

TRANSCRIPT OF PROCEEDINGS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CIRCULATORY SYSTEM DEVICES ADVISORY

PANEL MEETING

Pages 1 thru 252

Gaithersburg, Maryland
April 4, 2000

MILLER REPORTING COMPANY, INC.

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CIRCULATORY SYSTEM DEVICES ADVISORY
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Tuesday, April 4, 2000

8:08 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

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P A R T I C I P A N T SPanel Participants

Anne B. Curtis, M.D. Chairperson
John E. Stuhlmuller, M.D., Executive Secretary

Voting Members

Michael D. Crittenden, M.D.
Renee Hartz, M.D.
Tony W. Simmons, M.D.

Consultants

Kent R. Bailey, Ph.D.
Jeffery A. Brinker, M.D.
Anthony C. Chang, M.D.
Fernando G. Diaz, M.D., Ph.D. (Via Telephone)
Michael J. Domanski, M.D.
George W. Vetovec, M.D.

Gary Jarvis, Industry Representative
Robert Dacey, Consumer Representative

FDA Staff

James E. Dillard III
Marian Kroen
Megan Moynahan
Stuart Portnoy
Mitchell Shein
Frank Lacy

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P R O C E E D I N G S

CHAIRPERSON CURTIS: I would like to call to order this meeting of the Circulatory System Devices Panel. The first order of business this morning will be the reading of the conflict of interest statement.

DR. STUHMULLER: The conflict of interest statement from April 4, 2000. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit Special Government Employees from participating in matters that could affect their or their employer's financial interest. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interests of the Government. Therefore, waivers have been granted for Drs. Curtis, Brinker, Chang, and Vetrovec for their interests in firms that could potentially be affected by the panel's recommendations. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15, the Parklawn Building.

We would like to note for the record that the agency also took into consideration other matters regarding Drs. Curtis, Brinker, Chang, and Vetrovec. Each of them reported additional interest in firms at issue, but in matters that are unrelated to today's agenda or whose interest is imputed from an employing institution. The agency has determined, therefore, that they may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him- or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRPERSON CURTIS: What I'd like to do next is go around and have the panel members introduce themselves. I am Anne Curtis, and I am a cardiac electrophysiologist from the University of Florida.

MR. DILLARD: Jim Dillard. I'm the Director of the Division of Cardiovascular, Respiratory, and Neurological Devices, as it currently stands, in the Food

and Drug Administration.

DR. CHANG: Anthony Chang, cardiologist in private practice.

DR. BAILEY: Kent Bailey, biostatistician at Mayo Clinic.

DR. SIMMONS: Tony Simmons, cardiologist, Wake Forest University.

DR. HARTZ: Renee Hartz, cardiothoracic surgeon, Tulane.

DR. STUHELMULLER: John Stuhlmuller, Medical Officer, FDA, and Executive Secretary for the panel.

DR. VETROVEC: George Vetovec, chairman of the Division of Cardiology, Medical College of Virginia Hospitals in Richmond and Virginia Commonwealth University.

MR. JARVIS: Gary Jarvis, industry representative on the panel.

MR. DACEY: Robert Dacey, Consumer Representative.

OPERATOR: Hello?

CHAIRPERSON CURTIS: Yes?

OPERATOR: Okay. Dr. Diaz would like a number that he can call you back at, at 9 o'clock.

CHAIRPERSON CURTIS: Just a minute, please

OPERATOR: Okay.

[Pause.]

CHAIRPERSON CURTIS: Dr. Diaz is supposed to be

participating today by conference call as a neurosurgeon, and we will see if we can get him on in a little bit.

Next we will have a presentation on least burdensome provisions of the FDA Modernization Act of 1997 by the FDA Staff.

MR. DILLARD: Good morning. Dr. Curtis, thank you. My name, again, is Jim Dillard, and I am the new director for the past three weeks of the Division of Cardiovascular, Respiratory, and Neurological Devices. And what I'd like to do first off is to welcome you all and thank you for participating today. I think we've got an interesting agenda, perhaps a little bit different agenda than you're used to; but, nonetheless, I appreciate you coming.

One of the things that we are doing based on the 1997 passage of the Food and Drug Administration Modernization Act is training our panels on some of the additional provisions that are new. One of those is the least burdensome provision, and for that, what I'd like to do is provide you with about ten slides and a real quick overview, especially for your consideration--and I think today it's even most appropriate--about our concept of least burdensome as well as how we intend to move forward with that particular provision.

But to begin with, I am going to give you a quick

overview of the day that we have before us, and right after the least burdensome, I'll be introducing Marian Kroen, who is going to provide you a little bit of a general clinical design overview, and she is going to speak to three commonly used clinical designs for the three types of product areas that we're going to be discussing.

The next topic will be study design for spinal cord stimulation for angina, and Frank Lacy, another member of our staff, will be giving you a backgrounder, as well as for all of these topics we have got at least one industry group that will be presenting their particular opinions on the clinical designs also.

We will next move--and we will try to finish up this morning with the clinical assessment of rate-adaptive pacemakers, and Megan Moynahan will be presenting you the backgrounder for FDA's perspective.

And then, finally, this afternoon, where we will spend probably the majority of our time, will be on atrial fibrillation and the study designs for that particular type and multiple type of device therapies, and Dr. Stuart Portnoy will be presenting the backgrounder for that.

One of the other things I would like to do is just give you a little bit of a charge today as well, because today is a little bit different. We will not be asking you to vote on any of these particular topics. What we will be

asking you to do is give us your clinical expertise, statistical expertise, as well as from our industry representative's perspective and our consumer representative's perspective, interesting if not very pertinent considerations for the trial designs in these particular areas. And as you look at this list, some of the product types here are much more mature than some of the others. And so after you hear the least burdensome, I think it will become very obvious, perhaps, why we are here today.

And I think one of the main reasons is we are struggling with clinical study designs in many areas in the cardiovascular area, especially when the products are newer. But in this case, we have got some that are mature technologies, and so what we are asking you today is take a look at the particular types of technologies and help us understand what at this point in time might be appropriate considerations for the clinical study designs, for endpoints, for statistical considerations. And then following your recommendations today, after your discussion about these, I think, very important issues, we will try to use these in many of our discussions with industry as a whole as well as the specific manufacturers that may be coming before us to design clinical trials for their particular types of products.

So this should really be viewed as a beginning in

some respects. It may be a middle in other respects. But what we'd like to do is kind of take a reality check here. You are certainly the experts in the area, and I think from that we should have a good clinical as well as statistical kind of discussion today.

Okay, on to least burdensome provisions. Least burdensome, as I mentioned, was a section of the 1997 Food and Drug Administration Modernization Act, and it has not appeared previously. And what I'd like to do in terms of overview is tell you where in the statute in particular the least burdensome provisions are, talk a little bit about what our implementation has been and what our plans are for the future, and then really some of the take-home messages that, again, will be important today about the mechanisms that we will use as well as you as our advisory panel will have to deal with in terms of mechanisms to lesson the regulatory burden for manufacturers.

Next, please?

Least burdensome appears in two sections of FDAMA--which is our short acronym, of course, because we are in the Washington, D.C., area--for Food and Drug Administration Modernization Act. And these apply in two areas of Section 513: 513(a)(3)(D)(ii) and 513(i)(1)(D).

The first section appears because it really targets the PMA kinds of products, and the second part of

the section really targets the 510(k) type of interpretation of substantial equivalence.

Next, please?

This is a long slide which summarizes what is in Section 513 that deals with the PMA provisions, and I think the underlying section here is really the important part that I want you to focus on. But it does deal specifically with clinical data, and you won't find this particular provision anywhere else. And it is specific to device kinds of studies. And, in particular, "The Secretary shall consider"--and the Secretary in this case is the FDA--"in conjunction with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval of the product.

Next, please?

And it appears again when thinking about substantial equivalence in those 510(k) kinds of decisions, and in the same kind of vein, what the statute tells us I that, "In making such a request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly. And these are the two areas that are particularly important when we've been trying to write policy and/or guidance documents in how to interpret the least burdensome

provisions.

What FDAMA did not change is the standard for premarket clearance and approval. The standard is still the same for premarket approval applications. The sponsor must demonstrate that there is reasonable assurance of safety and effectiveness of the product for its intended use; likewise, for substantial equivalence, that the product will perform as safely and as effectively as the predicate product that a sponsor is claiming equivalence to.

Next, please?

What we have done for implementation, we started January 4, 1999, and we held a large open public meeting to try to discuss some of these concepts. It was a new concept for the agency. It was a new concept for the industry. Once we had that open communication, we've been working on a guidance document. Once we looked at some of these provisions, we knew that there would need to be a lot of internal training. This concept is one that is very difficult for us in terms of implementation. What does it mean? How do our reviewers interpret it?

So what we have done is quite a bit of scientific reviewer training, which will continue as the further interpretation of the provisions kind of come out of not only comments to the least burdensome guidance document but as we get more experience with the interpretation of this.

And we also have got some things that I've got Web addresses for here which deal with not only our draft guidance document, but what I believe is my next slide, which is a HEMA task force that put together some comments on what the industry perspective is for least burdensome. And both perspectives were a little bit different, as you might expect, and what we've been trying to do is work together not only with industry but within the scope of what the legislation told us to really move forward and get an interpretation on this.

That was attached and is attached on our website to our particular proposal, and it has been incorporated in Appendix D of that particular guidance document.

Next?

So what is our interim definition? We've been working now over almost a two-year--actually, a little bit over a two-year period of time to try to get some interpretation. And what we've come up with, at least as a working definition, is a successful means of addressing a premarket issue that involves the smallest investment of time, effort, and money on the part of the submitter and the FDA. And this is also interesting because this is the first time you will hear us use the terminology of money. I know that's been something not only for this particular advisory panel but for many advisory panels about factoring in costs.

And I think that is one of the things that we are being tasked with, if not from least burdensome but from other pressures.

Next?

So it does require a change. It requires a change in FDA, it requires a change for our advisory committees, and it requires a change from the industry perspective also. So how do we come to incorporate these changes in our day-to-day working environment?

There are really multiple approaches to satisfying the regulatory requirements, and, in fact, over the last couple of years, we feel that a number of the least burdensome--at least the spirit of least burdensome have been incorporated into much of what we have been trying to do; perhaps not to the satisfaction of everyone, but we're at least moving in that direction.

And one of those is communication and collaboration, which was the other overriding theme of FDAMA. And I think compromise is going to be something here that will be crucial when we move forward in interpreting and implementing the least burdensome part of the law.

And there is a spirit to the law. There's a letter of the law, which I think you have seen, but there's also a spirit to the law. And I think the spirit to the law is this overriding collaborative effort, and in that I think

factors in least burdensome.

Next, please?

There may be some trade-offs. We hope that there won't be some trade-offs, but in reality, when we're talking about the concept of least burdensome and we talk about scientific integrity, there will be those things where compromise I think will be inevitable. But I think our vantage point in at least what we believe is that scientific endeavors are affected by the availability of good resources, and they're affected by our resources and they're affected by industry resources. And good science should include cost-effectiveness measures, and they can be factored into FDA clinical study designs.

Compromise is always a necessity for successful research, and I think it's a commonplace when we negotiate with manufacturers to design a trial that will hopefully result in approval or a clearance of their particular product. And I think lessening the regulatory burden may serve in the end to enhance the scientific progress and advance medicine.

Next, please?

We need to also ensure that all regulatory decisions are made in accordance with these relevant statutory criteria and utilize the tools that we have been putting forward not only in re-engineering efforts, but also

through the other portions of this provision. And some of those others have to deal with exemptions. We now have a lot more tools that the Food and Drug Modernization Act has given us. We can exempt some Class II products from premarket requirements. And the industry now has the opportunity by statute to come in and ask for early collaborative meetings. And third-party reviews is another area that we've been trying to investigate whether or not outside third parties can take some of our review effort from us so that we can focus on perhaps work that's a little bit more higher risk. And, as usual--and I think based on good science--we need to factor in all relevant publicly available information in our decision-making process.

