials, whatever you decide upon, what turns out to be the ultimate definition of a stroke is crucially important, is it an event that is measurable at 24 hours and 5 minutes? Is it an event that's measurable clinically when the patient leaves the hospital?

It certainly is an event with a threshold lower than something disabling, but what is the bottom rung of that definition? I think that's terribly important to add to your deliberations.

CHAIRMAN YANCY: Thank you very much.

Dr. Rosenfeld, a very limited comment please?

DR. RUNDBACK: Dr. Rundbach, sorry.

CHAIRMAN YANCY: I'm sorry.

DR. RUNDBACK: First of all, I do want to say

that the ongoing registries are quite important. And SIR, whom I represent here today has endorsed the ongoing registries and participated in the development, the datasets for that. So I do endorse that.

Obviously the ongoing randomized trial part endartorectomy and stenting are salutary, and they will gain data really before we'll get into enrolling another randomized control trial.

So I don't think there is going to be much controversy there. There won't be much overlap either.

Of course those trials don't ask the major fundamental question about the role of contemporary medical therapy. We have discussed this.

What I really wanted to specifically address was the issue of neurocognitive function after endartorectomy versus stenting or other therapies, which was raised by a member of the panel.

You know the literature which I have here is all across the board for carotid endartorectomy, some showing no change in neurocognitive function using the old battery of tests; some showing improvement; and some showing worsening.

There's an interesting publication here from the Journal of Vascular Surgery in 2003, interestingly out of Columbia, in which 60 patients undergoing - 80 patients undergoing endarterectomy were compared to 25 patients who had spine surgeries in the control group. And there were several cognitive decline following the endarterectomy which occurred and persisted for at least several weeks after carotid endarterectomy, which was absent in the control group.

So clearly the data is all over the place, but carotid endarterectomy can be associated with neurocognitive damage.

There is probably quoting bias with the stenting stuff, but really after stenting, all the reports that have actually showed improvement in cognitive functioning, that's probably because those people are choosing to report.

But I don't think is a defined or a clear question in anyway that one therapy is better than the other in terms of neurocognitive function.

CHAIRMAN YANCY: Thank you.

Dr. Rosenfeld.

DR. ROSENFELD: I have two comments. One is about registries, and I would concur with you that the registry format is a - if it's a registry, it is not the same as a one-armed clinical trial or a single armed clinical trial or a randomized clinical trial.

However, as Dr. White alluded to, both the SBS and the CARE registry, which is the NCDRs, like similar registry, have components that are very rigorously set, the data collection, the analysis and so on and so forth, all the tools are there.

What needs to be ramped up are things like adjudication, clinical events committees, and auditing, site auditing and so on that are the types of things that are a little bit higher standards for a single-armed clinical trial for example.

DR. NAFTEL: May I ask you one question?

DR. ROSENFELD: Yes.

DR. NAFTEL: Do those registries require informed consent from the patients?

DR. ROSENFELD: They don't, because currently, because they fall under the rubric of quality of care, and that doesn't require informed consent.

But again they have the capability of turning on a switch, adding a few more data elements, and adding some adjudication and turning it into a clinical trial.

And I think the power of registries independently it can be quite significant, especially if they are required by CMS, as is the case, Dr. Milan can tell you that every single ICU that's placed in in this country requires a filling out a form in order to get paid.

And that has led to an incredible amount of data that is just very very useful in terms of defining the role of these devices in clinical practice.

So I think the possibility exists to what Rod was saying that these can be useful in terms of defining outcomes.

To the issue of defining outcomes, the one difference between registries and everything else we talked about is the clinical events committees associated with the post-market surveillance trials for example, it turns out I'm told that they increased the number of events by a factor of about 50 percent when they actually - when the events are adjudicated.

So assessment of clinical outcomes is incredibly important to Bob's real next point. It's what you define as an outcome, an important clinical outcome. And I'm not sure we've gotten there. It's really critical to your discussion.

And I do think that some of these subtle events that Dr. Comerota's comments, yes, there are several things that happen no matter what we do. We put people through general anaesthesia, that can happen.

But where is the break point between what is materially important in terms of a person's lifestyle and longevity and so on.

That was the main thing I wanted to say.

CHAIRMAN YANCY: Yes, Dr. Fink.

DR. FINK: Yes, so we've been involved in a large number of randomized trial, and also what you call single-armed trials.

And what Dr. Rosenfeld was alluding to was a capture trial, which is a post-market high risk trial in which every patient had a neurological evaluation before the procedure, after the procedure, and in 30 days.

And we send all our information to the

clinical events committee, we would get a bump up in our event rate by about 50 percent. So this is in a post-market trial in which every patient is getting a neurological evaluation up to 30 days and we get a bump up. Now I must say we have very conservative screening in terms of the clinical events committee. So I'm very skeptical about These registries in which there is - I don't know if the neurological evaluation is done at three time points. I'm almost positive there is no adjudication. So I just think we have to proceed with caution about using this registry data as a reflection of truly what happens in the community.

