

Enrollment of 2,500 randomized patients, is expected to finish in mid-2008.

ACT I is a trial sponsored solely by Abbott. It uses the EXACT system. We are enrolling 1,658 patients. We have close to 400 patients enrolled.

Just a brief overview of our commitment to the carotid therapy. In addition to the trials used for the pivotal - pivotal trials used for approval we've done a considerable amount of work in these high risk surgical patient cohorts in terms of post-market with over 10,000 patients enrolled. And we have a policy of sharing this information in almost real time with the medical community.

If you look briefly at the CREST and ACT I randomized studies, the CREST study was first initiated in 1999. The ACT I study in 2004. They are both randomized. They are both compared to surgery. The randomization ratio is slightly different.

One major difference is CREST enrolls octogenarians, where ACT I does not.

The importance of randomized trials, I think the biostatistician from FDA addressed this quite

eloquently. Just high level summarize. Randomization removes the potential bias in the allocation of patients to surgery and stenting. This can be a bias both conscious or subconscious.

But randomized trials tends to produce comparable groups, especially in unknown prognostic factors. And the validity of statistical tests are guaranteed.

So as stated, potential challenges to randomized trials are the length of the enrollment trial, the site availability, investigator and participant acceptance.

So let's look at the history of the CREST randomized trial. There were many early obstacles to the CREST trial to their ability to randomize. Initially when the trial was first started, CMS reimbursement for participation in the ID study was not available at the onset of the trial. And bioprotection devices were not available, and European studies were showing that this dramatically decreased the number of events per patient. So CREST basically kind of held enrollment until we could get embolic protection into

the device.

There weren't very many really experienced sites or clinicians. So there was a relatively large roll-in period for patients, 20 lead-in patients done before a site could randomize patients.

The original trial design included symptomatic patients only, which represents only about 20 percent of the normal risk population. There was a slow ramp up of sites.

CREST trial enrollment has increased to current levels, approximately 600 patients per year, after the early trial start up obstacles were overcome.

The current ACT enrollment, the CMS trial reimbursement was available when we started our trial. Embolic protection devices were available. The lead-in requirements have generally decreased, as there is a greater number of experienced carotid interventionists.

Asymptomatic patients were included, so 80 percent of the normal risk population was available.

A sufficient number of experienced sites for participation in randomized trials. And right now ACT I is enrolling approximately 250 patients per year with

about only 35 randomizing sites.

So what about the issue of site availability? Currently approximately 125 independent sites are enrolling CREST and ACT I. From our statistics we believe there were over 500 sites performing CAS currently. Therefore we believe there are a large number of untapped sites that could be used for new nonrandomized trials.

So in terms of the normal risk trials, randomized trials can enroll in a reasonable time frame we believe. There is a sufficient number of sites available to support randomized trial designs.

Randomized trials are the cornerstone of evidence-based medicine. Physicians and investigational sites should be encouraged to participate in normal risk carotid randomized trials.

So in conclusion, competing nonrandomized trials would undermine the completion of the enrolling randomized trials. For new therapy approval reimbursement requirements should be level one evidence as provided by randomized trials.

We believe multiple trials are beneficial.

Abbott is the sole industry participant in CREST. Abbott initiated the randomized ACT I study.

Fair balance for study sponsors, as FDA required randomized trials for product approvals in the normal risk patient populations for both Guidant and Abbott.

Abbott Vascular believes that nonrandomized trials should not be allowed to initiate until the randomized trials complete enrollment. We believe that this will ensure good science, provide evidence-based medicine, and address public health policy issues.

And per CMS randomized trial evidence will likely be needed to support a positive coverage decision for normal risk carotid patients.

Thank you.

CHAIRMAN YANCY: Thank you very much.

We will proceed with the next public speaker, Dr. John Rundback. If you will identify your conflicts and your affiliation please.

PRESENTATION OF SOCIETY OF INTERVENTIONAL RADIOLOGY

DR. RUNDBACK: Sure. My name is Dr. John Rundback. I'm an associate professor of radiology at

Columbia Presbyterian, director of Interventional Institute at Holy Name Hospital.

I'm currently a paid consultant for Medtronic and for EV-3 related to non-carotid protocol design.

On behalf of the Society of Interventional Radiology Foundation and the cooperative alliance for interventional radiology research, clinical trials network, let me thank the panel for allowing me to present to you the TACIT trial, the trans-Atlantic asymptomatic carotid intervention trial.

TACIT has been developed over the past several years by deeply collaborative and interdisciplinary group of interventionalists, surgeons, and neurologists, and you can see here that the study leadership is comprised of many individuals who have been deeply invested in treating patients with carotid disease. I'm the principal investigator of this trial. The study chair, neurology chair, is the Clinical Coordinating Center, and other study leadership is shown on this slide.

We have a number of subcommittees which are looking at critical intermediary endpoints as well as

critical components of development of the trial, as well as selection of sites. And those are shown here on this slide.

Very interesting, and marked here, is economics and quality of life, by Jonathan Michaels in the UK who has done extensive work in this area, and in neuropsychology committee, which is a unique component of TACIT.

Much of this background has already been provided, does not need reiteration. Suffice it to say that clearly carotid disease is a major public health problem, and that certainly asymptomatic carotid disease remains an area in which therapy remains somewhat undefined.

Interestingly, and it's come up earlier in this panel discussion, the real role of current or contemporary medical therapy such as statins and anti-platelets may have an impact on overall outcome in this patient population, and certainly we know that these medications in other clinical arenas have substantially affected outcomes and major adverse clinical events.

It's certainly plausible that modern optimal

medical therapy will stabilize atherosclerotic plaque in comparison to revascularization which resolves the underlying stenosis. There has not been consensus from existing trials regarding optimized treatment, particularly in regard to utilizing a medical therapy cohort for comparison.

It's also interesting to note that the asymptomatic population is both the largest treated population in the United States but more importantly it's the largest patient population that currently is not offered revascularization, suggesting that there is a large population that might be served by a trial which evaluates a medical therapy arm versus a revascularization arm.

This data has already been presented, both for asymptomatic trials as well as symptomatic trials. ACSD is the most recent asymptomatic surgical trials which showed in a comparison of endarterectomy versus medical therapy overall roughly a 5 percent reduction in all strokes and perioperative deaths out to three years.

However, it is important to note that ACSD had marked limitations, the most notable of which was

incomplete medical compliance, and a lack of a targeted endpoint for medical therapy.

You see here during the course of therapy - during the course of the trial initiation only 17 percent of the patients actually were compliant with antilipemic medication, even by trial's end, and only more than two-thirds of the patients, slightly more than two-thirds, were actually taking antilipemic medications.

Importantly, as I said, LDL levels were not monitored, or have not been reported, to see if adequate LDL lowering was achieved in these patients.

An interesting observation is that while there was a reduction in stroke, there was not a reduction in stroke and/or deaths, which is actually an interesting observation.

It is also notable that in trials of medical therapy and populations with atherosclerotic disease and not specifically carotid disease, that clearly optimized medical therapy can reduce the risk of stroke. Here you can see a relative risk of stroke in patients who receive the anti-platelet therapy clopidogrel on CAPRIE.

Simvastatin as a statin agent in the 4X trial. Similarly reductions in patients receiving lamopril and anti-platelet therapist group.

We feel that again there is a large population at risk that would benefit from further evaluation of asymptomatic trial, in which a medical cohort is evaluated.

This just gives you an idea, from our estimates of total number of patients who have strokes each year, the number who actually do have carotid disease, our estimation of the number of patients per year who are potentially valuable within a trial.

As we just heard from Dr. Fink there are certainly a potentially large number of sites participating in these trials as well. And we strongly believe that a randomized trial can be conducted with reasonable enrollment.

TACIT: TACIT is a three-armed trial specifically designed to answer the question whether optimized medical therapy, with or without revascularization, either by carotid or endarterectomy or stenting, can reduce the risk of perioperative

mortality and the five-year risk of all strokes and neurocognitive decline.