Next?

Non-clinical testing is another big area, and we do need to rely on non-clinical testing. It is a factor in all preclinical and moving towards clinical types of trials, and we need to rely on it whenever possible.

When clinical data is needed--and this is particularly where the focus is--we do need to consider alternatives to the randomized controlled clinical trials. And I think today this is really where the heart of the discussion will be. There are potentially many different trial designs that could be appropriate for these particular

products and other products, and I think this is where we need to focus and we need to keep in mind when we're having these discussions least burdensome clinical data and the use of surrogate endpoints. It has been prevalent in many other areas. In cardiovascular, I think surrogate endpoints--and it will come up today--is an issue for some particular types of clinical trial designs. That does raise a little bit of an issue for the interpretation of our PMA sort of standards where clinical utility does become a factor. But clinical utility, nonetheless, in a surrogate situation where surrogates are validated is a possibility in study design.

Next slide?

So what's the bottom line? And this is my last slide. We really have to factor least burdensome concepts into all of our premarket activities, not just design of clinical trials. So you will see us utilizing and talking about least burdensome in our guidance document development, in our regulation development, at our advisory panels, and within your recommendations. And we need to remain open-minded, and this is the key. Alternative proposals are available. We do need to consider things like time, effort, and money. And I think that will be interesting for us as we move forward. I think it will be a new concept. It will be something perhaps that you struggle with. We know we are struggling with it. But I think together we can move

forward and we can have a good interpretation.

With that, I think I will conclude, and if there are any questions, I'd be happy to answer them.

Thank you, Dr. Curtis.

CHAIRPERSON CURTIS: Thank you.

We're scheduled next for an open public hearing, but there is only one company that has requested time to speak, and if there are no objections from anyone in the audience, what we'd like to do is take those public comments with each of the different sections that we're talking about this morning instead of having one open public hearing on all the three different topics up front.

Okay. So, with that, what we'd like to do now would be to move to the open committee discussion, and we're going to start with an FDA introduction, and the first topic this morning is going to be discussion of clinical trial designs for angina pectoris using spinal cord stimulation. Go ahead.

MS. KROEN: Actually, the first topic will be clinical trial design.

DR. STUHLMULLER: As a point of clarification, FDA wanted to make some comments on trial designs, and then we'll allow the sponsor to get up and make their comments. This is a generic issue for all three of the topics.

CHAIRPERSON CURTIS: Okay. Thanks.

MS. KROEN: My name is Marian Kroen. I'm a reviewer with the FDA, and I'll be talking to you about clinical trial design.

Next?

Okay. We'll be talking about clinical trial design all day today, and it's important that we have a common vocabulary when we speak about these. I will speak about three trial designs, and we'll discuss the advantages and disadvantages of each of them.

Next?

The first trial design I'll discuss is a single-arm with baseline. In this we have a baseline observation period followed by a treatment period. Here the patient is their own control. Next is a randomized controlled trial. Here the patient is assigned to either the treatment or the control arm. The next topic is crossover. Here a patient is randomized to either treatment on or treatment off, and then after of time is switched to the other arm.

Here is a picture of single-arm with baseline. The vertical axis is a clinical measure, and this could be symptom level, this could be amount of atrial fibrillation, so down is good. And we see Sam on the left. He starts out in the baseline period. He's treated and he's happy, as indicated by the dotted line going down. So his symptom level went down.

Fred, on the other hand, his symptom level remained the same, as indicated by a horizontal line. So we can measure per patient results with the single-arm study.

Okay. So with the single-arm with baseline study, we can define a patient success as X percent reduction in whatever we're measuring, and that X percent would be prospectively defined. We can also define a trial success as Y percent of the patients have successful outcomes. Again, Y percent would be prospectively defined.

The pros of this kind of study is you can measure patient and trial success. On the con side, we do not have a concurrent control group. And, also, this does require a prospective baseline period. For this reason, it's not as popular with either doctors or patients since they must wait for treatment. Patients want to be treated right away.

The alternative is a retrospective baseline period, but this requires--this relies on the patient's memory of their condition before, and it's not as accurate.

Next slide?

The next trial design I'll discuss is randomized control. Here the patient is randomized into either the treatment group where therapies are on or a control group where therapies are off.

Next slide.

Here we can measure cohort results. On the left

we see a group of people in the control group, and we can measure the average of the control group, and we can measure 95 percent confidence intervals around that, which is approximately two standard deviations. Likewise, we can measure the average and the confidence intervals of the treatment group, and we can compare the averages in confidence intervals of the two groups.

Next slide.

The pros of this kind of trial is that you have a direct comparison while minimizing bias. On the con side, since the individual patient is in either the control or the treatment group, you can only analyze cohort results. It is difficult to identify individual patient successes. And an important thing to remember in cohort results is that outliers can affect the mean. If you have a patient who has spectacular either good or bad results, it will affect the outcome or can affect the outcome. The other con is that some patients do not receive treatment. They are in the control group.

The crossover design. Here patients are randomized into either the control or the treatment group first, and after a period of time are switched into the opposite arm.

Here we have Sam who starts out in the treatment group and is switched to the control group, and Fred starts

out in the control group and is switched to the treatment group. And we can measure individual successes.

We can also measure trial successes. Here we see Sam Sue, and Debra all have a decrease in the clinical measure, and John and Fred do not. And we can evaluate the percentage of patients who have successful outcomes.

Next slide.

So how do we define success? We have the patient success, which we already spoke about. A patient has X percent reduction in whatever quantity we're measuring. We have trial success, and this can be defined in two ways: Y percent of the patients were individual successes, or we can measure the treatment cohort. The treatment cohort has X percent reduction as compared to the control.

Next slide.

The pros for this kind of trial. For the same critical difference you need fewer patients for statistical significance. All patients eventually receive treatment, and you can look at both cohort trial success and patient trial success. The cons are you may need a washout period due to crossover--due to carryover effects, rather. There is potential for a period effect. That means you have to look at whether it matters whether the patient is in the treatment or the control group first. And there could be a longer trial duration to accommodate all phases of the

trial.

Next slide.

It's important to remember that it is possible to have acceptable cohort or trial reduction without having significant amount of patients who have successful individual reductions.

Next slide.

As an example, if we define a patient success as X percent reduction, you can have half of the patients who have greater reduction, X plus 10 percent, and half of the patients who have less than that, X minus 10 percent reduction. Then the average for the cohort is X, but you only have half of the patients with successful outcomes.

Next slide.

That's my summary of clinical trial design, and I'd like to turn the discussion over to Frank Lacy, who will discuss spinal cord stimulation for angina.

CHAIRPERSON CURTIS: Why don't we--we're going to let industry go first here, and I understand we have a representative from Medtronic.

Dr. Diaz, our neurosurgeon who's part of the panel this morning, got called to the operating room. He's supposed to be available at 9:00, and so as soon as he is available, we'll tie him in by conference call.

DR. DeJONGSTE: Members of the FDA panel, ladies

and gentlemen, Medtronic has invited me to discuss with you a new promising therapy for patients who have chronic refractory angina. I am a cardiologist. I'm working as the chief of staff in the Netherlands, and I started my career about 50 years ago in rate-responsive pacing. In fact, the first rate-adaptive pacemaker, the QT device. From then on we had a dispute with the R&D Department of the industry if we could safely--not safely--if it was useful to implant a rate-adaptive device in patients with atrial fibrillation. And we started to investigate it, and, in fact, exactly 15 years ago I was in Washington to present to the American Heart Association the first results by stimulating the ventricle and regularize the atrial fibrillation.

But, unfortunate, at that time, atrial fibrillation was not very attractive and not very appealing to cardiologists, so my chief of staff forced me to change the subject, and I was appointed the head of the Coronary Care Unit and there I came across quite a few patients who had refractory angina. And thanks to our government, we got a grant to study and evaluate the spinal cord stimulation feasibility study for different indications, and it turned out after a couple of years that angina was one of the best indications.

CHAIRPERSON CURTIS: Excuse me. Could you state your financial interest in what you're talking about?

DR. DeJONGSTE: None at all.

CHAIRPERSON CURTIS: Were your expenses paid here?

DR. DeJONGSTE: Medtronic paid my flight.

CHAIRPERSON CURTIS: Okay.

DR. DeJONGSTE: Next slide, please?

So what I'd like to stress is for this therapy you need a clinical organization. You need to collaborate in a team. And we have a group of cardiologists collaborating together and a secretary within the Department of Neurosurgeons, neurosurgeons doing the implants. And then we have the pain center, a nurse and a physiotherapist and an anesthesiologist, a neurologist, and a psychologist. You don't need all these people to involve, but you need for follow-up a team approach.

Initially, when we started 15 years ago, there was a lot of skepticism. The industry don't buy it. The cardiologists, they deny simply the problem. When they came across patients with refractory angina at that time, they just sent them to the home physician, and the problem was denied for a long period of time. So, initially, the spinal cord stimulator therapy met a lot of skepticism, but with critical use specifically in these patients, non-option patients, there was growing enthusiasm, specifically in Europe, and if you have a team approach necessary for the follow-up and the indication and you have a sound

indication, you will have a success rate of about 80 percent after a couple of years.

So what I'd like to focus on in the next 15 minutes is about the efficacy and to stress that it's a reversible therapy. It's comparable to pacemaker therapy. You do the implant and you can do it in a cat lab(?) even, and if there are problems with the system, you can easily remove it. It's not a destructive therapy. It's safe with regard to the low complication rate. The anginal pain is not concealed during an AMI. I'll come back to that later. The mortality and morbidity are not adversely--they appear not adversely to be affected. And the underlying mechanism we think appears to be related to a reduction in myocardial ischemia.

How we define chronic refractory angina, and then I'll go a bit into detail the procedures, to highlight very briefly the clinical studies, and come back to the safety.

We have defined chronic refractory angina as severe angina, disabling angina, despite where they have optimal medication and resulting from significant coronary artery disease, with demonstrable reversible myocardial ischemia, unresponsive to standard anti-ischemic therapist such as optimal pharmacological treatment, beta-blocking agents, calcium, long-acting nitrates and so on, and revascularization procedures such as PDCA and CABG procedures.

If you look at the demographic criteria, predominantly they are males. The age is really young, 62, and I have to stress that the history is about 10 years, so you're dealing with a specific subgroup of patients who have three vessel disease and they're still young and have a long history of coronary artery disease. And despite the fact that they have severe coronary artery disease, they have a moderately hampered left ventricular ejection fraction. So in some respect, these patients are survivors of the disease.

What about the procedure of spinal cord stimulation? I already mentioned that it's comparable to a pacemaker implant. You can do it in a cat lab(?), and in every hospital you have epidural punctures, several per day, maybe hundreds. So it's a safe procedure to do, and then you introduce the lead epidurally.

Excuse me. One back, please.

What you're doing is that in a (?) patient you insert a needle and you insert a lead up to T1, slightly left from the midline, and then you stimulate externally, and the patient has to feel the paresthesias, that's a tingling feeling, and covering the region where he or she is feeling the anginal complaints. Then the lead is tunneled to the device, and the patient can activate the device with a magnet, applying a magnet, and we advise it to--next

slide--to do that three times per day during one hour. That's completely arbitrary. In Sweden, they stimulate four times 2 hours. In Italy, they stimulate continuously. All the same results. So we don't know exactly at this time what's the best, and we do it just to save the battery because the battery will last about four years when you use three times one hour. Additionally, the patient can stimulate during an anginal attack.

The settings are subjective, standard factory settings, and the output is individually tailored to the patient when he or she is feeling--having the best comfortable paresthesias.

