specific points to follow. For that condition, can I take a vote for all in favor of condition No. 1.

MS. MOYNAHAN: Nine in favor.

DR. TRACY: Opposed? Okay. So condition 1 is approved.

Any additional conditions?

DR. WHITE: Can we discuss the follow-up of the paradoxical embolus indication? Add that as well as a post-marketing tool.

DR. TRACY : I think that might have been included in the prior discussion regarding the surveillance. I don't think we need a separate motion on that. That is included in the discussion that we had.

DR. WHITE: Then also can we discuss as a condition then that we adopt the labeling recommendations that we made, the changes to the labeling>

DR. TRACY: Yes. That's fine. Labeling changes. To summarize, the labeling changes that we are proposing. Help.

DR. SKORTON: They were in the indications

and contraindications and precautions and warnings.

DR. WITTES: Table 5.

MR. DILLARD: Yes, in Dr. Wittes' Table 5. I didn't hear this specifically but just a question, I think, for the committee. In terms of taking a look at some of the subgroup analyses, which I don't know if Dr. Wittes is going to bring up again, but if we look at some of the extremes, how would be handle that in the labeling and would you have any additional suggestions based on how we would look at the data? That's the only thing I didn't hear specifically about a labeling change.

DR. TRACY: Maybe Dr. Wittes can if she's had a chance to do some more calculations on that, but I think that the thing that we don't have data on should be stated what we do and what we don't have data on.

That canthenleave some discretion in terms of the operator how they want to handle that lack of data without specifically contraindicating the procedure for that type of clinical situation. Any other --

DR. WITTES: But, again, I think it's a little more subtle than that. It's that there are data but they are not directly comparable. I think that is the subgroup issue here.

I don't know how to answer the question and I don't know what I think. What I feel is that what is presented currently is not sufficient and doesn't reflect what the data show.

One of the problems is we don't really know what the data show because we haven't seen the analysis that would say, "Ah ha, this is what the data are showing relevant to specific questions."

I guess one of the things I don't understand is if you see a patient, do you say, "This is a five-year-old. Should I make this choice or that choice?" "This is a lo-year-old. Should I make this choice or that choice?" "This is an 18-year-old."

I mean, do you as clinicians think about the age of the kid or the adult and make a decision that is pertinent to that age, in which case I think it's very important, the age and the size.

DR. WHITE: I think that's a different issue

than this committee should decide, though. I think we're asked to look at the reasonableness or the probable efficacy and safety. I think we've seen nothing that suggest that it's not reasonable to think that's going to be safe.

I think that a clinician.might well make those judgements and individual patient interaction. I have seen nothing about the extremes of the device that make me nervous that it's not going to work.

DR. WITTES: No, I'm not saying that. But it seems to me we haven't seen the data analyzed in a way that addressed those issues at all. In a clinical trial you really wouldn't worry so much about it.

In a situation like this I think the data should be presented. The presentation may just make everybody feel great. This is fine. But in the absence of a good control, I do think that there needs to be more on the label that describes analysis.

DR. TRACY : Let me see if I can put this together. One condition is that we would recommend some changes in the labeling that would indicate who has and who has not been studied in this protocol more

clearly, the few little changes which you can refer back to the previous discussion regarding the nickel and the anti-coagulation issues, etc. That would be one condition.

I do think there is another condition that we will be asking the company to provide additional analysis of their data to the FDA that would take out those upper age ranges that were not really included in the surgical group. I think that is an additional condition that we might come up with. However, I would like to take a vote, if that's all right, on the condition regarding the labeling as we have discussed.

DR. SKORTON: I just have one question. I do share some of your concerns but I don't think they should affect the labeling. I don't think they are discrete enough to affect the labeling. I haven't heard you say anything.

I'm not convinced, for example, labeling should say this device is not proven to work in younger people or older people. When I'm going to vote on labeling, I'm talking about the precautions, warnings, indications, contraindications. The only

indication one that I thought we agreed on changing was the one having to do with the PFO.