As you can see this is a randomized unblinded three-armed trial for patients who are eligible based on duplex evidence of more than 60 percent carotid stenosis, with a second confirmatory imaging examination as I will show.

The three arms offer medical therapy alone, which will be targeted optimum medical therapy with close monitoring of LDL and other risk factor modification.

Optimum medical therapy with carotid artery stenting and optimal rate of endarterectomy.

You can see here, this matrix of the trial design, that actually, after accounting for some attrition, about 3,700 patients are anticipated to enroll.

The trial is designed to show superiority of revascularization compared to best medical therapy at 80 percent power, and non-inferiority at 80 percent power, and a delta at three, doing each form of revascularization, that is, endarterectomy and carotid

artery stenting.

By the way those event rates are somewhat based on the event rates that were observed in ACST with some adjustment for neuropsychological endpoints observed in other clinical trials.

There will be strict monitoring of medical compliance and cardiovascular risk factors, which is unique to TACIT, with a well developed medical and risk reduction plan utilizing statins as shown here, aspirin and periprocedural Plavix.

There will be forced therapeutic targets, particularly for lipid lowering, based on the baseline LDLC.

Similarly blood pressure management will be rigorously controlled with additional agents after our initial introduction of an ACE introduced in a systematic and predescribed fashion.

Patients are eligible as I said earlier with a more than 60 percent ICA cyanosis using a velocity criteria of 125 centimeters per second.

However, to make sure the patients can remain candidates for either endarterectomy or stenting, a

second confirmatory imaging test is necessary to make sure that they can be appropriately randomized.

TACIT is an asymptomatic trial, defined as no prior event attributable to the target lesion within six months prior to randomization.

There are a number of exclusion criteria which are not unique to this trial but probably worth mentioning.

Certainly patients need to be able to participate in the trial. We're studying adverse sclerotic disease. We do not have an upper limit at this time so octogenarians can be included in the trial.

As noted we need a second test to make sure that they can be stented or undergo endarterectomy. We don't want patients who have a very anticipated stroke risk due to non-carotid related factors.

This shows here some of those criteria which might prevent patients from randomizing due to a high risk for either surgery and/or endarterectomy - sorry, surgery and/or stenting.

Since it's anticipated that some percentage of patients who were originally assigned to medical

therapy will have progression of disease and/or have a documented TIA or stroke or evolution, TACIT does allow for crossovers in patients who have progressive disease.

This is based on the idea that the putative mechanism of medical therapy is plaque stabilization. And there are patients who progress in their stenosis from less than 80 percent to more than 80 percent using a PSV criteria of 250, or from initially more than 80 percent a trickle flow are allowed to cross over to revascularization.

Similarly patients initially assigned to medical therapy who experience a TIA or a documented neurologic event can cross over to revascularization. So in reality this will evaluate strategies of initial medical therapy and potentially deferred revascularization versus randomized initial revascularization with stenting or endarterectomy.

Obviously separate protocol analysis will be done. The study is powered for randomization based on intent to treat.

There are major secondary endpoints which are unique to TACIT. You can see here, we're doing

neurocognitive function testing using limited cogno-
testing on all patients where there is a component of
primary endpoint.

In addition a comprehensive battery of
neurocognitive, neuropsychological testing will be
performed on 400 patients. We have a very comprehensive
neuro-cognitive group both in Europe and U.S. who are
collaborating in developing this, to develop the tools
for this.

Health economic analysis is included. Like I
said this is conducted out of a group in UK, and we are
doing extensive duplex evaluation with the plaque
characteristics looking both at de novo risk of events
as well as procedural risk.

These are the two tests that will be
performed in the entire TACIT group to evaluate
neuropsychological function. These tests were selected
because they've been used in a number of prior stroke
trials; can be administered easily by a surrogate; and
are reproducible and validated.

Here is some background regarding the
rationale for using neuropsychological testing within

TACIT. You can see here that certainly asymptomatic may not be asymptomatic. The cardiovascular health cognition study showed that patients who have so-called asymptomatic carotid stenosis may indeed have evidence of vascular dementia or impaired cognitive function, cognitive decline.

The study similarly showed lower performance for attention, psycho-motor speed attention, memory and motor function in patients who have carotid artery stenosis.

Recently in a carotid artery surgery dataset from Spokane, Washington, there is evidence that there is improved neuropsychological function and vascular improvement in a subset of patients who undergo stenting. Although interesting on that study was the patients who had severe, greater than 90 percent, stenosis. It was a very interesting concept in that we think of the risk of stroke in patients with prior disease to be predominantly embolic, but there may be an element of hyperperfusion which continues - which contributes to neuropsychological domains and depression.

The health economic analysis conducted by Dr.

Michael's group is looking at increment cost-effective ratio using resource use forms, and will ultimately express the incremental benefit in terms of cost for additional quality adjusted life years.

A number of valuation scales are being used, with the health-related quality of life being the primary scale which will be used for the primary analysis.

Secondary analysis will include the SF-36, side effects and symptom distress index, and SF-6D.

In addition other scales of neurocognitive function will be used as I mentioned earlier, but not within the health economic analysis.

CHAIRMAN YANCY: Are we just about to the conclusion?

DR. RUNDBACK: Yes. Plaque characteristic is very important and quite unique. This is an example of an echolucent plaque which is suggested may be a high risk plaque. We have a group from Giorgio Biasi in Italy, and Andrew Nicolaides who have done pilot work on this which show that plaques can be evaluated, and plaque stabilization and plaque quality is predictive of

events. This is going to be looked at in a very detailed fashion in TACIT.

We have a whole host of secondary and exploratory endpoints, many of which we don't need to describe here other than to say that uniquely myocardial infarction will be evaluated as a secondary endpoint.

And again, some of the slides that have been provided to the panel, but the tertiary and exploratory endpoints are available as well.

Again, we have 3,700 patients as our enrollment matrix. We do believe that given the current climate, the number of patients and number of sites that we can reach these goals.

I think that's all. Thank you.

CHAIRMAN YANCY: Thank you very much.

We will proceed with our third speaker, Dr. Chris White, who will give us our last morning presentation.

Please identify your affiliation and conflicts first.

DR. WHITE: Thank you very much, Mr. Chairman, and panel. It's a pleasure to be on this side of the

table for a change.

I'm representing the Society of Cardiac Angiography, and the ACC, cardiovascular and cardiology organizations. I do not have financial conflicts, but my travel expenses today were paid - actually they're going to be paid by one of those two groups, I'm not sure which; one of them.

I wanted to explain besides conflict of interest which financially I don't have, I have significant bias, as I think many of us sitting around this table do today.

I am an interventional cardiologist. I have been practicing carotid stenting since January of 1994. I'm committed to carotid stenting. I think it's a good thing to do for my patients.

I was the national PI for a trial, so that I helped to enroll and organize that trial, and I do currently participate in two randomized control trials that are being conducted.

I'm concerned about the population of the panel, and whether or not this question today can get a fair hearing. I really don't mean to impugn any

individuals on the panel, but I notice that there really is an unbalanced makeup on this panel. And I'm surprised that there is not an interventional carotid stenting cardiologist on this panel.

If we look at the most recent demographics of this procedure, the majority of physicians who place carotid stents are interventional cardiologists, somewhere in the nature of 60 or 70 percent. So the lack of that viewpoint I think is significant.

I think like mom and apple pie randomized control trials are an excellent source of information, but they are not an exclusive source of information regarding clinical trials. There are many precedents for this group and for the FDA to approve devices with alternative non-randomized trial designs. And I think that the panel should ask themselves what actually is special in some way about the average risk carotid patients that would only require randomized carotid trials that would actually exclude any other methodology.

Again let's not kid ourselves about randomized control trials. They are important. They

provide good clarity for questions. But patients are highly selective. NASCET and ACAS which were landmark trials you've talked about today do not describe the outcomes in our hospitals today for carotid endarterectomy. They just simply do not.

This has been published. This has been looked at. And it's not my experience.