Now, what about clinical studies performed? There are several randomized and open clinical studies, and I would like to focus a bit on that. The problem with these studies is that there are methodological problems because spinal cord stimulation requires paresthesias, so you can't blind a patient. And, in addition, there is no real placebo for neuromodulation. Finally, stimulation artifacts you can see on the EKG, so you can't blind the doctor. So the only thing you can do is to randomize the patient or have open controlled studies, and that's what we did.

We selected patients, as I previously mentioned, patient with reversible myocardial ischemia without another option, and after selection we randomized the patient, and

we have baseline tests, exercise test, Holter monitoring and so on. And then we do the implant in both groups. So that excludes an operation bias. Then for three months the device is inactive in the control group, while it is immediately activated in the treatment group, and after three months, after a period of three months, there is no longer a randomization. Patients are their own controls. Now you can compare the baseline tests with the study period within the group and between the groups comparison.

We do that, for instance, with quality-of-life parameters in the treatment group, the number of anginal attacks, the number of nitroglycerine tablets, the visual analogue scale, and quality-of-life measurements. You can see that when you compare the baseline to the study period, there is a significant decrease in the treatment group, but there is no change in the control group. The number of nitroglycerine tables intake is significantly decreased in the treatment group per day, while there was no change in the control group. The visual analogue scale is improved. The patient has less pain, and the quality of life is significantly improved in this randomized controlled study, and this effect is maintained for a year.

If you are using harder parameters, cardiac parameters like exercise stress, you find the same results. This was published in the Journal of American College of

Cardiology a couple of years ago. The treatment group exercise duration significantly increased in the treatment group baseline versus study period; in the control group, no significant change. The time to angina in the treatment group significantly increased, and there is no significant change in the control group.

In addition to these findings, prolonged exercise duration, we observe in this randomized controlled study, when you compare baseline to study period, significant decrease in ST segment depression at maximum exercise duration in the treatment group and no significant change in the control group. So despite the fact that the patient had prolonged exercise stress testing, they have less myocardial ischemia with treadmill exercise stress testing.

Next?

Many studies have been published, at least 100 articles you can find Medline. We have used also open and randomized controlled studies with different numbers of patients. And, of course, I can't highlight them all, but they all pointed in the same direction, that it's an effective therapy.

We conclude on this slide about the anti-ischemic effect. I mentioned that the exercise stress testing, there was an increase in exercise capacity found by many groups working in this field, and in conjunction with less ST

segment depression. Ambulatory Holter monitoring had the same results, less total ischemic burden, less ST segment depression. Right atrial pacing study found the same results. Flow studies mentioned that there was an increase in the coronary blood flow in the apparently normal coronary artery. The stenotic artery is not--I can't go into detail with that in the other studies, but the stenotic artery is not able to dilatate. So we think that there is an opening up of collaterals, and finally, you can find in the PET studies a redistribution in coronary perfusion.

So it appears to have--it is an effective therapy, and it appears to have anti-ischemic properties, and what about the safety respects? There are at least two questions about that. Does it mask anginal pain specifically during an acute myocardial infarction? And what about the effect of spinal cord stimulation on morbidity and mortality?

To address the first question, I would just like to introduce you to one of the patients who had had successful spinal cord implantation a couple of years ago, she was excellent, but after one year she experienced an anginal attack for 30 minutes. And despite the fact that she was stimulating, whatever, she tried to do--and taking nitroglycerine tablets, she thought this is no good, and she was immediately reported to the hospital for help and an anterolateral acute myocardial infarction was diagnosed, and

she was treated with streptokinase at that time. The damage was mild.

So what about the literature? In the literature, six publications with different numbers, and they all pointed in the same direction that during an acute myocardial infarction, the anginal pain is not concealed by a stimulator. I don't know if that is related to the fact that maybe during an acute myocardial infarction the anginal pain is different from stable angina, or if there are other factors involved, necrotic pain or whatever. But the observation is consistently that you cannot conceal the symptoms of an acute myocardial infarction with this therapy, and that makes sense because also from a mechanistic point of view you are unable to block the signal. You're not abolishing the signal, the so-called warning signal of angina. You just modulate it, and you modulate it by stimulating the thick fibers, and you're not able to stimulate the thin fibers that are processing the pain.

Next?

What about morbidity and mortality? There is not a control group in the literature. You can't find anything about this group of patients. So we did a retrospective study and just one prospective study which I'll highlight very briefly.

The first is we published in Heart half a year ago the outcomes of two-year follow-up in 570 patients, and there was an improvement in the average Heart Association classification 3.4 to about 2, and the mortality--the overall mortality was 7 percent and the cardiac mortality was 5 percent. So I already mentioned that we're dealing with a group of specific survivors. They survive the disease. So the mortality rate is very low, the cardiac mortality rate. And 24 percent of the patients who died had an acute myocardial infarction and only 8 percent of the survivors. So the patients who died, they are more sick. And 66 percent of the diseased patients had one or more admissions during the 2 years follow-up. So the predictors of mortality were the same as for the group without any treatment. You could find in the literature left ventricular ejection fraction is the predominant predictor of outcome in this group of patients. Beta-blocking agents, age, sex, they were multivariate independent predictors of mortality. This is a retrospective study.

There is just one prospective study published in Circulation last year, and that's by Mannheimer, a Swedish group, who randomized patients who were high-risk patients on an intention-to-treat basis to electrical stimulation versus bypass surgery. And they found after a half-year of follow-up that symptom relief was comparable, not

significant. The myocardial ischemia was significantly improved in the group after bypass surgery while there was no change in myocardial ischemia. And that may be related to the fact that the patient--that this study was not designed for comparing myocardial ischemia with the secondary endpoint, so the patients were exercised with the stimulator off. That might be an explanation why there is definitely a difference.

The morbidity was not significantly different, but the mortality was significantly different in favor of the spinal cord stimulation. So they suggested that in a group of high-risk patients you can consider spinal cord stimulation as an alternative to bypass surgery, but I have to stress this is a specific group of patients.

So, Mr. Chairman, ladies and gentlemen, in conclusion, there is evidence that spinal cord stimulation is an effective therapy, as I previously mentioned. After four years follow-up, we have about 80 percent success. It is a safe therapy. It's reversible with a low complication rate. It's not like drugs. You can't overdose it. It's non-toxic. The anginal pain is not concealed, and the morbidity and mortality are not adversely affected, as we know by now. And the underlying mechanism for action appears to be related to a reduction in myocardial ischemia.

Thank you very much.

CHAIRPERSON CURTIS: Thank you.

DR. VETROVEC: Can we ask questions?

CHAIRPERSON CURTIS: Go ahead.

DR. VETROVEC: Two questions. One is, can you give us any insight into what the chronic heart rate changes are in response to this? In reading the literature, it looked like in some of these studies there's a 10 beat per minute chronic heart rate increase. Has that been your observation?

The other issue is, how critical is it in terms of where you actually put it in terms of stimulation? Because it seemed to me there was a lot of variation. Could you give some insight into what percentage of patients really get full effect from where it's placed?

DR. DeJONGSTE: To address your first question, I'm not aware of any literature that was an increase in heart rate. There is from experimental data, there is a decrease in heart rate that Maglio (ph) published in 1976. We have not found that there is an increase in heart rate. It's comparable.

What you can do is you can compare at the same rate pressure product the amount of myocardial ischemia, so comparable workload, and then you find the same result. There appears to be a reduction in myocardial ischemia. So with respect to your heart rate, I am not aware of any

literature that there is an increase in heart rate during spinal cord stimulation.

DR. VETROVEC: Even at rest?

DR. DeJONGSTE: Not even at rest. And to address your second question, that was related to the position of the electrode, the tip of the electrode. We are using now quarter polar leads so it's less critical, but experience is that if you stimulate--just patient experience. It hasn't been published. It's common knowledge in this field. If you stimulate another place, not at T1, slightly left from midline, it's less effective.

DR. BRINKER: Jeff Brinker. I have a couple of questions. One is you mentioned in relationship to comparison to drug therapy you can't overdose. In this form of therapy, I think I heard you suggest that you can't underdose either, because it seems to be a factor of whether it's on for short times during the day, intermittently, continuously. And it would seem to me that in almost any kind of therapy that we do, there is some sort of dose effectiveness and there is some level at which things are not as efficacious. And this puzzles me as to why this does not appear to be the case here.

DR. DeJONGSTE: This is time-related. In time you can stimulate continuously and you can stimulate for three hours per day. And it puzzles me, too, how you can cover

the anginal complaints when you only stimulate three times one hour a complete day. And that's related to the fact that there is a hangover effect or a carryover effect or post-stimulation analgesia, whatever you want to call it. So that is also related to the fact that you're not blocking the signals, because if you block the signals and you stop the stimulation, then you have immediately--you have no effect at all anymore. But if you stop the stimulation after one hour, you have prolonged effect.

So it's not only modulating the nerves, but there is more involved. And I go into the mechanism of that, and I think it's way beyond this scope, but there are more--it's quite difficult to explain, but it will take some time to explain exactly what I am meaning to you. But I don't think you were referring to that, what the underlying mechanism is.

DR. BRINKER: That's okay. Let me ask you sort of the second question that I have, and that is that in some of the data that we were given to read, the pulse pressure differences at maximum exercise at treadmill were different between control groups and--or with the stimulation on and with the stimulator off.

That bothers me a little bit because it's easy for me to conceive of a beneficial effect if with exertion you affect the pulse pressure product, and this, in fact, was

one of the thoughts about cervical sympathectomy in the past for angina.

I guess you hinted at another possible mechanism, which I'm not sure I completely buy into, but that is an increase of blood flow in normal coronary arteries which will there, via collaterals, effect a change in angina without--or perfusion, without causing a difference in pulse pressure product.

Of course, in patients with diffuse coronary disease, triple-vessel disease, who in general would be the kind of patient that this might work in, or might be chosen for, at least in this country, that may not be an effective mechanism of providing anginal relief. And the other piece of the pie is that this type of therapy seems to be effective in patients with Syndrome X, at least certain patients who have normal coronary arteries to begin with and probably have some sort of small vessel problem.

So can you provide insight in those two areas?

DR. DeJONGSTE: To address your first question, the rate pressure product in the treatment group is increased because they have a prolonged exercise stress test and beta-blocking agents. The majority have beta-blocking agents. Beta-blocking agents are less effective at heart rate of higher levels. So it doesn't surprise me that they have a higher rate pressure product within the treatment

group if you compare within the treatment group because they have a prolonged exercise stress testing.

DR. BRINKER: I was--

DR. DeJONGSTE: But despite that fact, they had less myocardial ischemia on EKGs.

DR. BRINKER: And the reason for that is? Your reason for less ischemia at a similar or higher rate pressure product is?

DR. DeJONGSTE: The comparable workload is lower and maximum exercise is also lower. And the reason for that is that I think we did a study with it prior to PDCA and so this had nothing to do with the PDCA. Published that in the American Journal of Cardiology two years ago. And we give the patient TENS half an hour prior to the PDCA, and we did double of all measurements, and we found that there was on the EKG less ST segment depression while there was an increase in flow in their apparently normal coronary artery. So the only conclusion we could have is that it opens up collaterals; otherwise, it's difficult to explain. And that was consistent with the finding of the PET scan, that it was more homogeneous, the question of variation was more homogeneous, represent a more homogeneous effect of spinal cord stimulation on the heart.

With respect to your second question about Syndrome X, we have a PET scan, and we're using PET scanning

in Syndrome X, and in Syndrome X there is also a high rest flow, coronary flow, and there is a kind of patchy distribution. So it might very well be that it is related to the sympathetic outflow, who is vasoconstricting some vessels, and some others not. And what we found with PET scanning is that spinal cord stimulation is also giving a more homogeneous distribution in the heart in these patients.