CHAIRMAN YANCY: So I know there is probably a long dialogue that could go on about those specific tools.

Let me see if we've hit a point of fatigue and need a break, or if there are some burning questions that still need to be addressed.

When we reconvene - we think this is one break where we need to think about our thoughts, so that we can do this in an efficient way. But we should all have the questions before us.

And let me just remind you that we've been reviewed today about data that demonstrates the benefit of carotid endarterectomy for symptomatic carotid artery disease. And we've seen the relatively low level support and guidelines for asymptomatic disease. That's a class 2B recommendation; that's one step above a 3, which is don't do it.

So at least in that regard, in terms of academic review, there is a significant question that remains about the appropriateness of carotid revascularization by any modality for asymptomatic disease.

The charge we're tasked with now is that for those patients that may be candidates for carotid artery revascularization, can we come up with a strategy that allows a stent procedure to be considered fairly and appropriately in a least burdensome way, but that is reasonably acceptable vis-a-vis efficacy and safety and allow that into the marketplace in the same way that an on-label appropriately indicated carotid vascularization procedures being done now.

I know those are a lot of words, but unless

we set some boundaries, we really will end up with a very tangential discussion when we come back.

So let's give that some thought. It's two minutes before 3:00. Is 3:20 -- 3:15, is that everybody's agreed upon time?

Okay, we'll break until 3:15.

(Whereupon, the above-entitled matter went off the record at 2:55 p.m. and resumed at 3:17 p.m.)

CHAIRMAN YANCY: I thought we were going to lose the critical mass of the panel. It looks like we lost the critical mass of the audience.

Sorry, everybody want to just mail in your opinions? I hope that didn't get caught on tape, geez.

DR. SOMBERG: Can we caucus in Iowa? It's eight hours, I understand.

DR. ZUCKERMAN: Dr. Yancy, before we start, I am going to have to step out for a few minutes, but Dr. Sapirstein and Dr. Dave Buckles, branch chief for peripheral vascular, will be occupying the hot seat. So please don't be afraid to ask those great questions that you've been asking all day regarding FDA policy.

DR. CAVANAUGH: Now we know how serious it is when Bram leaves. We've really gone beyond our allotted time.

CHAIRMAN YANCY: So we're back to mailing in our votes again.

No seriously, I think this has been an interesting, sometimes awkward but very important discussion about critical issues, and I would applaud the panel for the breadth of your questions and for the way that we've approached this topic.

And I think that we are prepared to move forward, so you have my thanks, and I appreciate the fact that we all are respecting time, because at least half of us have to leave at 5:00. So we will proceed.

At this point in time we are going to address the FDA questions to the panel. So all of our comments will be focused in direct response to the four questions that appear at our side.

There should be an FDA representative who will be available to post the questions for the panel.

Are you ready, Dr. Cavanaugh?

DR. CAVANAUGH: Yes.

CHAIRMAN YANCY: Okay, we'll start with question one if you will lead us, please. QUESTIONS FOR THE PANEL FROM FDA

DR. CAVANAUGH: Sure. Question number one, can acceptable nonrandomized control trial designs that compare carotid artery stenting to carotid endarterectomy in patients who are not at high risk for adverse events from surgical revascularization be developed?

If so, please provide recommendations regarding choice of control, subject eligibility criteria, endpoints, and selection methodologies for minimizing bias and confounding.

CHAIRMAN YANCY: So we - sure. My only train of thought is just in the context of this answer, just looking at question 2a about whether or not sufficient clinical equipoise still exists so that the performance of a randomized control trial to evaluate carotid artery stenting is scientifically and ethically valid is an almost similarly important question to address in the context of this question.

And I wonder if you would - if there is no

great discordance, so Dr. Comerota.

DR. COMEROTA: I would like to make a comment on how we got here.

CHAIRMAN YANCY: Sure.

DR. COMEROTA: And I think it's pertinent, it's so pertinent to the question.

The first FDA panel regarding this issue addressed the SAPPHIRE data, and there is a major difference we've all recognized in symptomatic versus asymptomatic patients, a major difference in neointimal hyperplasia recurrent stenosis versus atherosclerosis.

And what's happened is that many of the patients that have been treated in trials with carotid angioplasty and stents have addressed and treated patients with neointimal hyperplasia, fibrous lesions, not atherosclerotic, and then taken that data and then applied it in the broad sense to patients with atherosclerotic disease.

Now when we look at the SAPPHIRE data, and that was one of the most contentious panels at least that I've been involved with, it's the most contentious panel.

And every panel member missed their flight that night. I think we didn't vote until about 7:30 or 8:00 o'clock.

And the flaws in that trial were numerous. There were five cardiologists on that trial, Dr. White is aware, and the vote was six to five.