As has also been mentioned, the randomized trials take a long time. This is a field that rapidly evolves. The equipment changes on a quarterly basis. So looking at long trials is fine, but remember that the beginning of the trial does not describe the same patient outcomes as the end of the trial. And then perhaps most important, the investigators that are chosen for these trials are highly selected, highly skilled individuals that actually don't represent community physicians during these procedures, very similar to surgical procedures as well.

And so one of the solutions for that has been to require postmark surveillance trials, and that's one way to extinguish that problem. But also looking at this on the front end, more widely distributed access to

this device, among the community physicians, might also help us to understand the safety of these trials.

Now there are alternative trial designs that are acceptable, that are concurrent control designs. There are cohort control designs that you've heard about this morning, and there are registry objective performance criteria trials that have been used extensively in the high surgical risk population.

Now there are precedents for device approvals for surgical accepted gold standard procedures for percutaneous or endovascular approaches. The AAA stent grafts are the best example. These devices have all been approved with concurrent control, non-randomized control designs: endarterectomy, gold standard, surgical treatment has been largely replaced, or at least alternatively replaced, by endovascular treatment.

Why is it different for carotid disease? Why would we be inconsistent and not allow randomized control trials to collect some data on patients of average surgical risk.

There is a unique feature that is available for carotid patients, and that is, this is the only

endovascular bed or surgical vascular bed, that actually has a guideline requirement. There actually are guidelines that tell us that we have to achieve 6 percent or less outcomes for symptomatic patients, or 3 percent or less outcomes for asymptomatic patients in order to achieve benefit.

There is no other procedure that has these thresholds predetermined and accepted by clinicians. Why don't we use these OPCs for approval? What would happen if a randomized control trial was done that showed that carotid stenting was as good or better than carotid endarterectomy but that 30-day death and MI rate exceeded those guideline recommendations?

Well, this happened with CAVITAS trial. The CAVITAS trial had a 10 percent event rate in both arms. Both exceeded the 6 percent. What does that do for you? What does that tell you about that device? Wouldn't you rather rely on carotid stenting beating the threshold of less than 6 percent in symptomatic patients, and less than 3 percent in asymptomatic patients in a broad population of real-world patients to understand the safety and efficacy of that device.

In conclusion, carotid stenting is an FDA approved alternative in high risk patients, and I believe will likely become an option for average surgical risk patients. Any attempt to gather more information in a broader sample of patients from more inclusive operator sample size will be of value when you consider the context of data in randomized control trials.

Carotid stenting is a lesser operation than our patients deserve. We should be aggressively seeking ways to define the population that will benefit from this procedure, not restricting access to only those patients who can qualify for randomized control trial.

Thank you.

CHAIRMAN YANCY: This completes all of the scheduled speakers for our morning public hearing.

In the interests of time we had planned to start the next session promptly at 1:00. So we have a limited time for questions, but we need to get lunch done so we can resume our meeting at 1:00.

So if you have a very focused question for one of the presenters, please proceed now.

Dr. Somberg.

DR. SOMBERG: Sorry, but I do have an important question. I thought it was the TACIT, if I'm correct on the acronym, study presenter, it was a very elegant study. But I wondered if there were concerns by that consortium that some types of studies might interfere with the randomization of that particular trial.

Are there such fears? And what do you think could be done to allay them, say as the last speaker said that there would be some credence given to non-randomized control trials in this field. Would that interfere with the completion of the study?

DR. RUNDBECK: Well, I think there is two separate questions there. Certainly we believe the randomized trial is critical, particularly a randomized trial that includes a medical cohort.

And none of these other trials or the comments of the last speaker are relevant in this regard in which we are talking about stenting versus endarterectomy, and the idea this might exceed a standard. It may well be in a trial that the medical

therapy arm also exceeds this standard. So I think that certainly with regard to that that's not so applicable.

We do believe that we can randomize the trials. The trial is now enrolling, symptomatics are enrolling at a very rapid clip. There is no bias introduced in this design. So.

CHAIRMAN YANCY: Thank you.

Dr. Comerota.

DR. COMEROTA: John, very elegant study design. Question: Is atherosclerotic disease versus recurrent stenosis being stratified and specifically addressed? And what about stratification by gender?

DR. RUNDBECK: Thank you, Dr. Comerota.

So actually this is designed for evaluation people with de novo atherosclerotic carotid artery cynosis. It is not designed to evaluate patients with re-stenosis.

As far as stratification, we obviously have secondary endpoints that include stratification by a number of factors, both host factors and procedural factors and biochemical factors, which will be part of the secondary analysis.

And we actually have secondary power analysis for those comparisons, but it's not part of the primary endpoint.

CHAIRMAN YANCY: Dr. Good.

DR. GOOD: Just a quick point of clarification for the TACIT study. By the way congratulations also on an elegant design.

This study is ongoing from what you said, and you are anticipating five years. You also indicated that recruitment was going reasonably well at this point.

Are all those points true?

DR. RUNDBECK: Well, actually there is no recruitment yet. TACIT has been a trial in development, and actually was submitted to NINDS about a year ago - actually more, about a year and a half ago - which delayed the actual implementation of the trial.

It was not approved at that point by NINDS, and part of it, actually in your original slide show, 2,500 patients in two arms. Part of the problem in submitting to NINDS was there were budgetary constraints. So we had made it a two-arm trial to try

to meet the budgetary constraints. And the major complaint was it needed to be a three-armed trial which is how it was originally designed. Our intent, quite honestly, is to go back and work with industry, since this is an industry funded trial. To be quite pointed we've actually had conversations to some extent with FDA and some CMS about how we might accomplish this, and get a sufficient number of device implants to ultimately potentially support market labeling for some devices.

DR. ZUCKERMAN: Okay, Dr. Rundback, can you clarify your last point a moment? In your trial design how many different stent types would you consider?

DR. RUNDBECK: Well, Dr. Zuckerman, actually in part based on conversations we have had, preliminary conversations with FDA, it is our hopes that we can have three different stent designs with the embolic protection devices utilized within TACIT.

We don't want to have too many designs, because we are concerned about operator experience and exposure which can obviously compromise final outcomes, as you say for instance in EVA-3S.

On the other hand we need to make sure there is a sufficient number of device implants so it's reasonable for industry to invest in this trial.

DR. ZUCKERMAN: Right. I think that is an important point to keep up in discussing this morning the burden to individual sponsors.

There is no FDA regulation that precludes for a major trial like this several sponsors sharing costs working together to really address both of Dr. Somberg's points, which is to show both proof of principle, and an update of proof of individual device.

CHAIRMAN YANCY: Other comments or questions to any of the presenters?

Thank you, Dr. Lindfeld. And I would congratulate you on the design as well.

Dr. White, let me raise just one question. We've heard a fair amount today about recruiting patients, and about the number of available centers.

One of the statements made in the consensus document is outlining criteria for the practitioner, or for the person performing the stent placement. Are you of a mindset that there are a sufficient people who have

reached the bar that you outlined in this consensus document vis-a-vis the number of procedures, and the technical skills to do this?

DR. WHITE: Absolutely. The - in fact the postmarketing surveillance trials now have penetrated very broadly into the community hospitals. And enrollment have been large number of patients with postmarket surveillance trials.

These postmarket surveillance trials are ongoing, and they are not cannibalizing randomized trials. So the special interest in trying to keep randomized trials going are scaring you about not being able to randomize. We enroll in randomized trials. We enroll in postmarket surveillance trials. I could easily enroll in non-randomized trials.

Many patients do not qualify, as you well know. In any randomized trial they have narrow entry criteria for these populations.

I have lots of patients who I can put into a non-randomized trial, and would have no problem participating in a non-randomized trial that was a priori set up to not cannibalize. You could set up a

criteria as CARESS did to say that anybody who qualifies for this randomized trial will not enter this non-random. No problem with that. There are plenty of patients out there.

CHAIRMAN YANCY: So there are enough patients, enough sites, and enough qualified operators?

DR. WHITE: Absolutely.

CHAIRMAN YANCY: If there are no other questions, then we will break for lunch and resume exactly at 1:00 p.m. Thank you.