CHAIRPERSON CURTIS: I want to get back to this idea about duration of treatment. All the studies, it seems like they're either being used continuously or you have, you know, three times one hour. Wouldn't it be possible to do some sort of a dose response type of study where--I mean, how does the patient know that stimulation for five or ten minutes isn't enough? I mean, you seem to say that the paresthesias are important. But you know, maybe all the studies have been done with dose levels that are going to work no matter what. You say the paresthesias are important, but what about if you stimulated for five minutes twice a day? Would you really expect to see an effect? I would tend to doubt it. Ten minutes three times a day, something like that, I mean, isn't there some lower level you could get to where the patient would feel the paresthesias, but yet you wouldn't expect that you'd see an effect on the angina?

DR. DeJONGSTE: I think it's very, very complex to perform a study on dose response curve. The reason is, for instance, (?) published in Circulation in 1994 using TENS transcutaneous form, doing Doppler flow studies only five minutes. So you have to do that dose response curve in time, five, ten, whatever. Then you have to do threshold stimulation, higher stimulations, and whatever. So that's the problem. Because it's so subjective, every patient is responding in another way. So you have to tailor the therapy to the patient need, but you have no control what's the best for the patient. So I don't--to be honest, I don't know how you can form a dose response curve to address this problem because the variety is so huge.

CHAIRPERSON CURTIS: Well, maybe not a strict dose response curve, but what if you had your two treatment groups, and one you treated for whatever you thought the minimum you needed was, you know, an hour at a time, three times a day, plus as needed, and the other group was a much lower rate of stimulation but yet it wasn't off altogether, and tried to compare those two groups.

DR. DeJONGSTE: But then you have to separate the anginal complaints from the myocardial ischemia. We have the impression--but it's not proven, it's just very preliminary, but we collaborated with the Swedish group, Mannheimer, and we have the impression that you can

stimulate three times one hour and you get rid of the anginal pain, because that's a kind of hangover. But for myocardial ischemia, we got a feeling that you need--that it is better to continuously stimulate. So you have to separate the anginal from the myocardial ischemia. It depends on your endpoint.

CHAIRPERSON CURTIS: Renee?

DR. HARTZ: A couple of observations.

CHAIRPERSON CURTIS: Use your microphone.

DR. HARTZ: Hartz from New Orleans.

First of all, if this device truly is effective in Syndrome X, I have a great deal of difficulty postulating any kind of blood flow redistribution. No matter what your PET scans show, it just seems as though if the surface coronary anatomy is normal, that a redistribution of blood flow does not make sense. So that in my own mind this seems to be a purely neural phenomenon of some type. I don't think you can really tell us which it is at this point, but because that's the case, in any of your preclinical or your clinical work, have you used vagal stimulation as a comparison? Have you used very low level skeletal, say paraspinal muscle stimulation? It doesn't make sense to me that we can just assume that this is because of spinal cord stimulation, this is in some way some form of acupuncture and it's--one of the postulates for relief of pain in TMR is

vagal stimulation. So should we be looking more at the mechanism rather than a dose response curve? Because your slide on stimulating three or four times a day, decreasing the anginal episodes and the ischemic burden may purely be an effect that the patient is resting, doing something completely inactive during these times that they're stimulating. You need to tell us are they actively exercising during their stimulation periods, because if they're not, this effect could be purely arbitrary and because of their decreased level of activity.

Finally, I'm concerned and have not seen in any of these articles--I was aware--I added up 266 patients in the articles that we were given. I don't really see a lot discussed about diabetics. Have diabetics been included in any of these studies? Our whole concern in diabetics is masking of angina, and are they excluded from your studies?

DR. DeJONGSTE: No. I showed that slide about the article in Heart, and diabetes was one of the predictors of outcome. So we included in all the studies. I don't know about here, but I can give you the number of patients. We include diabetes patients as well.

DR. HARTZ: Did you notice whether your diabetics could distinguish their angina?

DR. DeJONGSTE: Yes, they can. And to address your other questions, Syndrome X is still a debate, but with

the PET scan we do pressure test, and nobody knows at this time where it is.

What Syndrome X stands for, micro-vessel angina. We did a lot of work, and we don't know exactly--this slide here.

No, sorry, it's not here. It is in the article, in Heart. In this article, we have diabetes as well, but it was univariate, related to the outcome. That is why I'm not putting it in the slide.

So about Syndrome X, I don't know, we just tried to figure it out, and we're working with (?) on that topic on Syndrome X. I don't know if it is related to flow or not, but this is what we found, and maybe it's just a phenomenon. I don't know.

With respect to your question about vagal stimulation, we're working with Forman(?) in Oklahoma and doing research on this vagal stimulation, because we have ideas that indeed it is affecting the vagal nerve, high entrance, because that's about the side where the vagal nerve is coming into the heart. It's more likely that it's kind of vagal stimulation than sympathetic stimulation.

DR. HARTZ: Because really, technically, it's much easier to stimulate the vagal nerve than to put an epidural catheter in.

DR. DeJONGSTE: Yes, but the depth--

DR. HARTZ: I mean, maybe a little bit more surgical, but a very easy thing to do.

DR. DeJONGSTE: You may be right. I'm not familiar with that, actually.

CHAIRPERSON CURTIS: Go ahead.

DR. CHANG: Did you observe any silent myocardial infarction such as new EKG changes, new abnormalities, or new deep space perfusions? Of course, the concern is that it does not--the spinal cord stimulation does not mask chest pain, angina during acute myocardial infarction, but what about silent myocardial infarction? Would that increase the risk of a silent myocardial infarction?

DR. DeJONGSTE: I can't answer that. We haven't looked for that, and it's very difficult to look for that. But there must have been--there should be patients who have been treated with spinal cord stimulators who have the silent myocardial infarction because that's normal in a population. So they're not aware of the myocardial infarction. That happens every day to everyone--well, not to everybody, but quite a few patients.

DR. CHANG: I think my question was: Does spinal cord stimulation increase the risk of silent myocardial infarction? But now, the patient may have a little bit of chest pain, now the patient does not have any chest pain.

DR. DeJONGSTE: No, because why should it?

Because their reports are clear in that sense that they all feel their anginal attacks during an acute myocardial infarction, and there must absolutely have been patients who have a silent myocardial infarction, as is the normal route, and it's very difficult to discriminate if that's related to the spinal cord stimulation therapy or not, because you have it in the normal population as well. So then you need a huge group of patients where you have a control study and you can figure out the number of patients with silent myocardial infarction with and without stimulation.

DR. CHANG: My second question is that the patients used spinal cord stimulation to prevent angina and to treat angina, according to one of your slides. Can you give us some insights how efficacious it was in preventing versus treating angina?

DR. DeJONGSTE: It's very efficacious in preventing angina, and the patients reported that they can master their anginal complaints better with spinal cord stimulation than with nitroglycerine intake. So they can really prevent it.

But, ultimately, they feel their anginal complaint. When they start exercising, that's what the study by Mannheimer in the British medical journal also showed in '93, that ultimately the patients all feel their anginal complaints. So it's just deferring the anginal

threshold.

DR. CHANG: If they did experience angina, did they turn on the machine to treat?

DR. DeJONGSTE: Yes, they did.

DR. CHANG: How effective was that?

DR. DeJONGSTE: Then it stopped. Not when they-- they--if they started prophylactically, then they go to heavy exercise, they will have anginal complaints, the majority, ultimately. So if they switch it on then, it's not working. But if they switch it on--if they don't use it prophylactically and they start exercising and they switch it on then, it will work, unless they start more and more exercise, and when they have profound exercise, it's not working anymore.

Does that answer your question?

DR. CHANG: I'm looking at one of your slides that's showing the stimulation protocol, either three times a day or four times, or whatever, and plus during an anginal attack. Is that anginal attack during stimulation or when they're not--when they were not stimulated?

DR. DeJONGSTE: When they're not stimulated.

DR. CHANG: So did the spinal cord stimulation work?

DR. DeJONGSTE: Usually, yes, it does, unless they have a myocardial infarction.

CHAIRPERSON CURTIS: Renee?

DR. HARTZ: In your country, is this a less expensive form of therapy than angioplasty?

DR. DeJONGSTE: No. What do you mean in my country? I mean, we all use it in Europe, and in my country there is no reimbursement for the therapy. So--

DR. HARTZ: I mean the cost, not the charge.

DR. DeJONGSTE: The cost of angioplasty is much cheaper. But these patients have no option.

DR. HARTZ: And a lot of these patients, however, would have been angioplasty candidates?

DR. DeJONGSTE: No. They're not amenable to revascularization procedures at all. So it's the same group as laser therapy, while not--

DR. HARTZ: It's interesting because the mean age is so young in your series and many of the others. It's hard to imagine here that many patients being not amenable to angioplasty because everybody has angioplasty. That's why I'm asking about the cost ratio.

DR. DeJONGSTE: Yes, that's exactly what happened. I'm fighting for 10 years or 15 years now. Sometimes it's not an option. When you have, for instance, these diabetes patients, they have diffuse affliction of the coronary artery, and you can operate on every patient you like, but is it useful to do that? So we have a team of thoracic

surgeons and cardiologists who discuss if a patient is amenable for revascularization procedure or not, and more than half of our patients are operated with complete arterial revascularization. So we use the radia (?) artery. So our surgeons have a lot of skills, and our interventional cardiologists also. But despite that fact, there is--it's a growing problem, but the majority of these patients have been operated on several times. They have had triple bypass surgery. So there is no re-operation anymore. I think 80, 90 percent have had PDCAs, more than one, or (?) procedures.

CHAIRPERSON CURTIS: Go ahead.

DR. BAILEY: A couple of questions. First, is there any way that you can look in your data to see whether--I know that you've observed both a reduction in pain at an equivalent level of exercise, and also the ST--the electrocardiographic changes. But can you tell from your data whether there's a similar relationship between the objective ischemia measures and the subjective experience of pain or whether it shifts the experience of pain? In other words, how much of it can you determine to be reducing ischemia versus the experience of pain at an equivalent amount of ischemia?

And the second question is--well, let me wait for that.

DR. DeJONGSTE: No, I can't tell you that. I don't know.

DR. BAILEY: But do you have data--would you be able to do experiments which would be able to distinguish what's happening by looking at the stimulation on or off and doing an exercise protocol?

DR. DeJONGSTE: With the stimulator off, they are not able to have that--we started originally--that's how we started in 1986, to perform exercise test with the stimulator off. And then we were not able to demonstrate significant improvement in exercise duration, so that's why I went to the Swedish and said how is it possible that you find an increase in exercise duration, and we compared the protocols, and they were always stimulating--the patient was always stimulating during exercise.

DR. BAILEY: I guess I'm suggesting you plot the ST data versus the experience of pain.

DR. DIAZ: Good morning. This is Fernando Diaz.

DR. BAILEY: I guess my question is: Does anyone have an ischemic model in animals that could be used to distinguish between subjective results and pure ischemic changes?

CHAIRPERSON CURTIS: Excuse me. It sounds like Dr. Diaz has joined us.

DR. DIAZ: I am on the speaker, and I can hardly

hear you. Would it be possible to turn it up a little bit?

CHAIRPERSON CURTIS: Can we do that? All right. We'll take care of that.

DR. DIAZ: Thank you.

DR. DeJONGSTE: We have an animal model, and we're working on that with Druamer (ph) in Nova Scotia, Halifax, and Forman in Oklahoma and Jeff O'Dell(ph). They're all neurophysiologists, and what we have done is we occluded the coronary artery and we register the EKG and we look at activity in the intra-cardiac neurons. And we found that spinal cord stimulation was silencing the intra-cardiac neurons activity very consistently, and I don't know if you're familiar with intra-cardiac neurons. They call it the small brain of the heart. It is maintaining the integrity of the myo side. And if the activity is increased, that is usually the case in myocardial ischemia, then you can have severe arrhythmias.

So in some way it is interacting at different levels, and we're working on that dog model.

CHAIRPERSON CURTIS: We probably need to get the FDA to make their presentation, and once they do, we can go back and forth with any of this if anybody has any questions. So why don't we table the rest of these questions for now and let the FDA make their presentation.