So there was some major contention. High risk patients as you know, but only 2 percent of the patients treated there had a 90 percent stenosis of their carotid by arteriography, which was the gold standard for all the other trials. Less than - only - less than 20 percent of the patients in SAPPHIRE had an 80 percent stenosis or more.

But these are high risk patients that have carotid disease by definition, 70 percent of them were asymptomatic; 25 percent of them have fibrous lesions; and the trial design was major flaws, and a very small percentage, the smallest percentage of the patients were randomized.

And our panel voted to recommend to the FDA approval.

Now that responsibility from that panel was

then translated. And then another device was brought before the FDA, and the Archer data were presented.

Well the Archer data, I just should summarize then the subsequent data on asymptomatic patients in SAPPHIRE. In asymptomatic patients the 30-day stroke and death, not stroke, death, MI, 30-day stroke and death rate in asymptomatic patients was 5.4 percent. The one-year stroke death rate in asymptomatic patients in the SAPPHIRE patients treated with carotid endarterectomy, 14.7 percent, far beyond the natural history of the disease.

And then there is a precedent set, and now we have a device that's approved. So now another data set comes before the FDA, and the FDA approves the data set which included the Archer trial data.

And there is a large percentage of patients in the Archer trial treated for recurrent stenosis of fibrous lesion, and they had a very low 30-day stroke and death rate. It was less than 1 percent.

If you look at the atherosclerotic patients who were treated in Archer, and a very large percentage were asymptomatic, 30-day stroke and death rate in

Archer is 9.5 percent for atherosclerotic lesions.

But yet that device was approved. So at the recent Vascular Society meetings in Baltimore, this June, McPhee and his colleagues, or the group from Temple University and the University of Massachusetts, reviewed the national in-patient sample following revascularization for carotid artery stenosis, and reviewed over 217,000 patients.

Carotid revascularization after stroke, so these are symptomatic patients, but even more than TIA, these are stroke patients, 30-day mortality for carotid endarterectomy was 2 percent following stroke; 30-day mortality for carotid angioplasty and stenting was 9.5 percent, albeit symptomatic patients.

But nonetheless we can see where - what our responsibility is, I hope, by looking at some of these data. And then when we look at hospital mortality and procedure related mortality relative to statin use alone, forget about blood pressure reduction, forget about ACE inhibitors and appropriate platelet inhibition, just looking at carotid endarterectomy in patients who are treated with statins, there is a 25

percent risk reduction in post-operative death if a patient is on a statin, and that's reported by Kennedy and Strobe just two years ago; 55 percent risk reduction of operative stroke because of appropriate pharmacotherapy.

And then the Sparkle trial which is a randomized trial demonstrated a 16 percent rate reduction in stroke, if the patient is on maximal dose statins versus placebo; 23 percent reduction in any cerebrovascular symptoms; and a 35 percent risk reduction of a major cerebrovascular or cardiovascular event.

So I think what we need to focus on is what is going to give us the best data to make patient treatment decisions? And if that means putting carotid endarterectomy on the line and saying we cannot accept the data from 14, 15, 16 years ago, that's fine, I do think. That procedure will stand up, but I'm happy to put it on the line.

The key is, can we accept the medical treatment data from 16, 17 years ago which is when the ACAS patients were treated? The asymptomatic patients

that we're using as a historical control were treated 17, 18 years ago, and I don't think that any of us would want to undergo the same medical care 15 to 18 years ago than we have today.

Thank you.

CHAIRMAN YANCY: I think your comments are very well placed, because they directly apply to any inferiority margins we may discuss, because you are obviously talking about differences between carotid endarterectomy and carotid stenting, and I think you are also bringing up once again this issue of what is the background noise for these patients as being their medical therapy, and we have to be sensitized to that.

DR. COMEROTA: I would just like to add one other comment. We do 100 percent of the carotid angioplasty and stents at our institution, we the vascular surgeons. So I'm not trying to protect our domain.

I would like to offer the best we can to the patient.

CHAIRMAN YANCY: I think we're all here for the same purpose, to really come up with a reasonable

decision that protects patient welfare and respects the requirement that the FDA has for us.

I'll permit one more comment, and then we'll get on with this process.

Dr. Somberg.

DR. SOMBERG: This is part of the process, because I do think we're addressing a question here, and that is, can we - acceptable non-randomized trial?

CHAIRMAN YANCY: With your permission, I think it's an appropriate way to think this through if we first of all deal with the randomized control trial.

Because the first question applies, we've already tacitly said we can go beyond a randomized control trial.

DR. SOMBERG: But okay -

CHAIRMAN YANCY: Let's do that first.

DR. SOMBERG: That's fair.

CHAIRMAN YANCY: And let's deal with the first part of the second question, because I think the language is really where we need to start.

DR. SOMBERG: But what I want to address, Dr. Yancy, is what Dr. Cavanaugh I believe was addressing.

And that does bear on the randomized clinical trial.