DR. TRACY: Correct.

DR. SKORTON: But we weren't going to have a disclaimer in the indications about the extremes of age. I thought that was the point of doing a post-market study.

DR. WITTES: I fully agree with that. All I'm saying is that when the data are presented as a summary, that summary should be expanded, but not to say don't include it.

MS. MOYNAHAN: Can we take a vote on the labeling?

DR. TRACY: Yes, on the labeling. All those in favor of the condition dealing with labeling that we've just discussed, please indicate so.

MS. MOYNAHAN: All right. That's 10 in favor. We do have 10 voting people here. I only counted nine in the last one. Was there anyone that abstained or voted against it that I missed or was everyone's hand up for the surveillance issue? Okay. That was 10 in favor then.

DR. TRACY: Okay. All right. Then there is nobody that's opposed to that condition. Any additional conditions? Do we want to try to turn the request for additional analysis into a condition? No. That's just simply going to happen. Okay. Any additional conditions? Okay.

At this point we need to vote on whether the device is approvable with the conditions as we have already voted on or not. All in favor of approval with the conditions as stated.

MS. MOYNAHAN: That's ten in favor. Then we can also go around and each person can state their vote and the reason for it.

DR. WHITE: I'm Chris White and I vote for the motion with limitations because I'm convinced that the data that's been presented today is reasonably safe and effective.

DR. WILLIAMS: Roberta Williams. I vote yes because I do believe it passes the reasonableness test.

DR. SKORTON: I'm David Skorton and I vote yes because I believe it shows reasonable evidence of

safety and efficacy.

DR. ZAHKA: I'm Kenneth Zahka and I voted yes because I think this will help a number of children and young adults with atria1 septal defects.

DR. HOPKINS: Dr. Richard Hopkins. I voted yes because I think it does meet safety and efficacy against the arbitrary standard. While the discussion well reflects our concerns about the relative efficacy with other options, that is going to be addressed by the conditions imposed and by clinician judgement.

DR. AZIZ: Salim Aziz. I voted yes because I think it does demonstrate safety and efficacy.

DR. TRACY: Dr. Laskey.

DR. LASKEY: Yes. Warren Laskey. I voted for approval with the conditions much as my colleagues have. I would like to also personally acknowledge the efforts of Dr. Amplatz who is standing in the corner there who made a major, major contribution to interventional cardiology.

DR. McDANIEL: Nancy McDaniel. I voted in favor of approval with the condition stated having met the safety and efficacy. Again, it's going to be a

great contribution to the care of these patients.

DR. WITTES: I votes yes for much the same reason as everybody else did.

DR. CRITTENDEN: I voted for approval with conditions for similar reasons. It was safe and relatively effective.

DR. TRACY : Any additional comments, Mr. Dacey or Mr. Morton?

If not, we will end this portion of today's meeting and break for lunch. We have a vote to come back at 2:15.

(Whereupon, at 1:34 p.m. off the record for lunch to reconvene at 2:15 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2:17 p.m.

DR. TRACY: I'd like to call to order this meeting of the Circulatory System Device Panel. The topic for discussion this afternoon is a premarket application for NMT Medical CardioSEAL Septal Occlusion System,with Qwikload.

At this point I would like to hold an open public hearing. There were no requests ahead of time but is there anybody here who would care to make a presentation on this or other topics?

Okay. If not, then we will close the open public hearing and move on to the sponsor's presentation.

MR. AHERN Good afternoon. My name is John Ahern. I'm the President and CEO and Chairman of the Board at NMT Medical, a public company and I am a stockholder in that company.

Madam Chairperson, panel members, and FDA representatives, we are pleased to have an opportunity to present data in support of the safety and efficacy of the CardioSEAL Septal Occlusion System device in

the treatment of complex ventricular septal defects. More common forms of congenital VSDs, which can be readily identified and repaired using standard surgical procedure, are not a subject of this PMA.