(Whereupon, the above-entitled matter went off the record at 12:12 p.m. and resumed at 1:05 p.m.)

CHAIRMAN YANCY: Thank you to everyone for respecting the schedule and reconvening so that we can resume our meeting. A number of the panel members have tight connections this evening, and we'd like to have a critical mass to do due diligence for our discussions. So that's the reason for pressing the time issues.

We will now proceed with the second open public hearing portion of the meeting. Public attendees

again are given an opportunity to address the panel to present data, provide information, or express views relevant to today's meeting agenda.

We have five speakers scheduled for this session. Each speaker has been allotted a maximum of 10 minutes to speak. In the interests of time, we ask that each speaker be as brief as possible, and that the panel again will hold all questions until after everyone has presented.

The speakers are Drs. Zweig, Baccarat, Szwalek, Irene Katson, and Dr. Kim Rosenfeld.

The first speaker will be Dr. Rodney White. Please identify any conflicts, any disclosures that you think are relevant, and your current affiliation.

DR. WHITE: Thanks for the opportunity to address the panel.

My name is Rodney White. I'm a vascular surgeon from Los Angeles. I'm here representing myself, and I have no commercial support for this presentation.

The topic I think is relevant though in the experience that I have had particularly with CARESS that I'd like to review with you and then make a proposal to

answer this question I think is relevant. And the obvious question is, the evidence-based guidance.

My conflicts are, and I will present the CARESS data briefly, is, I'm past president of ISES which had an investigator IDE, for that trial. I'm a vascular surgeon. I make my living doing interventions, particularly vascular interventions. And I'm a consultant and adviser for several manufacturers. But, again, none of those have supported my attendance today.

The issues are, and I think a primary point is, is randomized trial an appropriate and only endpoint for carotid interventions? And in that regard, the randomized model came from drug trials, but in this particular division for devices I think the model is different, and to make an exception to that would not be any change. And there's sort of been an air in the room that this, we're doing something different. We're not, for the device trials in fact, randomization has not been a good prototype. Endoluminal grafts was mentioned by Chris White as an example of that, aortic valve technology.

Many of the device trials themselves do not

fit the randomized model, and even in some cases, where the endoluminal graft trials were proposed and initially tried that way, it turned out not to work, and even some IRB said it's unethical to offer a patient a lesser intervention and then take it away.

So there have been many failures related to just RCTs under that particular environment.

Points of agreement are thus far that carotid intervention is about 30 or 40 percent of strokes. In the United States 70 percent of these patients are asymptomatic. So that's the other focus is this high risk issue. And that is relevant for the risk stratification of high risk and low risk is a question that I would propose we're never going to answer. If you go on the Internet today and you put in high risk in carotid interventions you'll come up with more than a million citations.

There are many many studies. It's been argued for 50 years. We're not going to answer this question. Some people would say they're all high risk; some say they aren't.

And the proposal that I would make is that we

need to look at all of them as a group to answer that question.

But level one evidence is obviously important if we can get it. But there is in this case, and with the device technologies in general, as was mentioned earlier by Chris, a lack of correlation as to what we see in the broader population, which is in fact I think the charge of this division of the FDA. What is this going to look like when it gets to a patient for a drug trial, randomized trial, to do it for devices, that's rarely the case.

I'd like to review for your CARESS which was the trial that was mentioned earlier, and just update some data. I don't want to be repetition. You heard some data from Wolf as to what that looked at. But these are the two year results. And this looked at all comers in a concurrent cohort model. Everybody was entered, and the attempt was then to be able to look at all of the patients, and include carotid endarterectomy and carotid stents, with that decision being made by the interventionist and the patient as to what was appropriate.

These are the demographics, but the bottom line, that little yellow thing at the bottom, shows you that in that model 70 percent of the patients were asymptomatic. So that fits what we know is the current practice pattern in the United States.

These are the 30-day endpoints. And if you look down at the event rate, that second line from the bottom, comparing carotid endarterectomy to carotid stents, they are similar; no significant differences. And then what Chris White had mentioned as the acceptable ranges.

This is the one year result. They remain the same. And these are again at four years now. Comparability between the two.

So in that particular model this would suggest maybe they are equivalent, although the numbers as Wolf mentioned are small. These are the just grafts of what those two look after the time frame.

Efficacy was also looked at, re-stenosis, residual stenosis, carotid revascularization, repeat arteriography endpoints that are obviously important.

In follow up, 30 day they're comparable, and

after four years they remain so.

So that the ability to collect that data longitudinally and look at it in a group of patients in a broad applicability should be possible.

Now what would be the proposed model here? There has been a lot of work done by the vascular societies to look at registry outcome. Although we are not talking about reimbursement, it's been mandated by CMS. It's something that we are all going to have to look at for outcomes. And it's a clinical tool that needs to be developed.

The societies, SBS and ACC, have spent a lot of time putting those data sets together. They can be audited prospective and available for use.

And so the ability to combine this -- and it wouldn't be to eliminate what is now randomized trials that can be accomplished. It would be to supplement that dataset, which does not apply to broad-based knowledge, and use these prospective concurrent studies from the registries to make broader availability.

There's also another concept that potentially would work, and that is in the CARESS type of model, if

you were to have an investigator IDE scenario, where the central body holder for that data would be able to consent the patients; have these be entered; manufacturers would then have an option to take devices based on that, like a subset of population, or even a broad approval data set, and use that to be able to approve the devices.

Another advantage of that would be that under the current environment approved IDs are funded by CMS, so it is an incentive then to enter patients into those trials to provide funding for appropriate data collection that would stimulate what's really needed in terms of being able to do this from all perspectives.

Thanks for the time.

CHAIRMAN YANCY: Thank you very much.

Is Dr. Bacharach available?

DR. BACHARACH: I will.

CHAIRMAN YANCY: If you would identify your conflicts and your affiliations.

SOCIETY FOR VASCULAR MEDICINE AND BIOLOGY PRESENTATION

DR. BACHARACH: I will, thank you. I want to thank the panel for having be speak today. My name is

Michael Bacharach. I am here on behalf of the Society for Vascular Medicine. I have no conflict, and no financial disclosures.

I am a practicing cardiologist, a vascular medicine specialist, and someone who does do carotid stenting.

Just as a way of explanation the Society of Vascular Medicine is a multidisciplinary society in which clinicians from many different backgrounds come together and promote both clinical care and research in the area of vascular patients.

It is our belief that carotid stent technology has now evolved as an important therapeutic modality and option for some of our patients, and that we are here, or I'm here presenting on behalf of the Society really to try and help provide some input as to how we gain the appropriate information to make the determination of what optimum utilization of this technology should be.

In the past decade there have been numerous randomized control clinical trials, series and industry sponsored registries that have looked at carotid

stenting, and while not conclusive many have demonstrated safety and efficacy for carotid stenting in certain cohorts.

Moreover these studies have helped establish that carotid stenting is an acceptable therapeutic modality for patients with symptomatic and asymptomatic disease who are at unacceptable risk for traditional therapeutic, or traditional surgical revascularization, or have other medical or anatomical considerations that put them in this high risk category.

There is probably no other area of vascular intervention that has been as contentious, or created as much inter-societal politics as carotid stenting, and we think that to some extent this has actually been counterproductive to determining what the best utilization of this technology should be.

Now as a society we fully recognize that evidence-based guidelines in determining how a procedure is best used are ideal. We think that the demand by some groups that only randomized clinical control trials be used to make the determination for this is unreasonable.

And basically it's our position that this creates unreasonable burdens with regard to costs, patient inclusion, which is often not real world, and that potentially will prolong making a timely decision about how we can best use this technology.

So the challenge before all of us, both those of us in the clinical world and certainly the panel here, is to proceed with some sorts of study designs and data collection that will allow us to make good decisions with regard to performing carotid stenting.

Now it is our belief that non-randomized trial designs can be developed using objective performance criteria based on historical controls, such as ACAS and ACST.

Additional study designs using concurrent controls have been effectively used to evaluate other types of vascular technologies, and both Dr. White's prior to my presentation have given you some ideas about how it's been used for endografts. These types of trials are much less expensive. They can be completed in a timely fashion. And they have real-world application to patients that we see and treat on a daily

basis.