And that is, I do not think we are here to decide whether carotid endarterectomy versus carotid artery stenting, which is the optimum procedure.

You mentioned two numbers, national, all statistics, 2 percent, carotid endarterectomy, 9.5 percent for carotid stenting. I can think of a lot of reasons why stenting might do worse, and I'm not saying that shows that one is better than the other. And they both need maybe decent modalities.

So I think on an appropriate randomized control trial should be emphasized, and it can be for approval process, it can be versus the endarterectomy, the device versus the endarterectomy, it can be the device versus medical therapy.

And we have enough information, if these are adequately powered studies, and you have a point estimate, we can get enough information to design for safety and efficacy. And I don't think we should be locked in, and here's the point I was making, and I think Dr. Zuckerman was feeling that it was a valid point, I don't think we should be locked in with a

mindset that the only question is CEA versus CAS.

CHAIRMAN YANCY: Accepted.

So if you will pose a question to - and let's begin a very rich dialogue now about whether or not sufficient clinical equipoise still exists that the performance of a randomized control trial is scientifically and ethically valid.

Dr. Johnston.

DR. JOHNSTON: Just to begin the discussion, my answer is yes. I believe there is sufficient clinical equipoise. I could add qualifiers beyond that, but for that question I believe the answer is yes.

CHAIRMAN YANCY: Feel free to develop that if you'd like.

DR. JOHNSTON: Well, this relates to RCTs, and I think I would then go on and argue that probably that approach is not feasible, even though there is clinical equipoise in CAS versus endartorectomy, and indeed, as we've said, CAS versus medical therapy.

So I believe there is clinical equipoise that we can ethically and scientifically do a study. I don't believe probably it's going to be a randomized control

study though.

CHAIRMAN YANCY: Okay. Additional comments on this issue?

DR. KATO: Well, from my perspective, I think yes, there is enough clinical equipoise. But I think all the more reason to do a randomized control trial. I think whether a sponsor wants to do stent versus medical therapy or stent versus surgery, I think that is there prerogative. It's not the right of this panel nor the director, we are not here to tell the sponsor which way they want to plan their trial.

But I think that for all the reasons we've gone through not only in today's panel but in other panels before this that randomized control trials are the only way to go, that said, how they want to develop their trial, that's up to them.

And however, I still think that given what Dr. Comerota said, that there's enough question about asymptomatic disease and how that's treated given today's anti-platelet therapy, that there should be enough patients out there to get adequate informed consent and power the study appropriately.

CHAIRMAN YANCY: So we have one opinion that says there is residual equipoise and a randomized control trial absolutely has to be done.

We have another opinion that says, yes, there is clinical equipoise, but a randomized control trial may not be the way to get at it. So these are the two opinions we've heard.

Are there other comments about this question?
Dr. Blackstone?

DR. BLACKSTONE: Is it possible to segregate this according to the type of disease we have? Because I think my response to this would be different depending on whether we're talking about the extension of the current FDA approvals, which is to the low risk asymptomatic patient, as opposed to the symptomatic low risk patient as opposed to the high risk symptomatic patient.

CHAIRMAN YANCY: So develop that further. Deal with the symptomatic patient first, what would you say?

DR. BLACKSTONE: If we're dealing with a symptomatic patient, I believe that there may be room

for non-randomized carefully controlled study.

If we're dealing with low risk asymptomatic, folks in the audience say that they are not doing any stenting in these patients. If we believe them, there are no barriers to doing a randomized study, because they said they are not stenting those patients off label.

I'm not sure I believe that. But if that's true then it's a wide open field.

CHAIRMAN YANCY: So we have three reasonable statements that have been made in response to question two. This is the way our discussion needs to evolve.

So please, this is an opportunity particularly for those who haven't yet spoken. Dr. Jeevananadam.

DR. JEEVANANADAM: I would completely agree with the other three that I think we need to do a randomized clinical trial.

CHAIRMAN YANCY: The three were all different.

DR. JEEVANANADAM: I think they all said we should do a randomized clinical trial. I think that one of the main reasons is that the medical therapy

we have now is totally different that this was all based on, especially the statin drugs and the the effects of antihypertension. And as Tony brought up, if statins work after a carotid endarterectomy, they may work very well before carotid endarterectomy as well, especially in asymptomatic patients.

So you are dealing with a totally different patient population who is asymptomatic. And if you look at the advantage of carotid endarterectomy, which was saving one out of 18 procedures over five years, with the new drugs that we may have, it may actually be just as good as the procedures.

So I think we need to include looking at medical therapy.

CHAIRMAN YANCY: So you agree that clinical equipoise exists, and randomized control trials are needed?

DR. JEEVANANADAM: Correct.

CHAIRMAN YANCY: Correct.

Okay, Dr. Hirshfeld.

DR. HIRSHFELD: I will also agree to the clinical equipoise issue.