MR. LACY: Good morning. My name is Frank Lacy,

and I'm an electrical engineer in the Division of Cardiovascular and Respiratory Devices. I'm here to open a discussion amongst the cardiovascular panel members regarding clinical study design issues for spinal cord stimulation for angina.

We are here today because we are struggling with spinal cord stimulation devices in terms of clinical study design for angina. We are working with sponsors to develop clinical studies which will demonstrate safety and effectiveness. Currently, there are no medical devices on the market for spinal cord stimulation for this indication. Today we would like to obtain your input to several study design issues to allow sponsors to collect data that could potentially support the safety and effectiveness of spinal cord stimulation for angina.

Our presentation will provide an overview of spinal cord stimulation, the components of the system, the indications for use, the study design issues, as well as the panel questions.

As you can see, the components of the spinal cord stimulation system include programmers, the stimulation circuitry, the generators, the receivers, the stimulation power sources, as well as the electrodes.

Currently, there are two types of systems: a totally implanted system as well as an RF or radio

frequency-coupled system. No matter which technology is used, similar stimulation therapies are possible. For the totally implanted system, the programmer is outside the body while the pulse generator, stimulation circuitry, stimulation power source, and electrodes are located inside the body.

On the right-hand side of the screen, you'll see an RF-coupled system where outside-the-body components include the programmer, the stimulation power source, the stimulation control circuitry, while inside the body there is a receiver, stimulation decoding circuitry, and electrodes.

Here we have examples of how the two different spinal cord stimulation systems might look. Spinal cord stimulation is accomplished by placing the electrodes in strategic locations on the spinal cord. The flexible electrode is passed percutaneously into the epidural space of the spinal cord, while an extension lead connects the electrode to the pulse generator. The totally implantable system shows the internal battery receiver and power source while the RF-coupled system shows an external transmitter worn by the patient with an antenna that transmits stimulation parameters to the implanted receiver. Both receivers in turn transmit the signal to the electrodes via the leads.

While the mechanism of action is unknown, there are several possible mechanisms cited in the literature. One such mechanism is gate theory, which postulates that the neurons involved in modifying the output of the dorsal horn include afferent fibers whose activity results in a sensation of pain and an inhibitory inner neuron that normally inhibits the projection neuron.

A second mechanism indicates the chemical neuronal interactions at the dorsal horn site are affected by spinal cord stimulation.

Then, finally, a third mechanism of action postulates that the release of the amino acid GABA acid increases significantly after an hour of spinal cord stimulation when compared to the baseline levels recorded before stimulation.

As far as the indications for use, cleared spinal cord stimulation devices are indicated for chronic intractable pain of the trunk and/or limbs. The RF spinal cord stimulators have been cleared under the 510(k) review process while totally implanted spinal cord stimulation systems have been cleared under the PMA process. All previously applications have been for a general indication. Any indication for the relief of anginal pain or the treatment of angina we believe should include a clinical study.

There are several clinical study design issues for the treatment of angina. They are: what is an appropriate control group, masking, the duration of study, effectiveness endpoints, as well as safety endpoints. What I will do now is spend a few moments outlining each of the issues with regard to study design.

While I've provided the background for our discussion, we would like to discuss study design issues for the treatment of angina. Much of the published literature in angina has focused on using the patient as his or her own control to establish effectiveness. There are other types of study designs besides using the patient as his or her own control. One alternative study would be a randomized controlled study where patients are randomized either to a treatment group having the stimulators or a control group that does not. Ethical concerns may be raised if the control group does not receive stimulation but receives an implant.

Another alternative study would be a crossover design which Ms. Kroen spoke about earlier this morning. Thirdly, there is a single-arm historical control study. Last, there have been several published dose response studies where stimulation parameters can be adjusted.

We will be asking you as members of the advisory panel to focus on the pros and con of a control group and

different alternative studies.

Another issue that we would like for you to discuss is masking the patient. Patients under local anesthesia feel a tingling sensation to guide the physician in placing electrodes for proper coverage of the pain site. Therefore, the patients will always know whether stimulation is on or off. Even if the stimulation is delivered at very low levels and/or at short time intervals, the literature indicates that even these stimulation parameters may provide some relief from anginal pain.

In your discussion of a dose response study, you may want to consider these points.

The case series reported in the literature report patient outcomes at intervals that range from a few weeks to one year. Any attempts made to determine study duration need to consider the potential placebo effect of this procedure, any questions about the duration of the effect of this, as well as any other assessment of safety measures. We would like for you to discuss study duration while considering the potential effects listed.

Effectiveness endpoints include physiological measures such as pulse rate and ST segment depression, one or two class reduction on Canadian Cardiovascular Scale, angina scale, or the New York Heart Association anginal scale; treadmill exercise testing has also been reported as

an endpoint; reduced consumption of pain medications related to angina; hospital admissions related to angina; and quality-of-life measures related to angina.

We would like for you to discuss study duration while considering the potential effects listed above, as well as discussing the primary potential and secondary effectiveness endpoints.

Safety issues in any trials of implantable medical devices, for example, include infection, battery failure, lead migration, as well as electrode breakage. But the literature provides minimal information data on safety data in terms of endpoints. One article evaluated whether stimulation may mask symptoms that signal an acute ischemic event. Whether there are safety endpoints specific to this indication is a question we would like for the panel to discuss.

To recap, clinical study design issues for spinal cord stimulation for angina include: what would be an appropriate control group, masking, duration of the study, effectiveness endpoints, as well as safety endpoints.

Please note that our panel questions have been revised from what was originally posted on the Web and sent to the panel members in an effort to facilitate the panel discussion. These questions have not changed in overall content, but changed only in terms of organization. These

questions will be displayed on the screen in front of us today.

Based on the literature information and other known clinical information, please discuss the advantages and disadvantages of the following study designs for spinal cord stimulation for angina. Also, please discuss any clinical issues that would be specific to these issues, and we mention the single-arm with the baseline period, the randomized controlled study, the crossover study, the single-arm historical control study, as well as the dose response study.

The second question to the panel is we would like for you to please discuss the advantages and disadvantages of the following effectiveness endpoints. For example, I showed you a slide about five screens ago where we talked about the physiological measures, the treadmill exercise testing, the one or two class drop in the angina scales, hospitalizations related to angina, as well as treadmill exercise testing and quality of life. And we can go back to that screen at a later point if you need to.

What primary and secondary endpoints would be important to collect to fully characterize the effect of spinal cord stimulation for angina? What would be a clinically meaningful response to each of these endpoints? As well as for each endpoint, we would like you to discuss

what follow-up duration is necessary to capture a clinically meaningful benefit, taking into consideration the duration of the placebo effect.

And, finally, our last question to the panel regarding spinal cord stimulation for angina: Endpoints such as lead migration, infection, electrode breakage, and battery failure have been reported in the literature for active implantable medical devices. What we would like for you to do is to discuss any safety endpoints that would be important to consider during a clinical investigation, as well as discussing the follow-up duration necessary to capture the safety endpoints.

At this point I would like to turn the discussion over to the panel, and I am available for any questions that you may have.

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CHAIRPERSON CURTIS: I want to ask you one thing. It goes back to a question I asked you before. I wasn't aware in any of the readings that you gave us that-- obviously, the patients are aware when the stimulation is on or off, but I wasn't aware that there was any data on extremely short durations or intervals of therapy. I don't mean the pulse width and that sort of thing, but I mean--

MR. LACY: Time-wise.

CHAIRPERSON CURTIS: Time-wise, you know, ten minutes three times a day. Has anybody looked at that sort

of thing?

MR. LACY: We have looked at it. Some of it may be in literature that I didn't provide in oversight looking at the bigger issues, I guess, that we wanted to discuss today. But in several meetings with sponsors, that's been called to our attention and shown to us in several articles. So if there's not one there, I apologize for that.

CHAIRPERSON CURTIS: Well, is it effective?

MR. LACY: All the articles show they're effective, but there are certain design issues which are up for discussion today because we're not sure that they are actually either following the patients for a long enough time or using the appropriate primary and secondary endpoints or things like whether they used the right testing for the patients to determine whether there was a decrease in anginal pain.

CHAIRPERSON CURTIS: I was just trying to search for some way that we could have not just, you know, the device turned off in a group of patients and follow them.

MR. LACY: Sure.

CHAIRPERSON CURTIS: Because of placebo effect.

MR. LACY: Exactly.

CHAIRPERSON CURTIS: Every time you have implantable devices, those issues come up.

MR. LACY: Exactly.

CHAIRPERSON CURTIS: I just find it so hard to believe that hardly turning the thing on at all works just as well as using it frequently.

MR. LACY: Well, I don't know if it works just as well, but the literature reports that it does give some relief from anginal pain. And then you have the treatment group which has some range of level of treatment effect. And when you put all that together, you can't decipher between the control group and the treatment group, and that's sort of one of our dilemmas that we've had over the last couple of year with sponsors.

CHAIRPERSON CURTIS: Any other questions for Mr. Lacy?

DR. DIAZ: If I may offer a comment on that placebo effect?

CHAIRPERSON CURTIS: Sure.

DR. DIAZ: In studies that were conducted at the University of Minnesota in the late 1970s, early 1980s, with the use of spinal cord stimulators for the control of peripheral pain, the placebo effect was as great as 28 percent. Even for patients who did not have batteries on their stimulator, they felt relief of pain.

MR. LACY: Interesting.

CHAIRPERSON CURTIS: I think that's exactly the issue that I'm thinking about. Whenever patients have

implantable devices, this just--it's not like a drug placebo. There's such a strong placebo effect, it's hard to sort that out with everything else.

MR. LACY: Yes.

DR. VETROVEC: Has there been any attempt to control this? Since the real issue is the patients feel some kind of tingling, one could provide tingling to the skin externally with something that wouldn't require putting in the internal device. So that one could imagine every patient having a device put in, but half of the patients having the device turned on early and half of them having it turned on late, but also wearing throughout the course an external just skin stimulator so that in a sense the patient wouldn't know why they were being stimulated or which was the effective treatment, so they'd be experiencing some symptom or some stimulation all the time, one theoretically effective, spinal cord, and one not because it's just a cutaneous.

I'm wondering if that's been tried or if any of the sponsors have looked at how they could provide that.

MR. LACY: We haven't seen the scenario that you just described. One of the bigger problems that we have is that when we sort of come up with on paper these design issues, there inevitably ends up being one of the problems with regard to the placebo effect, how long should we follow

the patient, should there be a crossover--the issues that I sort of raised for you. And while I think that you may have a very good point, that's one of the things we'd like for all to discuss today.

DR. DOMANSKI: I guess I have a fundamental question that we should answer, too. Clearly, when you're dealing with medical therapies in general, you'd like to have a therapy that has a distinct mechanism and provides therapeutic benefit. Clearly, placebo effect from a symptom standpoint can provide a fair amount of benefit, and I guess the question that I have for the FDA is: Should we be working to ferret out, to try to make as sure as we can that we're not dealing with placebo effect and perhaps fail? Or are we willing to accept placebo effect as a mechanism of action with these devices? I mean, we went down that road a little with the TMR discussion, and I think that's a fundamental question.

If the answer is we don't want to accept a placebo effect for approval, then we need to be smart about helping design a trial that really does everything to eliminate it. And on the other hand, if we're willing to accept it, then perhaps, you know, the least burdensome approach would be not to pursue it, you know, to the nth degree. And I guess that's the real question, at least a real question that would be worth considering.

MR. DILLARD: Let me comment to that. This is Jim Dillard, FDA. I think in this situation where we do have an implantable component to either one of these particular types of devices, obviously our task is to prove reasonable assurance of safety and effectiveness and that there's a risk/benefit ratio that is reasonable for the patient population that's intended. And in this case, we are talking about an implantable component to a particular type of device which is not of insignificant risk, obviously.