Careful thought does need to be given to outcome measures. Standardization of these outcome event measures, and specific parameters of follow up will allow for improved comparison interpretation between different studies which has been one of the things that has plagued the current literature that is available to us.

We do acknowledge that there has been a gap exist between randomized control trials and the registry studies. In the literature there exists variable outcomes for both carotid stenting and carotid endarterectomy. And as with many other procedures, we know that experienced operators do better. Centers with high procedural volumes also seem to have better outcomes than those with lower volumes.

Independent adjudication appears to make a difference. Failure to -- if an operator adjudicates their own cases, reported event rates have been published that are three times lower than those in which they are independently adjudicated.

So the use of standardized, validated, and

widely accepted patient assessment tools, such as the NIH stroke scale, is crucial in evaluating the success of carotid revascularization.

So as you're faced, as panel members, to make some of these decisions, we would ask that you consider the following recommendations that we as a society think have merit.

First, with regard to data collection, we encourage the establishment of uniform standards for data collection, objective and reproducible means of assessing patient outcomes, along with independent adjudication of events.

And we do encourage you to set standards so that the results of carotid revascularization for both modalities, both carotid stenting and surgery, are reported.

This will enable ongoing comparison of results in contemporary real-world practice, and helps refine the understanding of which patients are most likely to accrue benefit from carotid revascularization.

This is especially important given some of the stellar results that we have seen in carotid surgery

such as the NASCET trial have not been replicated in community based programs.

Number two, really, is that all, we would like to see that all centers who participate do data collection and trial should be required to participate in either the SDS or the ACC registry for both stenting and surgery.

At present only stent cases must be enrolled. This has benefits to the structure of data collection. It can help address some of the complex issues such as operator experience and institutional procedural volumes.

By requiring standardized reporting and data collection and uniform objective outcome measures, alternative study designs such as concurrent controls will have greater scientific validity.

All these measures will potentially help us determine optimum utilization of carotid stent technologies.

And I wish to thank the panel for allowing me to present today.

CHAIRMAN YANCY: Thank you, Dr. Bacharach.

The next presenter is Dr. Zwolak. If you will tell us of your conflicts and identify your affiliations.

SOCIETY FOR VASCULAR SURGERY PRESENTATION

DR. ZWOLAK: Good morning. My name is Bob Zwolak. I'm here representing the Society for Vascular Surgery. And I appreciate the time you've offered me on the panel.

I have no personal or financial interests or arrangements or affiliations. The Society for Vascular Surgery is paying for my trip here today.

You've heard a fair bit about the country and cohort trials suggested by use of the specialty society registries. I'd like to fill in a few details of that.

First of all certainly the Society for Vascular Surgery supports and gives appropriate respect and homage to level one evidence development by RCTs over other forms of approaching this issue.

But at the same time, while the scientific analyses and benefits and advantages are well established, certainly there are some disadvantages of selection and treatment due to the issues of real world

data collection.

And there in we see significant opportunity for non-RCT studies to fill with detail. These can be corrected to a great extent with propensity scores and covariant adjustment, and do hold significant scientific validity.

So the concept that I'd like to propose here is evolution of non-RCT studies monitored with specialty society registries, and the registry that I'm familiar with of course is that promulgated by the Society for Vascular Surgery, realizing that the American College of Cardiology has another very robust registry.

So in the CAS and endarterectomy world tools already exist in the clinical realm and are in significant use for these. And we feel these tool are appropriate to answer subset questions sufficiently that may not be answered by the randomized control trials.

The answer to the questions may exist within these bodies of evidence as currently being developed, and as proposed in future studies, and may help us identify those at high risk for carotid artery stenting, in addition to the established high risk subgroups that

we already know about for carotid endarterectomy.

So what about this tool, the current carotid stent and endarterectomy registry tool we use is economical and completely web based. It can analyze baseline risk factors, routine major adverse events, plaque characteristics -- those had been mentioned this morning as important considerations during the discussion; the impact of variable stenosis in our particular registry, over 150 such variables are included for analysis.

In addition the registries offer a significant opportunity for long term follow up of these patients. The original goals of our registry were to allow compliance with the CMS facility requirements. But also on a scientific basis to allow analysis of risk adjusted large numbers that accrue when a great number of facilities across the United States perform these studies.

We are very much interested in analyzing the registries, endarterectomy and stent subgroups. But it could be a perfect opportunity for ongoing study of these other variables that have been discussed here

today. Our registry steering committee is multi-specialty. We have ad hoc members of the steering committee from the AHRQ, the FDA, the CMS and the New England Research Institute.

There is multi-specialty participation in the registry. These stents are not just put in by vascular surgeons because it's the SVS registry, but also large numbers of stents are being deployed and entered in our registry by interventional cardiologists, interventional radiologists, neurosurgeons and interventional neuroradiologists.

The data engine for our particular registry is a well respected New England Research Institute, or NERI, founded more than 20 years ago. NERI has contracts with NIH, and does additional private biomedical research.

The system is web based, very detailed, pre-procedural diagnostic forms, procedure forms, follow up visit forms, all readily entered data, and you can't see the details here, but there are as I mentioned more than 150 collected variables.

The system allows for online help and

particularly important hyperlinked definitions. If there were any question thereof, those are readily available.

There's online validation. For instance if I were to enter a patient whose age turned out to be 210, the system would flash a sign at me saying it's unlikely your patient is 210. Please enter the correct birth date.

And there are corrections of that sort all through. There are mandatory data entry items. For instance if one fails to enter the percentage stenosis as obtained on the arteriogram the system reminds you that's a required element.

Validation of course is also necessary to ensure that all the patients at individual institutions are entered, and this registry format allows for validation at whatever level would be felt necessary for studies that would be designed.

In addition the system allows for independent patient outcome analysis. And those can be readily incorporated into the system.

I have two slides here that are examples of

the reports that are currently generated in real time for members of the registry. This is an example of the basic demographics report of one's own site as seen in the first column compared to other sites.

Carotid stent outcome analysis. You see here this particular site has entered 153 patients and 170 total procedures. You see mortality and stroke statistics. And outcomes also available for carotid endarterectomies, and it's important to note that we have entered approximately equal numbers of carotid stents and carotid endarterectomies, now more than 2,500 procedures recorded in the system, about a 50-50 mix of endarterectomies and stents; more than 2,000 follow up forms have been entered. Approximately 140 now terminations, terminations would be patient deaths, while the majority of patients are still undergoing active follow up.

So in conclusion our recommendations really would be the following: a concept that it's been mentioned by Chris White; it's been mentioned by Rod White. The design of carotid stent versus endarterectomy trials for conventional risk patients

using the specialty society registries as tools. These provide, or have the potential to provide accurate, audited, real world, large numbers, in terms of data collection. And that would allow subset analysis that may not be available in a randomized control trials.

And in the best of worlds too this would -- although it's not the intent of this panel to discuss coverages, it would hopefully satisfy CMS coverage concerns as well.

Thanks very much for the time.

CHAIRMAN YANCY: Thank you very much. We appreciate your brevity and your clarity.

Irene Katzman.

AMERICAN ACADEMY OF NEUROLOGY PRESENTATION

DR. KATZMAN: Thank you. I'm Irene Katzman. I'm representing the American Academy of Neurology. I have no disclosures related to this. The AAN is paying for my trip here.

The American Academy of Neurology appreciates the opportunity to comment on this important issue. They support the need for well designed trials to evaluate the use of carotid artery stenting in

conventional risk patients.

And as I think everyone here, randomized control trials is considered the gold standard and a strong preference of the academy.

However, they feel that the consideration of alternative designs may be appropriate in situations where completion of RCT is not feasible for many of the reasons that have been discussed this morning.

One of the big concerns of the AAN is the possible interference with recruitment of current trials, CREST and ACT I, should alternative designs be utilized.

And one of the other main concerns of the Academy is the use of off-label devices which they believe impedes the enrollment of patients in the current clinical trials.