I am very concerned that it will be impossible to do any kind of adjustment to derive valid data from non-randomized trials. I think there are too many variables that go into the decision to select a patient as being preferable for stenting versus preferable for surgery that would be major confounders of any type of comparison that was not a randomized trial.

CHAIRMAN YANCY: So permit me to say that you are making comments with respect to the not-high-risk asymptomatic patient.

DR. HIRSHFELD: I think I would say it's a generic comment that I think that any comparison of stenting to endarterectomy whether in symptomatic or asymptomatic patients high risk or low risk patients, if the physician is permitted to select the modality of therapy, that that would be a confounder. It would be very difficult to recover from.

CHAIRMAN YANCY: That's a very interesting perspective. Appreciate that thought.

Dr. Weinberger.

DR. WEINBERGER: I agree with the sentiment of

Dr. Blackstone. I have one point I'd like to make, and that is, I believe equipoise exists for carotid endarterectomy versus stenting for the symptomatic group.

For the asymptomatic low risk group I don't think they have equipoise versus surgery. I make, entertain equipoise versus medical therapy, but I think in the asymptomatic low risk group, I think that with today's medical therapy I would be just as happy or even happier to show that there was effectiveness against medical therapy rather than as against carotid endarterectomy.

CHAIRMAN YANCY: A valid point.

Dr. Good.

DR. GOOD: So you're suggesting a randomized clinical trial for that group?

CHAIRMAN YANCY: Yes.

DR. GOOD: And I would agree with that. And I guess one of the questions, we talked of these three groups. The severe stenosis that is symptomatic, there already are two randomized clinical trials that have been published in the last year.

Now they may be flawed, but they didn't show that there was - they didn't show non-inferiority for the stenting.

CHAIRMAN YANCY: Do you have reference to EVA-3S?

DR. GOOD: Yes, EVA and the SPACE. And I think that's a concern. So to say that we should give up the idea of a randomized clinical trial for that group too seems a little bit worrisome to me.

CHAIRMAN YANCY: Point well made. This is the purpose of our discussion.

Dr. Lindenfeld.

DR. LINDENFELD: I agree with that. I think that it is equipoised, and I think randomized trials need to be done. I agree with Dr. Hirshfeld, but I couldn't possibly figure out how to get these equal.

I think it also brings up - I've not reviewed these trials in detail - but we now need to pay some medical attention - or some attention to the medical therapy, I think both pre- and post-enrollment in these patients and whether or not those are equivalent.

They may be, and you all know more about that

than I do, I think. That may have different effects down the line.

So we haven't talked about making sure medical therapy is equivalent in these arms.

CHAIRMAN YANCY: So I have not yet heard anyone express a sentiment that it is appropriate to forego randomized control trials in this area and just focus on non-randomized trials.

Dr. Buckles.

DR. BUCKLES: Thank you, Dr. Yancy. You made some comments earlier about setting boundaries around the discussion, focusing on the reason we're here, and I think those comments were very appropriate and I appreciate that.

I think we have heard some discussion about comparisons with best medical therapy, and this regime, and I think that is an important issue. It's important for science, and it's important for medical practice.

That larger discussion may be beyond the scope of what we can accomplish today. I think we are very interested in hearing those issues.

We really would like to, as you said earlier,

focus the discussion on the questions where we really need immediate advice, to go to the regulatory issues that we have to deal with.

And in that context, the comments that I heard about possibly differentiating between symptomatic and asymptomatic patients in this non-high risk population, that may be something that we would really like to hear more about with respect to the clinical trial designs.

CHAIRMAN YANCY: I think again respecting what can and can't be done, the statements referable to the changes in medical therapy really strengthen the notion that the study should be very classical randomized so that those issues can be accounted for and you can have some protection with randomization.

So the prevailing though I hear around the room is, with regards to number two, there is sufficient equipoise, and randomized control trials should still be respected to generate level one evidence.

And I hear it in almost every scenario that we've discussed.

I'm sorry, Dr. Yaross.

DR. YAROSS: Yes, I don't know if you were going to get separately to the second half of question two, because while that equipoise issue has been established, I think reasonably, the question of barriers is still an important one.

So I don't know if you were going to get to that or not.

CHAIRMAN YANCY: And so duly noted, and we do need to proceed. Because the important, especially to address Dr. Buckle's comment, is to take our discussion about 2a and then go back and capture the first question and say, what can we tell him now about designs that are coming forward that are comparing two active treatments?

And so let's address this issue of barriers. Now what are the current barriers to enrollment in randomized control trials?

Remember we've seen two that are ongoing one that will be completed within months. I didn't get the timeline of completion for ACT I. Maybe someone else was able to sort that out. I saw that the randomization was reasonable.

And there was a third randomized trial, the

three arms set to start once funding is cleared, and that was TACIT. So that's kind of the denominator we have right now in that regard.

So what other barriers to enrollment? Dr. Somberg?