And so I think that when you're talking about trying to weigh whether or not the placebo effect and if it's only a placebo effect will counterbalance the particular safety issues with an implantable device, I think that would be very difficult for us. And I think that what we need to be able to show is that overall when you looked at the product that there was some benefit associated with the device. If the placebo effect is not enough in that case, which I think, again, would be difficult for us alone to say, then I think we are faced with needing some additional benefit above a placebo effect, and I think that's something that has to be considered.

CHAIRPERSON CURTIS: Dr. Hartz?

DR. HARTZ: I don't think this placebo effect is very difficult to sort out. We haven't even mentioned wall motion abnormalities. And at implant, why aren't these

patients having some form of stress echo?

Now, we all know that wall motion abnormalities occur before ST changes, and in this particular group of patients, we can't even detect the ST changes because of the electrical interference. So should a patient leave that laboratory with one of these devices if one does not see invoked wall motion abnormalities which can be decreased by simulation? I mean, this can be done. We do it all the time in the operating room. This may even be a form of ischemic preconditioning that's helping these patients rather than placebo effect. I don't think we have that.

But I think it's easy to find out if there's a benefit by looking at wall motion abnormalities rather than ST changes.

DR. DOMANSKI: I really don't agree with that at all. I think that one might get rid of the pain by a mechanism that is indeed neural that might be useful in a patient who can't revascularized, and whether it gets rid of the wall motion abnormality or not, it takes care of the problem that we can take care of. So I don't think that's correct.

DR. HARTZ: Yes, but wall motion abnormalities are a precursor to ST segment abnormalities, and that's what we're talking about as--

DR. DOMANSKI: You know, I mean, that's well

known. That, of course, is clear. But the question is what we're trying to do, and if you have a patient who you can't revascularize--and that's the only patient I think this really should be used in--then whether or not you--you know, you can't cure the disease, and in this case you're not doing it. But you can fix the problem that the patient is having to the degree that science lets us do it. And the elimination of wall motion abnormalities and objective evidence of ischemia is not necessarily the only appropriate goal.

DR. HARTZ: Although to go back to risk ratio, we're talking about lead breakage, but one thing that has not been addressed in any of this is the risk to a patient with an epidural catheter who may subsequently need Coumadin. Now, I haven't seen any epidural bleeds mentioned here, but this is a tricky topic. And should a patient leave the lab if we can't prove that we're changing their ischemia in the laboratory?

DR. DOMANSKI: It depend son whether you improve their quality of life enough.

CHAIRPERSON CURTIS: But I think the thing we have to remember here is we're not voting on anything today. We're not being asked to say whether or not the therapy is safe and effective. We're being asked how you design the trial to get at that.

I think what we ought to do is go through the questions and use that as a framework for the discussion here. So why don't you put--

MR. LACY: Can we go back and--

CHAIRPERSON CURTIS: Yes, get the first question back up.

MR. LACY: There we go.

CHAIRPERSON CURTIS: What we're being asked to look at, then, is clinical issues related to the types of study designs, and we have had a description of what the different study designs are. What I'd like to do is throw it open for discussion now about any thoughts about what the appropriate way to design studies for the spinal cord stimulation for angina would be.

DR. CHANG: I just want to comment on dose response study. I think it's important, not only allow us to look into the mechanism of the therapy, also. Let's say it works, and if you can reduce the stimulation from three hours a day to three minutes a day, that would save the battery a lot and reduce the need for repeat explant and implant.

CHAIRPERSON CURTIS: I suppose a formal dose response study might be the sort of thing that would be difficult for some of the reasons that were talked about before that different patients may have different levels

that they need, and I've been constantly fishing for some way to have three minutes a day versus three hours a day and say have those be the two patients groups, and yet I'm hearing that there's some data that everything works, which I find very hard to believe. But, you know, we'd either have to take that sort of approach or the on-off approach, either the patients have it on or the patients have it off. And, of course, the problem with the off is that we don't have--the patients know it's off.

DR. DOMANSKI: But one thing is that from the standpoint of approving it for safety and effectiveness, it's conceivable that some of these studies are spurious. Perhaps the thing really works well at a proper dose. We don't know the proper--you know, we don't know the proper dose. But perhaps in designing a study what one would seek to do is to take a dose that it's reasonable to assume if there is an effect it's causing it.

I mean, it's hard to do the dose response thing on the front end, is the point. I'm not sure we really need that.

DR. DIAZ: I wonder if I could interject on that dose response. In studies done in (?) repeated spinal cord stimulation that is long-lasting, there is a change in impedance on the electrode ability to conduct because of the development of fibrosis. Also, the movement of the

electrode will alter the dose response curve, so you will not have consistency unless the electrode is placed always in the same spot and it doesn't move.

CHAIRPERSON CURTIS: Are you suggesting, then, that there is a possibility of stimulating too much?

DR. DIAZ: Or too little, because of the development of fibrosis or movement of the electrode.

CHAIRPERSON CURTIS: Dr. Diaz, in your opinion, if you were designing a trial for this, do you think there's any way that you could have short low levels of stimulation versus a level that was compatible with what's already been published? Or would we have to have a strict therapy on, therapy off kind of design?

DR. DIAZ: I guess my view is that to be able to have a dose-related response, you have to have consistency on the placement of the electrodes, because otherwise your ability to reproduce that dose given to the patient is not going to be uniformly viewed to make the study valid.

So I am a little concerned with the idea of using a dose response curve in the analysis when you don't really know that the electrode is always going to be in the same place or is going to be in contact with the dura or the nerves, which you really cannot ascertain precisely through a fluoroscopy, and you may end up with a variety of stimulation doses that do not mean anything.

DR. BAILEY: However, it seems to me that inexactitude of placement would affect an on-off study as well. It seems that on average, if you increase the dose, most of the patients will have--or some fraction of them will be getting indeed a higher dose.

One question I have: Is the patient going to be always aware of how much the device is on?

CHAIRPERSON CURTIS: Apparently. From what I understand, when it's on you're feeling paresthesias, and if it's off you don't. And so that's the problem. So you can't have a blinded control. They know if they're on or off.

So the question is, if you have--whichever design you pick, you know, baseline period or randomized control and half-on or half-off, that patient knows whether they're on or off, and the placebo effect factors into that. Once it's turned on, how much of it's placebo effect, how much of it is real?

DR. BRINKER: Can I ask a couple questions, perhaps? One is when we talk about dose, I think we're only talking about duration of stimulation during the day, not frequency or amplitude of stimulation, and I assume that studies done with changes in frequency and amplitude have shown no variation as long as there's paresthesias. Is that correct?

[No response.]

DR. BRINKER: Okay. So we're only dealing with duration of stimulation per day.

It seems to me that it would be appropriate to have some comfort that the duration of stimulation that one picks, if it's an arbitrarily chosen single duration, is relatively correct.

The easiest thing to assume is that since we're not sure whether there's long-acting effects of stimulation intermittent to--stimulation given intermittently, that one could stimulate 24 hours a day and be sure that any potential episode of ischemia would be covered in that way.

On the other hand, that's a little bit uncomfortable to many of us who would think that it's best to get away with potentially the least.

I would like to see some sort of dose response measurement either in a pilot study or in what I would consider necessary, and that is a randomized controlled study, and this can be done in a number of different ways with each patient being his own control for the dose delivery. One can either up the duration or assign randomly periods of 2, 8, 24 hours, or whatever is thought appropriate, and see since the patients also have the ability to activate the device themselves in times of need, one could amongst measurements of nitro--anti-ischemic

therapy intake and quality of life, et cetera, at each duration level, also measure the number of times the patient felt it necessary to activate their own device. And the durations can be assigned randomly so that it's not necessarily a dose escalating since there appears to be no risk of lengthening dose.

I mean, what I'd like to see is either that in a pilot study or in a controlled study, patients randomly assigned to device on or device implanted but on a tiny period of time, a minute or two a day, just to check that it works and give the patient some semblance, and the group that has it on for three to six months, they would get monthly changes in the dose based on the randomization scheme. At the end of three to six months, the group randomized to control would be activated, and then they would be followed for another six months to see if the effect was maintained in the original group and actually there was a response in the subsequently activated group.

I'm not concerned--you know, it would be great to see mechanistic changes and to understand why this stuff works, but that is not paramount in my thinking because I echo Mike's comments. There is a simmering group of patients who have failed every opportunity we have for revascularization and medical therapy. Some of them have now failed PMR, TMR, some of them have failed extracorporeal

counter-pulsation, and some of them have failed gene therapy--all given on an investigational basis.

It seems to me that when we look at many of these other forms of therapy that have been approved or being evaluated, this is really a low-risk therapy. And if it provides anginal relief, I would be very, very in favor of it, even if it didn't change ischemia per se.

CHAIRPERSON CURTIS: I can see one of the problems with using two groups of patients with very short durations of therapy and longer durations of therapy and then letting them use it as an as-needed basis. If the patients who only had a very short duration then needed it a lot and used it a lot, they might wind up with the same sorts of effects as the other group, and then I don't know that we've really learned anything or distinguished the two.

DR. BRINKER: Well, if they need it a lot, then that automatically suggests that short duration--

CHAIRPERSON CURTIS: But, I mean, over time what could happen is that by using it a lot, then they wind up needing it less. You know, if there's some conditioning effect to using the therapy at all.

DR. BRINKER: Well, I think there needs to be some guidance in terms of how this thing would be labeled once it reaches the market. In other words, is it going to be uniformly--and that will have to be tested during this phase

of evaluation. So either you say that it has to be on 24 hours a day and everybody's committed to that since that's the way we're going to test it, or we're going to test it in lesser durations, suggesting that it may be effective in two- or four-hour intermittent periods, and that, if necessary, it can be tailored to the patient clinically once it's available. But to say that if you only tested at 24 hours a day, then it's labeled at 24 hours a day, and it doesn't really give one the wherewithal to manipulate the dosing strategy.

DR. DOMANSKI: There's another interesting, I think, or at least puzzling to me trial issue that we need to resolve, and that's really what we're trying to ask with this. I think the likelihood is given the preliminary data, that if the trial is unmasked, we're probably going to see a benefit, a symptomatic benefit. The concern is probably more safety. That is, are we doing something that is unsafe? And when goes to power of the trial, some consideration should be given to making sure that there's sufficient power to see what safety concerns exist. Actually, I think this is probably a pretty low-risk intervention, but I think that perhaps is an important thing in sample size calculation.

DR. DIAZ: In regard to the issue of safety, I'd like to make a comment because I think we need to make a

distinction on what it is that we're trying to accomplish with the study. I like the idea of the randomization. I like the idea of having the patient be his own or her own control. My concern is that if we are trying to address the issue of symptomatic relief, that is one thing. But if we are trying to address the issue of ischemia, we are not really addressing it by purely asking the patient to be relieved of symptoms. The patient may be improved symptomatically, but very happily end up with an MI shortly thereafter or at some time interval later that may be only provoked by the absence of pain.

DR. DOMANSKI: Well, that's why the concern about the safety endpoint, you see.

DR. DIAZ: Right.

DR. DOMANSKI: I think we're probably--just, again, from the literature, it appears that you can--if you implant these things for whatever reason, even if it's placebo, you get a benefit. But the safety thing is the question, and that's one element of safety. Another element is just the mechanical one. You're putting an implant in. Probably the latter is less important, frankly.

DR. BRINKER: Can I ask the original presenter-- I'm sorry. I came in late, and I don't know your name. You suggested that you measured coronary blood flow in normal coronary arteries at the time or in conjunction with

angioplasty. My question--and I guess you used a TENS unit or something similar.

My question to you is: Did you actually study whether application of neurostimulation or TENS stimulation prevented appreciation of pain brought on by balloon inflation in the coronary artery?

DR. DeJONGSTE: Yes, I had a slide, but it's a bit difficult to change it now, I understand.