And as has been discussed this morning, some of the stent trials that were recently published, conventional risk patients that were symptomatic were not that positive, space failed to demonstrate the periprocedural non-inferiority of stenting to endarterectomy, and EVA-3S was stopped for safety and

futility.

CARESS is not on here, but CARESS by itself is not -- does not provide sufficient evidence for stenting in conventional risk patients.

So these data actually highlight the importance of gathering information to evaluate the role of stenting in conventional risk patients.

And we feel that for now stenting is proven only for symptomatic patients that are at high surgical risk.

These are some of the desired elements for a future trial, whether it be the traditional randomized trial, or other variants of trial design.

We feel that both symptomatic and asymptomatic subjects should be rigorously evaluated.

The range of stenoses that should be included in trials we feel is in the range of 70 to 99 percent.

Along with many others at this point we don't feel an upper base limit, i.e. greater than 80, is necessary at this point.

For endpoints the total stroke and all cause mortality as well as the endpoints of ipsilateral stroke

and MI are prudent to include with a special caveat that event severity will also be important to keep in mind.

In regards to follow up, 30 day and one year of course, with longer times as able and especially for those -- that would include a medical management arm.

So two years for those involving symptomatic disease, and five years for those involving asymptomatic disease.

So just to conclude, and I know this presentation has been very brief, these are some of the thoughts, our final concluding thoughts from the Academy, that there should be a multidisciplinary approach to the conduction of clinical trials; that a clinical trial should include all of the relevant specialties.

And if alternative designs are utilized, that it is important that we do not interfere with the recruitment of the current RCTs, CREST, and ACT I.

And perhaps in addition to looking at alternative designs, trying to enhance the recruitment of randomized control trials, and trying to utilize methods to do that is also an avenue to pursue.

And one of the ways to do this potentially is to limit off-label use of devices, and although outside the purview of the FDA, potentially linking reimbursement with clinical trials, because this might be a timely and cost-efficient method to gather additional evidence regarding efficacy of stenting.

Thank you.

CHAIRMAN YANCY: Dr. Katzman, thank you very much for your presentation, and for your very crisp summary statements. It's much appreciated.

Dr. Rosenfeld.

AMERICAN COLLEGE OF CARDIOLOGY PRESENTATION

DR. ROSENFELD: Thank you, Mr. Chairman and panel, for allowing me the opportunity to speak.

I am the section of vascular medicine and intervention at Mass. General Hospital, and I have the following disclosures. My way here is paid by the ACC. And I'm representing them formally.

But I also have multiple other disclosures. I receive honorarium and am involved in trial support and financial support by various companies including Abbott, Boston Scientific, Lumen, EV-3, Medtronic,

Cordis, Bard, and Medical Simulation Corporation, all of whom have an interest in carotid stenting.

I also am the principal investigator of the ACT I trial, which is a real and important disclosure in conflict I guess. I'm also the principal investigator of the VIVA trial which is just completing. It's a high risk carotid stent trial that is supported by Bard.

Other disclosures and conflicts are that I am a cardiologist that also performs, has been performing carotid stenting since 1995. I believe in this therapy for appropriately selected patients, and by appropriately trained interventionist.

And I do believe that patients also like to have access to this therapy, and like to have the choices available to them if those choices are appropriate.

I have many different hats I'm wearing here. But I will mostly speak from personal gut feeling, which I was asked to do my Dr. Zuckerman, which is that I believe in level one evidence that is produced by randomized clinical trials. I think it's incredibly important from a scientific standpoint to complete those

trials and not to allow them to be cannibalized just as Irene Katzman was just saying. I think we need to do everything we can to encourage the completion of these trials and not allow trial designs that would interfere with their completion to come to the fore.

That said, I do believe there are windows of opportunity to create alternative trial designs that might be either by the type of patients they would enroll, the sites they would enroll at, or by the timing of the onset of those trials, be able to be created and not jeopardize the completion of the important randomized trials which will provide level one evidence.

I want to make a couple of other points. I think that it is encompassed within these randomized trials and all trials -- I agree with Dr. Zwolak and others who have commented that independent neurologic review and assessment is important for both carotid artery stenting and for endarterectomy, something that has not been a standard of care in the past. And I think that is a new standard that is the inclusion of independent neurologic assessment, no matter which trials are created. And it should be the case for both

surgery and stenting.

The question came to the panel here because of the difficulty in enrolling these randomized trials. And I think it's a multifactorial thing which has caused this to come about. The presentation about CREST earlier alluded to the issues that CREST faced early on with enrollment. And I think a lot of those issues have been resolved; some that have not been completely resolved and may never be are the politics that surround this whole arena of carotid stenting and endarterectomy. The economics that are obvious if a person does surgery and doesn't do stenting, then they would lose the patient and lose the economic incentive if that patient underwent stenting.

I think that has unfortunately muddied the waters in this whole discussion about carotid therapies. And I honestly believe if economics were not a role here and politics in control of patients were not playing a role here, then this therapy would have been very well studied by this time, 10 or 12 years into it.

It's unfortunate -- side comment, but it's unfortunate that that actually has had an influence on

the enrollment in trials and the engagement of this therapy.

Such was not the case with aortic endographs, by the way, a little bit more -- everybody was a little bit more in synch with that.

Another thing that is an important fact that has limited enrollment is the payers. And that was alluded to by Dr. Katzman just now. And it is a fact that the lower -- the non-high risk surgical patients often tend to be a little younger, and they often tend to be covered by non-Medicare carriers and many of those carriers do not allow enrollment in investigational trials. And that has -- at my site it has significantly limited enrollment. And that is something that may be beyond the purview of this panel. But I think while it is a public forum we're speaking at, I think it's an important point to make that if there is clinical equipoise, then I think that non-Medicare payers should also be agreeing to help satisfy the science so we can get to the end of the road in terms of defining therapies.

Finally, just to summarize, I do believe that

timing is a big issue. I think the randomized control trials are enrolling at a reasonable rate now. I think that they should be -- the structure of any new trial and the timing should be such that it allows these trials to complete their enrollment. And I think that -- I do think that actually with a fair amount of planning and coordination that it might come to pass that we sort of see on the horizon when the trials are going to be completed. For example we know that CREST, which enrolls octogenarians and symptomatic patients is probably going to complete enrollment in the middle of 2008. There is an opportunity to engage in a new more flexible trial design at that point for those patients that will at that point no longer have a randomized control trial to enroll in. And at that point it might be the opportune time to engage in a concurrent control or cohort control trial, or a more real-world patient trial that Bob Zwolak was referring to, perhaps using the registry format for collection of data.

So timing is everything, and I do support the use of flexible trial designs. But not if they cannibalize either by timing or by design the current

trials.

I do want to make a comment about the CARE registry because we at the ACC have a similar registry that was developed concurrently with the SBS' registry. And I think that the power of these two registry formats will allow us to really collect a significant data about the -- with respect to the real world patients that Dr. Zwolak was referring to.

Thank you.

PANEL DISCUSSION

CHAIRMAN YANCY: Thank you, Dr. Rosenfeld.

At this point are there any other individuals in the audience who would like to address the panel?

Since no one has come forward, we'll proceed with our agenda.

As a point of information, let me remind the panelists that there is a yellow folder at your seat. And inside that folder are statements, two of which capture the statements that we already heard. But there is an additional statement from the American Heart Association that you may want to peruse. And then there are reprints from circulation that capture in a point-

counterpoint format some of these issues.

But I would advise you to at least make some cursory review of the American Heart Association statement signed by the president, and a recognized expert in vascular medicine.

What I'd like for us to do now is approach first of all questions to either of the eight presenters, the three before lunch, and the five that we've just heard.

Looking at the audience, I think everyone is still here. So we have an opportunity to seek clarification if there are specific issues raised by a presenter that merit additional questions.

Following that we should have an internal deliberation in general about the issues. I'd like to bring that deliberation to a close no later than 3:00 o'clock, so we can start addressing the specific FDA questions at 3:30, which would allow all of us to meet important connections by 5:00 p.m.