DR. SOMBERG: We heard in post-testimony a number of points, and I don't want to get into - because those were mentioned as barriers, but we're not supposed to talk about what each party told us, and I'm having trouble remembering if that ever came out in open testimony later, because some of it did.

But I wanted to come to this point, there was some interesting trials, methodologies that were mentioned in closed session, and I would be curious to know if my colleagues felt as I did that while randomized control trials are preferential, and they can be done, if someone found the barriers that were outlined to be formidable, this alternative I would personally consider, at least one of those designs, as being possible, and bringing up useful information.

You never know, and we did talk about risk, risk up front versus I think you mentioned that, risk up

front versus risk later on. And that is a very important topic to be taken into consideration.

But I'm not sure, because there was a strong emphasis on randomized control trials, we should say that non-randomized trials are worthless.

CHAIRMAN YANCY: We haven't yet said that, but your points are extremely well taken.

Dr. Blackstone.

DR. BLACKSTONE: So let me try to pose a couple of non-randomized designs that are not exactly like anything we have heard yet today.

One is a cluster randomized trial. In a cluster randomized trial, a given institution does one thing by randomization. Another institution does another thing. So that one ends up with a bunch of patients in one institution operating say in one way, and operated in the other.

Now there is a lot known about that particular trial design, and that is a possible design that might allow increased enrollment. But in that design the sample size tends to be enormous. These are designs used where you randomize schools to certain

treatments; where you actually randomize countries to economics; and it's a huge thing. However it is very relevant to the idea of including everything in practice. So it is often used to test things like EMR versus no-EMR, or clinical things.

So that that is a design for which there is a lot known about the sample sizes, and in general that really inflates hugely your sample design.

But that would be a completely different kind of design as a cluster type of design. So that's one possibility.

We also heard in the open session the idea of say a propensity-adjusted type of design where you have a very careful inclusion criteria. And one could imagine trying to keep say various risk factors in balance and so on.

I'm not sure that one needs to do that, because that's what your propensity score is trying to do. But that is a design that could be used, particularly might be valuable if it included the medical patients as well as the surgical patients.

And while it can't adjust for everything, only those things that you have measured, it's a

reasonable way to do a non-randomized trial, especially if it is otherwise conducted exactly like a randomized trial, and has the advantage of including more of the whole real life spectrum.

Having said that, I didn't gather from anything today a quantitative idea of what the barriers are to randomization other than the usual barriers for any randomized trial, which is the physicians and surgeons treating these patients, and patient preference, and the important ingredient of the payers.

So those are the three things that I heard today, no quantification of those. But I'm not sure that those barriers can be broken down by anything that we might discuss or be able to fix. And I think it's very different say from our discussions of April 5th where there were some specific recommendations that we could make that broke down barriers for randomization. And I haven't heard anything today that helped me know how to break those barriers besides totally new designs.

CHAIRMAN YANCY: So Dr. Milan, you had your hand up first.

DR. MILAN: I too favor randomized control

trials. Everybody seems to think that they are in principle a good idea. I want to point out that at least one of the trials that we are looking forward to having the results hopefully pretty soon is the CREST trial which has been around since 1999, and there have been questions raised about it, a randomized trial that took eight years to complete enrollment, and whether or not those patients can be compared, those from 1999 to current.

So I think there is a tradeoff really between lengthy randomized control trials with barriers that seem that they are going to be difficult if not impossible to overcome, and possibly alternative trial designs.

And I think it really goes back to what Dr. Somberg touched on, and what was brought up in the FDA presentation, which is, a sponsor who adopts some non-randomized control trial design is really accepting a higher level of risk, because although compensatory score analysis can adjust to some degree for differences in the populations, if the populations are too divergent, you could make whatever adjustments you want but the

panel that will review that data will be suspicious of the results.

CHAIRMAN YANCY: Point well made.

Dr. Gravereaux.

DR. GRAVEREAUX: In addition to what was earlier said about barriers, unlike say Dr. Comerota's institution where, I'm a vascular surgeon as well, so we maybe do 50 percent of our carotid stents in the institution.

I think any new trial design should mandate a multidisciplinary entry point for the patients. It would encourage collaboration, identification of what I think importantly is an anatomically high risk for carotid stenting patient, which I think is somewhat underappreciated by people who have less experience with the carotid stenting technique, and that might - and that is an interesting point about how to divide the patients into maybe a surgical arm versus an endovascular arm.

So that is one way to hopefully reduce some of the barriers to entry.

Unfortunately, with all the registries out

there currently, without eliminating them entirely, there's always going to be those who will take their patients through the path of least resistance, be it to a registry because the entry criteria might be a little less rigorous, or because they don't have to go through a multidisciplinary panel.

But at this point I think that might be a crucial point to continue to include in any new trial design.

CHAIRMAN YANCY: Very good points.

Dr. Abrams.