DR. BRINKER: I mean, you could just say yes or no. Sometimes a word is worth a thousand pictures.

[Laughter.]

DR. DeJONGSTE: What we did is we applied TENS in these patients prior to PDCA, and we applied it at different regions of the trunk, patients were controls, and we were able to demonstrate an increase in the apparently normal coronary arteries, and in the stenotic artery, there was a decrease in flow.

DR. BRINKER: Okay. My question is: Did you take the opportunity to see whether there was any pain relief during balloon inflation or whether it interacted with the sensation of pain during balloon inflation?

DR. DeJONGSTE: We score that in the visual analogue scale. There was slightly an improvement. I don't know exactly--I have to go through the article--if there was a significant improvement in the visual analogue scale.

DR. BRINKER: It wasn't like when you stimulated they didn't appreciate the pain of acute coronary occlusion?

DR. DeJONGSTE: I don't know. I have to figure it out.

DR. BRINKER: Okay.

DR. DeJONGSTE: Sorry.

CHAIRPERSON CURTIS: Let me try to get at--you can sit down; it wasn't a question for you--get at this clinical trial design in a different way. If we were to accept the fact that we have a control group where there is no therapy or the patient is their own control, basically the first four choices that were listed there, does anybody on the panel have any thoughts about what the best way to approach that would be? I would probably be least in favor of a single-arm historical control study, but in terms of the other ones, you know, single-arm with a baseline period before patients get therapy, the randomized controlled study, or a crossover study.

DR. BAILEY: I like 2, 3, and 5, randomized controlled study, crossover study, and dose response study.

CHAIRPERSON CURTIS: All right. Do you want to elaborate?

DR. BAILEY: Well, I think you can do all three of those at once, and that's more along the lines of Dr. Brinker's suggestion. I mean, it seems like you've got

tremendous power to manipulate the stimulus here, and I think, you know, you've got to take advantage of that. And indeed I agree with Dr. Domanski. There are two important things here: pain relief per se and ischemia. And it would be very important for understanding which of those effects is occurring.

You know, do an exercise test at varying lengths of time after stimulation or after various amounts, lengths of time of stimulation. Do you get ischemic protection? Or is it just pain relief?

And with the possibility of masking, it would seem that you could--I mean, if Dr.--I'm sorry--Vetrovec? If his suggestion of masking is feasible, then you have that option as well to mask it, and you could even apply the fake treatment for the same length of time.

CHAIRPERSON CURTIS: But if we have a randomized controlled, crossover, dose response study, doesn't that wind up being very large and complicated and expensive?

DR. BAILEY: Why? Everybody gets the device. It's just a matter of programming and--

CHAIRPERSON CURTIS: I mean, I'm being facetious a little bit here, but, you know, just in terms of numbers and design and all of that.

DR. DOMANSKI: Well, I'm not sure it is so big, as a matter of fact. Kent, you would be smarter than I am

about actually punching the numbers, but I'm not so sure that's true.

DR. HARTZ: I think--I really appreciated the overview given to us on the study designs this morning. And if you look at the summary statements, the crossover consideration, the crossover study is perfect because the n is smaller and address some of the other concerns, and the cons really could be covered after the number is coned down and the data is obtained and we know that the device is effective, then choose the pilot group out of those patients in whom we've shown efficacy.

So it looks to me from what we heard this morning--and I really appreciate this overview because you forget when you're reading all these papers which study is which--that the crossover study is perfect, with a subgroup dose response in that group.

Dr. Curtis pointed out that we're not here to vote on anything, but to go back to our background that we were given for this meeting, Neurological Devices Panel reviewed a reclassification in September '99 and recommended that these stimulators be down-classified from III to II. And so really we are talking about not making it a vote or a recommendation, but discussing whether we're ready to do that or whether we ought to still be premarketing. Premarketing includes both safety and efficacy, doesn't it?

MR. DILLARD: Can I make some comments? Jim Dillard.

I think maybe let me refocus kind of the issue here on the question, which I think that some of the discussion here has been very good. And there are obvious advantages and disadvantages to all of these different trial designs. And I think from the clinical perspective, if we can get from you the issues, if we were to choose one of these or a number of these particular types of trials, the kinds of clinical issues to focus on during those periods and/or what questions you think would be very important for us to look into, and then try to relate that to some of the trial designs, I think it would be helpful.

And so if you had particular points, for example, if you believed that the randomized controlled study is a reasonable study to look at, number one, what should some of our considerations be? What should some of our considerations for the controlled group be? And any other recommendations that you might have for us to consider during that time frame I think would be exceptionally helpful. And if you can give us some of those specifics, I think that will help.

One other quick comment on the dose response study. I think that--and one thing I haven't heard is what is the issue we want to focus on for the dose response

study. And let me put it from a device perspective maybe a little bit differently. Is it enough to just know that there is a dose that can potentially be effective, look at it in a particular clinical trial design, and then if it is effective, put that in the labeling, and is that satisfactory enough given a safety profile? Or is there a need to titrate and understand really what a dose response relationship is here? And I know that's difficult when you think about a typical dose response drug study. This may be a little bit different. But is there a necessity from your clinical vantage point to understand what might be the dose response for a particular type of patient? And if you could address that, I'd appreciate it, too.

CHAIRPERSON CURTIS: I'm more concerned about whether it works compared to not using the therapy than really whether it's 30 minutes, 60 minutes, or 120 minutes we need to get at. I don't think that matters so much, and I think that could be--people can fine-tune that later on, and it just really comes down to issues of battery life and whether--the issue of impedance was brought up and how that factors in over time.

I was just mostly concerned about having a control group where the therapy is completely off and following them and comparing that to where the device is turned on. You're going to have a placebo effect in there, and you're never

going to know how much that is.

So, I mean, I think there are some trial designs that we've got up there that--nobody seemed to be very thrilled with the single-arm, either baseline period or historical control study, on the panel, so that would be out least favored way of approach this. And, you know, the randomized controlled study, the crossover studies are reasonable approaches to this, I think, from what I've been hearing everybody say. And, you know, I'll say it a last time and then lay it to rest: If there was some way not to have a strict dose response study but to have some minimal amount of stimulation compared to a larger amount, whatever that is that's expected to be effective, and have that be the two comparison groups rather than a straight on or off, I would think that would be a better way to go.

DR. BAILEY: I wasn't saying that--these are not three separate studies. You can sort of build all the features of those studies--

CHAIRPERSON CURTIS: Yes, you were actually suggesting to combine the features of all of them.

DR. BAILEY: Right, right, because if it implies putting a device in everybody--well, actually, that raises the other point. You might want to have a trial in which a device wasn't put in one of the groups, but have two other groups, a group with fake stimulation and a group with an

implanted device so that they would be--at randomized times they would have real stimulation and at randomized times they would have the fake stimulation. You could do a lot of teasing out then of how much pain relief you get from having an operation done and something put inside you versus--and how much you get from thinking that something is being turned on. Then, you know, you can also--you know, I think pain relief itself is worthy, but if you can get it just from having some device put in and nothing really happening, that's probably not what you want. So I think you could develop a trial with all three levels of intervention.

CHAIRPERSON CURTIS: One thing I have a hard time with on all these kinds of implantable device studies is putting a device into a patient and never, ever turning it on, you know, having them be followed, because what happens to them then is they take the risks of the implant and they never get any potential benefit out of that. I mean, I think, you know, a period of observation whatever was decided, three months, six months, even if it's a year--well, to me a year is a little bit long to get somebody convinced to go through it. But I think at some point you have to be able to offer patients therapy; otherwise, they accept all risk, no benefit, no potential benefit.

DR. BAILEY: And this type of scenario I'm envisaging, everyone who got the device put in would at some

point have the device on.

CHAIRPERSON CURTIS: Right, but that's what I'm saying. I think we should--any clinical trial design ought to have that built into it.

DR. DOMANSKI: I think, you know, there is an attractiveness to doing a randomized trial in which one group doesn't even get the implant. I think the difficulty there is probably going to be feasibility. I'm not really sure that people who come in who are completely intractable with everything are going to be enthusiastic about being randomized to a rotten existence. I mean, they need some promise to, you know, be enthusiastic about coming into the study. So I think it's feasibility. I think the randomized design idea is a good--I think that's the basic trial design that one should have, perhaps incorporating the other things, but I think it's going to imply that you implant the device in everybody.

CHAIRPERSON CURTIS: I guess another here, too, is if you're talking about various kinds of crossover designs or different doses and all that, how long would any one observation period have to be in order to satisfy people that you had an adequate trial of that effect? I mean, it sound to me like these effects are fairly immediate, that you're not having to stimulate somebody for a month before you see anything.

You know, but the other issue then is going to be if you switch to a different dose or a different method of stimulation, how much of a washout period does there need to be? You know, how much does the effect linger?

You know, if you had a particular level of stimulation, is a month enough to know what you're doing? Do you need longer than that? Because, I mean, if you're going to have four different ways of looking at it and they're three months each, that's a year's observation. If it's a month each, it takes you four months to do that.

Any thoughts on that?

MR. DILLARD: Dr. Curtis, could I make a comment on that?

CHAIRPERSON CURTIS: Sure.

MR. DILLARD: I think that's the focus of Question 2. I don't know if you want to move that to there right now, if you think you've addressed this question well enough. But I think duration of effect and endpoints is part of Question 2.

CHAIRPERSON CURTIS: I think we've addressed Question 1, unless anybody in the FDA still has a specific-- oh, George?

DR. VETROVEC: Let me just ask one question, and this comes out of the old angina trial data. With doing stress testing, one has to be very careful that there isn't

a training period related to sequential stress testing, and I think it's going to be critical that baseline stress testing data probably incorporate two stress tests before any intervention, and then using the last stress test as the baseline, because there is a certain learning or improvement just with sequential stress testing and this could corrupt the data.

CHAIRPERSON CURTIS: Let me ask you something about a washout period. Are there any data from the studies that have been done already that if you stop stimulating somebody, they still have a good effect on their angina for some period of time? Or is it immediate that they get their angina back?

DR. DeJONGSTE: It depends. We published a piece last year, a study, where we withhold the therapy, we stopped it in, I think, about 20 patients, just withhold it. And it depends completely. Some patients, after two years of stimulation, where we have refractory angina, even after a month they have no recurrence of angina, and some have ten days. So the washout period should at least be two weeks, but I think even up to a month or six weeks, if you'd like to have a crossover design.

CHAIRPERSON CURTIS: At the end of a month all the patients were back to their baseline, or is--

DR. DeJONGSTE: No. Some have no recurrence at

all.

CHAIRPERSON CURTIS: Even after a month.

DR. DeJONGSTE: Correct.

CHAIRPERSON CURTIS: Okay . Thank you.

DR. VETROVEC: Was there any risk to withdraw?

Did this occur during withdrawal?

DR. DeJONGSTE: We follow them with Holter, ambulatory Holters, and there was no significant increase in myocardial ischemia. So there was no rebound, and that's the same we found in the open design in Heart, that if you withhold for--if you stimulate three times one hour, within the period there was no increase in myocardial--we couldn't find that there was an increase. So there is no rebound as far as we have found in myocardial ischemia.

DR. SIMMONS: Let me just ask just a technical question. This fibrosis or changes in electrode position, are you constantly changing the voltage and the frequency when these patients come back to clinic, they tell you they don't get as much relief, or they don't feel the stimulation as much? Are you upping the voltage or changing the pulse width on a regular basis? Or do you put it in, turn it on, and that's it?

DR. DeJONGSTE: I'll come back to your question, but the first thing is the patient has to feel comforted with the therapy. So that will at least take six weeks

before the patient is used to activate with a magnet, to feel the paresthesias and to handle the device. After that six weeks, it is pretty much stable. We published that in Pace six years ago, that is, there is no tolerance or no adaptation phenomenon, and the patients are not increasing it more and more during their therapy.

So I don't know whether this fibrosis or impedance is really a serious problem. We have not come across that problem.