So with that having been said, are there questions for any of the eight presenters, specific questions for any of them?

Yes, Dr. Yarros.

DR. YAROSS: We've heard a couple of things from a variety of speakers, including Dr. Katzman and others, about the impact of off-label use, as well as the challenges based on the reimbursement environment.

I don't know if any of the speakers have any reliable estimates of the prevalence of off-label use in this population. Is that information available?

CHAIRMAN YANCY: It's an excellent question.

DR. WHITE: I'm Chris White again, and I don't have any financial conflicts.

Off-label use is a big deal for PFO closure devices and other options where you get paid for the procedure in the hospital regardless of the device you specifically used.

To my knowledge, again, over thousands of carotid endarterectomies I don't think one percent of those devices is done under off-label use simply because payment for that procedure is not predicated specifically on the device. It can use any approved device.

So I don't see off-label use in carotid -- I

was confused actually. Perhaps Dr. Katzman can clarify. But I'm confused about off-label use impacting carotid stenting, because I don't see that as an issue in practice.

CHAIRMAN YANCY: Dr. Katzman, might we have your comments please?

DR. KATZMAN: And I don't actually have any good estimates. But I can tell you my experience at our institution.

So before things were approved, at least for high risk patients, we did a lot of them. And I as a neurologist constantly going over the hospital, we did hundreds of cases of stents.

We don't do that many anymore. So for instance a group that used to maybe do 300 a year, ballpark, now do maybe 80. And it's because they are out in the community, and they're doing things out in the community. And they're doing things for indications that are not quite what has been FDA approved.

So I can tell you what has been the experience at my institution. I cannot give you data from anywhere else.

I don't know if anybody else has any comments, any of the other speakers.

CHAIRMAN YANCY: Dr. Rosenfeld.

DR. ROSENFELD: Ken Rosenfeld. And I disclosed my conflict before.

With all due respect, I actually don't think -- I'll agree with Chris White, I don't think that off-label use of these devices is a huge issue.

I'm sure it is somewhat of an issue. I mean you always sort of hear about those few patients, and a big deal is made of it. But by and large most of the patients that are undergoing carotid stenting now are done in the post-market surveillance studies, which are carefully monitored, and yes, there are thousands of those stents being placed, but it's almost unprecedented, because the FDA has required the post-market surveillance for broad widespread use for asymptomatic use, and I think most of those patients are being captured by those post-market surveillance studies.

I -- you're never going to be able to control everything that tightly, and I'm sure there are a lot of

endarterectomies for example in this country that are done for questionable indications.

But by and large I think most of these are being monitored and captured.

DR. ZUCKERMAN: Dr. Rosenfeld, before you leave, can I ask you a question, please.

You made an important statement that for the field it's important that the CREST trial be completed before other potentially more flexible trial designs be inaugurated.

One question regards, since there is no one here from the CREST trial per se, are the - do you know if this trial is a sponsor investigator trial, and if the investigators there have ever considered allowing other companies or sponsors to use their final data as control data, number one.

Number two, would that be inadequate control for trials going forward, given that it's a recent historical experience? Otherwise, I don't necessarily see how you can generate the idea that one trial must be completed before another one be initiated from a

regulatory perspective. I can appreciate it from a scientific perspective.

DR. ROSENFELD: I can't answer your first question because I don't know what - your first question was about the -

DR. ZUCKERMAN: Well, who actually owns the data for CREST, and what is the availability of using those data as control?

DR. ROSENFELD: I don't know the answer to that. I am actually involved in the interventional management committee of CREST. But I think the data are owned basically by NIH and the principal investigators.

I don't know to what extent the Guidant slash Abbott now has access to the data. That is probably a contractual arrangement with the NIH and the Pis.

With respect to the use of the CREST data to then generalize to other manufacturers and use it as a comparative group, I would think that that would happen. I don't know about the regulatory issues involved in that, whether you need three randomized control trials before you can then use other alternative designs. I would think that would not be a practical solution to be

perfectly honest. I think that the data should be useable, and I think they will be valid.

I also think the ACT I trial and the CREST trial are distinct and different, and they will provide two separate sets of information that are really quite a bit different from one another.

As you know CREST includes both symptomatic and asymptomatic patients. And the statistical power is based on including both of those group, whereas ACT I is a different trial design, and it's only asymptomatic patients, and it's non-octogenarians.

I think it's really important to look at the non-octogenarians separately and differently.

So there's a lot of valuable information that's come from these two trials. And just to reiterate, I am a fan of alternative trial designs because of the difficulty in getting these kinds of trials completed. You can only do them once or twice and that's it.

So and I think from a practical standpoint, for all the reasons that have been mentioned earlier, we need to have alternative trial designs.

Does that answer your question?

DR. ZUCKERMAN: Yes.

CHAIRMAN YANCY: Dr. Rosenfeld, before you leave, let me just get you to address something that you mentioned briefly in your presentation. And it relates to what you and Dr. White just attested to, the minimal if any use of the devices off label.

I'm assuming you're meaning that there is negligible use of carotid stenting in not high risk asymptomatic or minimally symptomatic patients.

So if that's the case, that's usually what we've seen in other scenarios where off-label use is competing against enrollment into clinical trials.

So if that is the case, that there is negligible activity off label, then will you enumerate again the reasons why it's so hard to recruit? Because it's not because these patients are getting stented?

DR. ROSENFELD: Politics, economics, payers. So just to go through them and be very blunt, in my place any patient that comes to me, who is referred to me who is an asymptomatic patient who is non-high risk I immediately consider that patient for one of the two

randomized trials.

And by and large, unless they're excluded because they've had atrial fibrillation or some other issue, I will enroll them in a trial. And I will send them to a surgeon to talk to the surgeon.

Occasionally the surgeon will convince them otherwise and they don't get enrolled. That's a rare thing, because I now know which surgeons are willing to work with me.

But at other places that is a problem.

Secondly, if the patient is referred by a general internist to the surgeon, though, the same interest in enrolling in the trial is not there.

And I think my surgeons are great. They are phenomenal, as a matter of fact; they're very talented. I have the highest respect for them.

But quite bluntly a large part of their economic basis is based on carotid endarterectomy, and so what is the incentive for them to then send a patient and take a three out of four shot that the patient will be stented?

It turns out that in my place that there is a

surgeon who does stenting, and is part - I embraced and brought him into the randomized control trials.

So in that case it's really not the incentive economically to - the disincentive economically to enroll.

But there is this - there's an - either the surgeon might not feel that there is equipoise, or the surgeon, a given surgeon might say, well, I need to support my program. I need to have enough endarterectomies to train my fellows, and on and so forth.

It's a very complex matter. And in every institution it's a little different.

Finally at the end of the day the payers may determine. Because Blue Cross-Blue Shield will not pay for enrollment in one of these trials.

So the very best candidates, the ones that we really need to know the answers about, the patients who are 65 years old, or 60 years old, and have a severe unilateral carotid stenosis, which probably is the very best stent candidate by the way, and also the best endarterectomy candidate, may not have the choice to

enroll in the trial.

CHAIRMAN YANCY: Other questions from the panel? Yes, our consumer representative, Dr. Nachtel.

DR. FLEMING: I'd like to ask you another question if you don't mind. I'm here as a consumer rep, but I want to ask you from a patient's point of view.

Tell me why I should be part of the clinical trial? Why would I want to participate in the trial when I can go out on the town and get it done outside the hospital setting, because I know that's being done.

Or just give me - this is a hypothetical question - why should I participate in your trial?

DR. ROSENFELD: Well, that's an hour long discussion or more that I have with every patient that is a possible candidate. And I mean an hour long discussion.

It's very difficult to have the discussion with patients too. It's more than just if I were doing an endarterectomy, and weren't doing the trials, I'd say you need this done, I think you need this done. It's probably better than medical therapy in this particular instance. And you need it revascularized. And that

would be a quick discussion; end of discussion.

So it's actually tough to - you have to present the different options and convince the patient that there is clinical equipoise.