DR. ABRAMS: Actually, I was just going to echo what was previously said. I mean the fact that off-label usage was not a barrier. And I think it's very important for the FDA to find out what the barriers are.

I presume it's the economic issue that's the barrier. And I think in order to - before they start on any kind of trial this kind of thing needs to be resolved in the way that was just suggested.

CHAIRMAN YANCY: That's very good input.

Additional comments? Let me see if I can

frame what I heard regarding barriers. Off-label use is not a barrier. Economic considerations vis-a-vis payers and reimbursement for participation in these trials is a barrier. Physician preference is a barrier. Patient preference is a barrier. And I've heard some fairly sobering statements, particularly with regard to physician and patient preference. There really are no features of design that we can invent that would overcome that. It seems as if the best way to facilitate enrollment is to address perhaps the payer issue, or something else that we have not yet uncovered.

Dr. Blackstone.

DR. BLACKSTONE: So could I add one more barrier? The other barrier is the short term follow up with these patients that affects greatly - it is the whole problem of sample size in these patients. Because the effective sample size is not the number of patients you enroll; it's the number of events that occurred.

And so long as we're focused on 30 days and one year, that actually creates a barrier by inflating the number of patients to treat whereas even if it went for two years, the randomized trials are going five; but

even if it went for two years it would greatly diminish the sample size needed.

So, we should think about that design issue itself as a barrier.

CHAIRMAN YANCY: So that's actually the second parameter that's been commented upon that facilitate enrollment, that is, increasing the window to capture more events.

And I don't want to dismiss Dr. Lindenfeld's comments about having events carefully adjudicated by neurologists, because it looks like that too has some impact on the sample size.

And I see mostly nods that are going along with that.

So where we are now is that we've agreed in aggregate that the panel continues to have equipoise about this issue; and we believe that more data are required; and that the majority of us believe that those data should be in the form of a randomized control trial.

We've also said that there are specific barriers that we have enumerated a list. And we've just

touched on one or two modest approaches that might impact that, recognizing that the big issue is the payer.

So we're at a point now where if we assume that the current randomized control trials are moving forward, and will yield evidence, and now the agency has a finite task of adjudicating PMAs for carotid stenting methodologies, and are wanting to understand how to entertain the non-randomized trial.

What I've heard so far is a clustered randomized trial. I've heard a propensity adjusted design. I've heard a requirement for a multidisciplinary involvement. And I've heard a statement that no matter what the non-randomized trial is, we can't sufficiently control for bias.

So that is a summary of where we are now on the first two questions.

And so let's continue to develop that and see if we can give the FDA some more input.

Dr. Naftel.

DR. NAFTTEL: I'm sure everybody has answered this, but I just want to make sure that I understand.

Are we talking about equipoise of stenting versus surgery or stenting versus medical? Because I've heard Dr. Blackstone say medical and other - I'm not sure which thing we're discussing.

CHAIRMAN YANCY: Well, actually both sentiments have been expressed, that there is some equipoise about stenting versus surgery. And I think Dr. Comerota really captured that nicely in his opening comment.

But I think Dr. Weinberger also said that there is, particularly for the not-high-risk asymptomatic patient equipoise for surgery versus medicine.

DR. NAFTTEL: So should we make sure that we make that distinction, that we are addressing both things in this discussion? It's like part A and part B, isn't it?

CHAIRMAN YANCY: We are indeed. But what we are also doing is taking a bit of a turn at the advice of Dr. Buckles acting in place of Dr. Zuckerman that we have to get this focused a bit on PMA applications that are coming forward.

And so great sensitivity to the medical therapy issues, and again, I think a lot of that gets built into what kind of margins we are willing to accept.

But we really need to keep moving with regard to these applications that are coming forward.

DR. NAFTEL: So the answer then is stenting versus surgery?

CHAIRMAN YANCY: Yes.

DR. NAFTEL: Okay.

CHAIRMAN YANCY: Dr. Haley.

DR. HALEY: So just to clarify part B of this question, what are the current barriers, I guess is the FDA requesting opinions from this group regarding what the impact - I mean a potential barrier to enrollment of ongoing randomized clinical trials would be the beginning of a bunch of non-randomized control trials that would then compete for these patients.

CHAIRMAN YANCY: So we've heard comments today about this very issue of competition, and we should probably go ahead and develop that some.

Dr. Yaross.

DR. YAROSS: Yes, I think that while the issue of competition between trials is practically a reality in some circumstances, I think we get back to the regulatory arguments as to whether or not the agency can decline one trial because of its impact on the others. Each sponsor needs to be dealt with independently I believe.

CHAIRMAN YANCY: I think we did hear an opinion expressed by Dr. Zuckerman that there really is no leverage to put everything on hold pending another trial.

Dr. Somberg.

DR. SOMBERG: I don't really think there is too much of an issue here, because the timeframe, where one frame is ahead of the other, and there is a certain momentum.