DR. HARTZ: So in those patients who were rid of their angina--I'm going to beat a dead horse because I can't read an EKG very well, but I can look at an echo. Are you sure those patients didn't have new infarcts, small infarcts and that explained their relief? Did you have good echoes pre- and post-entrance into the study?

DR. DeJONGSTE: No, there is just one study on echocardiography where they give adenosine to reduce left ventricular ejection function, and they start stimulating, and then the stimulator was improving the hampered left ventricular function. But I think that is related to the interaction with spinal cord stimulation and adenosine. There is some evidence that spinal cord stimulation is acting by modulating the adenosine handling.

So with respect to your question, it might very well be, but echoes are very difficult to perform in this

group of patients who have been operated on. They are usually pretty fat people, and to visualize even with a second echocardiography, we have a lot of difficulties. So we started a couple of years ago to perform echocardiography, but we are not able to do it in all the patients. So it's difficult to visualize.

DR. HARTZ: Were these all surfaces that you were doing, surface echoes? You haven't tried TE in these patients?

DR. DeJONGSTE: No, we haven't done that.

CHAIRPERSON CURTIS: Okay. Thank you.

So it sounds like a crossover design would involve a fairly--you know, possibly a month washout period, that sort of thing, if it were to be designed that way.

DR. BAILEY: You would probably need to get some pilot data to see what--you know, to find out what the time course of these effects might be and then use that in designing the time periods, I would think.

CHAIRPERSON CURTIS: All right. If there are no other comments, we'll move on to the second question. So we need to look at the advantages and disadvantages of the following effectiveness endpoints. All right. So let's go first. What primary and secondary endpoints would be important to collect to fully characterize the effect of spinal cord stimulation for angina? There are some

suggestions: treadmill testing, physiologic measures, quality of life.

DR. CHANG: Quality of life, I think those patients will be enrolled in the trials, kind of end-of-road patients, three vessel disease, not a candidate for any intervention, CABG or percutaneous intervention. So to them, as Mike was commenting, quality of life is the single most important thing.

CHAIRPERSON CURTIS: So you would suggest that as a primary endpoint?

DR. CHANG: That's right.

DR. DOMANSKI: You know, I think obviously for the device to be meaningful in terms of its efficacy, it has to improve quality of life. I guess this is a more tactical question of how you calculate your sample size, though. I suspect, again, given the preliminary data, that there's going to be a pretty substantial impact on quality of life regardless of the reason for it. I mean, there may be a placebo effect. But I suspect that if there's a difference in safety, the difference is going to be substantially less, so that if you want to pick up a risk of this thing, of an infarct, of death, you know, of other complication, there needs to be some composite endpoint, obviously.

It may be that you want to power it to pick up a safety problem and not just the quality of life.

DR. CHANG: I don't see mention of a mortality or myocardial infarction or LV function in the endpoint. I would just like the FDA to give some comments.

MR. DILLARD: Jim Dillard. I think that one of the things that might be helpful here, because the next question, of course, deals with the safety endpoints, is perhaps to make a distinction in your minds for us what you would consider to be an effectiveness endpoint and what you would consider to be a safety endpoint, and that would be helpful also.

DR. DOMANSKI: Well, the efficacy thing, it seems to me, is obviously quality of life.

CHAIRPERSON CURTIS: Yes, death and MI are safety issues, because the device we don't think is going to be effective to prevent death. I mean, that's not what we're looking at. So quality of life, you know, could be the most important endpoint that we're looking at, so that would be for efficacy.

I don't know. Are there any other thoughts about an alternative primary endpoint or is there--yes?

MR. DACEY: When we start dealing with quality of life, which is a subject that I have spent an awful lot of time with, I get a little nervous, because as I understand this patient population, these are people who are--their lifestyles, whatever their quality of life is, are severely

compromised already. But even at that point, there are so many yardsticks, and I'd be very interested in knowing what kind of index measures would be used in any kind of study to test this idea of quality of life, because my favorite line is my quality of life changes every night when I take my leg off and in the morning when I put it back on again. And I think that's a metaphor for a lot of issues that patients themselves have to deal with that are not often expressed.

This also gets into the problem of patients self-reporting around these issues, which, as we know, can be problematic. So I'd like to see some sharper focus around this. Can we, in fact, index quality of life in meaningful ways in any kind of study?

DR. DOMANSKI: Well, of course, those of us who are in the clinical trials business have a high enthusiasm for counting bodies as opposed to trying to do the softer endpoints like quality of life. But here clearly that's not appropriate. Clearly here it is quality of life, and there's a body of science, if you will, devoted to quantifying quality of life. I don't regard myself as an expert. Obviously, NYHA class is a gross way; we do it clinically every day. But there are a whole series of fairly well-validated instruments for assessing quality of life. So I don't--I think within the bounds of that, I don't think that's a--this is not difficult to design in

terms of assessing what you're discussing.

MR. DACEY: Well, the general health policy model and well life expectancy model and the Rand, was it, the SF-36, and there's a host of others. And there is some new work being done on especially as the playing field is changing now with the Internet on information, of information seekers and information repressors among the patient populations, we get into some very muddy areas. So I am just looking for clarity in that area with that patient population, with the understanding that we have a very severe quality-of-life issue with this patient population. But if this turns out to be effective, then we're marching down the scale of people with angina that could benefit from this type of intervention and that broadens the quality-of-life issue even greater.

That's my comments on that.

DR. DIAZ: I wonder if I could interject. The quality of life from my perspective is a pretty broad waste basket that would be very difficult to assess without very specific parameters like exercise tolerance, duration of stimulation to pain relief, ability to handle daily life tasks, and I think that there is specific measurements that can be used for that purpose rather than using just a broad quality-of-life concept.

DR. DOMANSKI: Well, I'm not suggesting a broad

quality-of-life concept. Obviously, when you design the trial, you pick very specific instruments that have been well validated, and so certainly not just--you know, it's not just a kind of wishy-washy thing. We do quality-of-life assessments in a lot--in fact, in all of our trials now, and we do it with, again, pretty focused instruments.

DR. BRINKER: I would second that, but I would also say that we do need some objective quantification of the problem, and exercise tests, I think performance on an exercise test will have to be obtained. And I'd like to see perhaps some measurement of not only the ability to do more exercise, but it would be nice if there was some evidence of ischemia relief per se. That would do wonders for our perception of the device, and from a marketing point of view, whoever is going to go through this process, there is a quantum leap, I think, between the acceptance of only pain relief from ischemia relief. And it would be well worth the investment to try to divvy that out.

CHAIRPERSON CURTIS: Well, we could have--I mean, we're talking about primary and secondary endpoints, I think, and if a primary endpoint is quality of life, a key secondary endpoint could be treadmill exercise time, I would suppose.

DR. BRINKER: Well, one other issue that I think the FDA should take into consideration is the yardstick for

the PMR, TMR demonstration. I think that there should be basically the same primary endpoints for regulatory study as that particular modality, after all is said and done.

CHAIRPERSON CURTIS: Do you recall what they were?

DR. BRINKER: I thought that exercise testing was a major part of that.

DR. HARTZ: Wasn't there a huge attempt to try to determine improvement in ventricular function which turned out to be the reason--I mean, we can't use that here. We're not looking for an improvement in ventricular function in these patients.

DR. BRINKER: Say that again? What did you say?

DR. HARTZ: Improvement in ventricular function was one of the goals of--

DR. BRINKER: But did that--that wasn't a primary endpoint of that study and, of course, it doesn't do that. But--no, it wasn't a primary endpoint. They had perfusion scans, and exercise perfusion scans I think was a primary endpoint. And I think that it would be necessary--I agree with quality of life after all is said and done, but I think that they should be co-primary endpoints.

CHAIRPERSON CURTIS: Well, let's say you have quality of life as a primary endpoint and use exercise treadmill time maybe as a secondary, or you're saying co-primary, but as an important factor to measure. I think a

third issue would be what you were getting at before, Renee, about measure--some objective measurement of ischemia. Is that necessary? I mean, certainly if you could show that wall motion improved, that would make everybody more enthusiastic later on of saying, well, now I understand why they have pain relief because the wall motion improved. You also have to look at the possibility that the patients will feel better and they'll walk longer on a treadmill, and your wall motion won't change much. Then how is that going to affect things?

DR. BAILEY: Doesn't that also get at the issue of whether you're masking pain or actually addressing the root cause of it? And so it has to do with the safety as well. So I think it's--I agree, it's very important to distinguish between the two mechanisms.

We accept drugs to relieve pain, and with that being the main purpose of it, but it's nice if the mechanism is reduction of ischemia.

CHAIRPERSON CURTIS: So should there be, then, maybe as a secondary endpoint some sort of objective measurement of ischemia? Thallium? Stress echo? Something like that?

DR. DIAZ: That probably needs to be decided with the primary question of what it is we're trying to establish. Are we trying to establish that the procedure is

efficacious only to produce pain relief and angina control? Or are we trying to demonstrate that what we are actually producing is an effective change in the amount of circulatory function of the myocardium? If we're looking for improvement on ischemia, the question is very different than if we're looking for improvement on pain control.

DR. HARTZ: Just to go back, I think this issue is so important that I'll reiterate what I said earlier. I think this should be done at implant. We should find out if the device works at implant. And stress TE echo would probably answer this question. If people have objections to that form of testing, maybe there's another form of testing. But if we don't do that and we're putting these devices in without knowing the scientific effect, the physiological effect on ischemia, then the statistical effect of the placebo might outweigh the actual effectiveness of the device.

DR. DIAZ: I agree wholeheartedly. It needs to be done.

DR. BRINKER: I disagree. I mean, I think the primary issue here is pain relief. And I don't care about a stress echo, especially not at implant. I think that also if this isn't a totally novel procedure that hasn't been done in man and it doesn't have a correlate for other forms of pain relief. Now this may--this may be a two-pronged

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form of therapy. It may relieve pain just as spinal cord stimulation relieves pain for other parts of the body. And it may also serendipitously have a beneficial physiologic response. I think the minimum level of evaluation would be not to say this is only a device for relieving pain, but this is at least a device for relieving pain and, if so, and if it were simultaneously safe, that would be in my eyes enough for approval.

It would be helpful to know if, in addition to relieving pain, it also relieved ischemia, that would be a secondary tier because it would be immensely better appreciated by the practicing physician as to who and when to apply this form of therapy--

DR. DIAZ: But if you don't ask a question about the effect on the ischemic myocardium, you may be creating a problem of safety, because if you allow the patients to become more active and their pain is masked and they end up with more myocardial infarctions, then instead of doing them a favor, you've created a problem.

DR. BRINKER: Well, that's why we want to power the study to look at safety. But even if you show slight pain relief--even if you show a lot of pain relief and very slight ischemia relief, you may still be potentially putting patients at risk, and we do that all the time with some of the treatments we do, anyway.

DR. SIMMONS: You know, based on some prior devices that came through here, I mean, really the question that has to be answered is: What is the company going to claim? Unfortunately, we've been through this road before with some of the pacemakers, that, you know, we have wanted them to prove that certain bells and whistles they put on the pacemaker worked, and then the bottom line is, if they don't claim it works, then they don't have to prove it works. And so--I mean, am I wrong about that? If they're going to claim that this device only relieves pain and don't claim any effect for ischemia, then all the things we're talking about here are moot.

We probably need to know what the question and what the device is going to come to us with before you actually sit down to design the study. So if they don't want to claim ischemia relief, then trying--as much as we would love to put some science into this product, it doesn't matter. The only thing we could possibly do in the long run would then be to, you know, actually power the study to make sure that it's safe. You know, what is the risk of invest? Well, every pacemaker implant has a risk of infection. Somehow infection in a pacer pocket doesn't seem to be that bad. An infection in a spinal cord seems real bad.

So, you know, we have to probably step back and ask what's the product actually going to make claims for and