The reason that I would urge my patients - that I urge my patients to enroll is because we don't know the answer. I think they are both equivalent therapies. They each have their advantages and disadvantages. And I explained very carefully what those advantages and disadvantages are, and what the individual risks of the two therapies are.

And then I give the surgeon the option, the opportunity to go through the same exercise so the patient gets a fair and balanced viewpoint.

Why is anybody, any patient - some patients don't want to participate in the trial. Some people think that they are being a guinea pig.

But most patients I think understand that we are trying to further science, and we need to get this important information.

And given that we - I really believe in my heart of hearts that these are two equivalent therapies.

Most people will buy into that.

CHAIRMAN YANCY: Please, Dr. White. DR.

WHITE: Thank you. In CARESS we had some information on this issue of does the broad label studies impede the randomized studies. Because it was built into CARESS that an exclusion criteria for entry was that the patient is CREST eligible. And so anybody in the center who was doing CREST who also was in CARESS, which could be the theoretical situation, if that patient is CREST-eligible, they automatically were not able to be entered into the CARESS study.

Now we actually had some data, and Sandy is here, and she can correct me if it's not right, but we had entered some 350 patients, and there were only two patients out of that total number who in fact were eliminated from CARESS because they were CREST eligible.

And that actually reinforces the point that they are complementary rather than conflicting in the sense that the randomization process, which is very important, it gives us the high level science, eliminates most of the patients that would be eligible for the treatment, and what the registry option to do is

pickup the remainder of all of those patients, and look at and make a study option available here.

So they are not conflicting, and the data that we have would support that they are actually complementary and put the two together.

We did talk to the CREST organizing committee about a data swap. And the agreement that was available was that there as a phase two CARESS study that somewhere down the line, once CREST was finished, the data ownership was done, and everything was published, that it would then be a capability to swap the data and actually put the two together.

The other advantage of the registry options would be all those patients would already be there, and that would already be accomplished. But those kinds of negotiations were worked out, and it was not an issue.

CHAIRMAN YANCY: Dr. Zwolak.

DR. ZUCKERMAN: Dr. White, before you leave, can you just clarify something for me? That complementary relationship, did most of the data though come before CREST started enrolling asymptomatics? Now that CREST has included asymptomatics as well as

symptomatics, are there that many patients that you could see fall outside the boundaries of the CREST trial?

DR. WHITE: Yes, I think so. And I just talked to Gary the other day about the CREST. But the total CREST entry is, what, 2,500 patients. And we're talking about, in the scenario with 70 percent asymptomatic, and 100,000 some carotids being done a year.

The numbers are the same. If you blow those up an order of magnitude, 95 percent of the patients are not going to be CREST eligible. And where they are, it would be an exclusion criteria, and that could easily be tracked and that data put together at some point.

So again, I think it's complementary, and that question, and what we've learned is, the majority of what is clinical practice, and where this will be used eventually, is being eliminated by the randomized trials, not that the randomized data is bad; it does not translate to clinical practice, which is what we know about devices in general.

CHAIRMAN YANCY: Dr. Zwolak, did you have a

comment?

DR. ZWOLAK: Thank you. Two very brief comments.

With regard to off-label use I think I would concur with the previous speakers that I believe anecdotally - and again I don't have hard evidence - but I believe anecdotally the off-label use of product stents in the situation is very low across certainly our region.

My second point addresses Dr. Fleming's comment about randomization. In our facility there is very little in the way of political issues, because the surgeons deploy about 95 percent of the carotid stents.

Nevertheless it's still quite difficult to convince a patient that randomization is something that they should by into. In a situation where there is clinical equipoise among the providers, it's still difficult to talk patients into randomization.

CHAIRMAN YANCY: Dr. Bacharach, did you have a comment?

DR. BACHARACH: Yes, thank you. I just also wanted to address the issue of off-label use.

I'm here not from an academic center or large foundation. I practice medicine in the middle of South Dakota. So I represent what's really out there in the plains. And first, I don't think we have an off label use. And of course we have limited providers and so on. But all the centers that in fact are currently providing carotid stenting are doing so within the mandates of either FDA-approved trials or within the CMS guidelines.

So we really don't have an issue of off-label use. And I think part of that is the fact that we don't have independent institutions or foundations that in fact will support it. And you can't bring those patients into the hospital and not get paid. That's the bottom line.

The other issue, I am a participant in a number of the trials, both the post-registry as well as the randomized trials. And the difficulty that we have, and I think Dr. Rosenfeld alluded to this, we for example, we cannot randomize patients who are non-Medicare age into ACT I, into the non-high risk group. The insurance companies categorically refuse to cover it. It's an investigational procedure. The Blues won't

cover it. Dakota Care won't cover it. So it's basically despite letters and all kinds of things saying that we think it's of value.

I would reiterate much of what Dr. Rosenfeld said. I do believe that there is equipoise assuming that you have good operators doing both of the procedures. And in fact where I am patients are relatively trusting. We don't have a difficulty in presenting I think fairly both options, and most patients are willing, and in fact our greatest difficulty in the non-Medicare group is the fact that we can't randomize it basically because of economic issues from insurance companies.

Thank you.

CHAIRMAN YANCY: Thank you. Dr. Hirshfeld.

DR. HIRSHFELD: I think maybe Dr. White might be the best person to start answering this question, but other speakers have also. I've been very concerned about the asymptomatic population. With the extremely low spontaneous event rates that occur on medical therapy.

And although the guidelines now say that it's

a Class 1A indication for carotid revascularization, it's clear that this has to be done with an extremely low morbidity in order to meet those criteria.

So ACT I is comparing two revascularization techniques without a medical control arm. TACIT has a medical arm.

I'd like some thoughts about whether any of these trials that extend into asymptomatic patients should have a medical control arm in them.

And one of the reasons I mentioned Dr. White was when I looked at the CARESS data that you showed, which is more updated data than we had available to us, it looks as though the event rates overall are high compared to what would be expected spontaneous event rates for asymptomatic patients.

DR. RUNDBACH: Well, I'm not Dr. White, obviously. I'm Dr. Rundbach, but Dr. White can address this afterwards.

Actually I wanted to make a comment. And this was actually gratuitously much of what I wanted to comment about.

In the asymptomatic population which is the

majority of patients who potentially can benefit from evaluation to the best therapy, it seems to me that registries are markedly limited in allowing you know fair comparisons between treatment populations.

And they do not include a medically treated arm.

We know from the trials that have been conducted, as well as trials which have included populations of significant atherosclerotic disease, that as you have pointed out, the rates really are quite low.

And this has not been rigorously evaluated in the first couple of trials.

It's also worth mentioning to the consumer advocate, Michael Fleming, as to why this is important, and why you might participate in the clinical trial, is that particularly in this population you should not underestimate the importance of determining or evaluating secondary or intermediary or mechanistic endpoints which might impact overall clinical decision making.

Now it's very important even in this context that we look at such things as duplex criteria, and

plaque characteristics, and neurocognitive function and some of the other things that we have delineated, because only in this way can we sort of move this forward and really provide the level of public health benefit that is needed in the vast majority of patients who are contemplating therapy.

CHAIRMAN YANCY: Dr. White, I assume you wanted Dr. Rodney White.

DR. CHRISTOPHER WHITE: I thought you were looking about the good looking Dr. White.

CHAIRMAN YANCY: Since we have two Dr. Whites, I'm sure they both have thoughts, maybe we could hear from both.

DR. CHRISTOPHER WHITE: I would say there are two ways to look at this issue, John. And I think that clearly, if you want to know the right way to do medicine, the right way to practice medicine in patients, then you cannot make these decisions without modern best medical therapy information.

Because none of the trials that we currently have do it the way we do now. You don't have the anti-platelet therapy. You don't have the aggressive lipid.

Even ACST only touched a little bit of that at the end.

So we don't have that decision. That's one issue.

The second issue, though, is that we currently practice in an environment where you've got revascularizations being done, best medical practice, I take care of patients the best I can.

And so my issue is, is there a less invasive way to do that? And that's where the comparison of stenting and surgery comes down.