So while one of the studies we heard was unfortunately not started, that was the one with the medical therapy arm, the others are moving along.

So I would say, especially with the reticence of some people in starting their studies, even a single arm study, I don't think that is going to be an issue.

So I don't think that should - we have to worry about that at this time, and it shouldn't discourage us from pretty much encouraging randomized trials, but saying nonrandomized trials are potentially feasible but have their problems.

CHAIRMAN YANCY: Dr. Blackstone.

DR. BLACKSTONE: Let's go back to this barrier where you have 100 institutions or more involved in these trials.

And so I'd like to know from FDA whether it is possible to have a design whereby multiple companies go together and do a single trial that is in these 100 things designed exactly the same. Is that really - must one in fact have each one independent?

DR. ZUCKERMAN: No. Dr. Blackstone is making an extremely critical point. It is possible to do this combined proof of principle, a multiple proof of device trial concept.

In fact when FDA first planned the CREST trial with NIH and CMS in '99, we advised the developers of this trial to try to include multiple companies so that we wouldn't run into this conundrum.

Unfortunately it didn't work out because it's not tradition for companies to work together perhaps, and to think about how certain barriers can be overcome.

But from the regulatory perspective in multiple areas where we need proof of principle trials, and you've been on these panels, whether it's PFOs, carotid stents, or atrial fibrillation, having multiple sponsors in one trial is acceptable.

CHAIRMAN YANCY: Additional comments now.

The issue that we're addressing is the barriers, the impact the barriers have on trials, and how non-randomized control trials can be designed, or other trials can be designed to overcome this.

Dr. Milan.

DR. MILAN: Just a follow up. This brings to memory the atrial fibrillation ablation discussion that we had before, which going into that discussion I had imagined that it would be possible to propose that different sponsors share controls.

But it turns out that the timing of the different enrollments and the issues of the trials was such that it wasn't going to work out. But here is a

situation where you could imagine that the sponsors could each have a pooled control, even perhaps medical or surgical, and thereby change the ratio of enrollment between CEA or a medical therapy, either a control group and an investigational arm, in such a way that it would reduce the total number that is required for each sponsor.

CHAIRMAN YANCY: So would that control be a new cohort, or would it possible be the CREST data?

DR. MILAN: Well, actually I was thinking more of the TACIT trial which has yet to begin enrollment, and even I think we heard they're in some ways shopping for sponsors, and they are going to include a medical therapy arm and a surgical arm too. So it seems that might be one way to do it.

CHAIRMAN YANCY: Dr. Gravereaux.

DR. GRAVEREAUX: I just wanted to respectfully disagree with Dr. Somberg with the impact about some of the registry trials for lack of a better term impacting on enrollment for the randomized control trials.

I think being part of both and seeing my colleagues wrestle with these issues, I think again the

path of least resistance wins out a lot, and patient demand and what referring doctors expect play into part, I think, as another barrier. I think the reality is, despite what we'd like to believe, or maybe the data presented, it's probably not that way in the real world, and it might limit enrollment.

The TACIT trial also with the third arm is I think a very pivotally important trial, because it addresses the subissue, the undercurrent of the whole sort of rumbling we're doing. We need to reinvent ACAS and NASA with better medical therapy, and tear down the house and start from the foundation before we even address these issues.

On advice of our other colleagues we need to narrow it down. But these other ongoing registries and trials may actually impact the TACIT ability.

Dr. Ken Rosenfeld mentioned the difficulties in getting people even to be randomized just to the CEA versus stenting in the ACT trial. I felt the same pain in some ways of trying to get people to appreciate the science and the academia behind the CREST enrollment. And imagining a medical arm on top of that with the

other ability to go across town, across wherever. I'm from Boston, and we got a lot of people doing this, and vying for these procedures.

Maybe in other areas it's a little more captive audience. But I think we need to, if we want the data, we have to be part of the solution to get the right amount of patients and clean data.

CHAIRMAN YANCY: Well, there is concern that trials say for example like TACIT may be the perfect design that is hopelessly futile.

We did hear one element today that I don't know that we expanded on, which was in CARESS, where patients that were candidates for CREST represented an exclusion criteria. And so maybe we can't proscribe that.

But we can certainly say that is a reasonable design feature to exclude patients that would be candidates for a really rigorous randomized trial. I'm just throwing that out there.

Dr. Johnston.

DR. JOHNSTON: I'm struggling with the length of time to do a randomized control study, especially in

some of these difficult areas, with the requirement to have a least burdensome approach for the manufacturers.

And I wonder if I could have a comment on how the FDA would see trying to balance that. Because the proposals we are hearing here are going to be very long burdensome studies, not non-burdensome.

DR. ZUCKERMAN: Okay, we've heard today that certainly this is a very challenging area for manufacturers. No one is going to discount that.

But by the same token we also need to recognize at the end of the day that we want to be able to establish with reasonable certainty the right answer for patients, and