Clinical data used in support of this PMA were obtained from a ongoing clinical trial sponsored by Children's Hospital, Boston, and provided to us under a licensing agreement.

Following my brief introductory remarks our presentation will proceed as follows:

We'll have a device descriptionpresentedby Carol Ryan who is the Vice President of Research and Development of NMT Medical. Followed by discussion of indications by Dr. John Mayer. Dr. Mayer is a Senior Associate in Cardiovascular Surgery at Children's Hospital in Boston, Professor of Surgery, Harvard Medical School.

We will then have a discussion of the procedure by Dr. Peter Laussen. Dr. Laussen is Co-Director, Senior Associate in Anesthesia, Children's Hospital, Boston, and Associate Professor of Anesthesia, Harvard Medical School.

Following that we'll have the clinical trial overview by Dr. Kathy Jenkins. Dr. Jenkins is Associate in Cardiology, Children's Hospital, Boston, Assistant Professor Pediatrics, Harvard Medical School.

Then we'll lead on to trial results and analysis by Dr. Kimberlee Gauvreau. She is an Associate in Cardiology, Children's Hospital, Boston, Assistant Professor Pediatrics, Harvard Medical School. Also Dr. Gauvreau is the Assistant Professor of Biostatistics at Harvard School of Public Health.

Then we'll follow with conclusions by Dr. Jenkins.

We've also invited a number of experts who are familiar with either the VSD device in clinical trial or the statistical data, the clinical data involved with that.

I would like to introduce Ms. Amy Britt who is the Research Manager of Children's Hospital in Boston, Dr. Mark Boucek who is Medical Director of Pediatric Heart Transplantation, Children's Hospital in Denver, and Professor of Pediatrics at University

of Colorado, Hill Sciences.

Also Dr. Mark Hoyer. Dr. Hoyer is the Director of Interventional Cardiology, Riley Hospital for Children, Indianapolis, and Clinical Associate Professor of Pediatrics, Indiana University.

Finally, Dr. James Lock, Cardiologist-in-Chief, Children's Hospital in Boston, Professor of Pediatrics, Harvard Medical School.

They are here today and available to answer any questions as needed.

Just a brief marketing history of the CardioSEAL device: The FDA has already approved the device based on its safety data and it's commercially available in the United States under the Humanitarian Device Exemption Regulations for three different HDE approvals, one of which is the same indication proposed by the PMA which was approved by the FDA almost two years ago.

The other two HDE indications were for a PFO closure in patients failing medical therapy and also the fenestrated Fontan procedure. The device is also commercially available in the European community,

Canada, Latin America, and the Pacific Rim. Approximately 10,000 CardioSEAL devices have been implanted since 1996.

I would like to introduce Carol Ryan who will provide data on the device.

MS. RYAN: Good afternoon. Again, my name is Carol Ryan. I'm an employee of NMT Medical and a shareholder.

The CardioSEAL Septal Occluder is a second generation device which has been designed for percutaneous closure of intracardiac defects. The CardioSEAL implant is comprised of a structural framework and a tissue scaffold.

The structural framework is fabricated primarily from MP35n, an alloy which has excellent corrosion resistance and is inherently non-ferromagnetic. MP35n has been used in a variety of implants including pacemaker leads, stents, aneurysm clips, and orthopedic applications.

The tissue scaffold is knitted polyester fabric similar to those commonly used for vascular grafts and cardiac patches.

The implant is available in four sizes ranging from 17 mm to 33 mm. The design is similar to a double umbrella with each umbrella comprised of four MP35n springarms or eight per device.

Each springarm has three functional coils per arm. The center coil, which is called the shoulder coil, the elbow joint and the wrist joint. These coils are put there to control functional stresses within the springarm and provide adequate fixation within the heart.

A pin is centrally located on the proximal side of the device for attachment to the delivery system. Platinum springs are soldered to the end of each springarm for enhanced radiopacity. The tissue scaffold, a knitted polyester fabric, is attached to the framework using polyester suture.

The implant is packaged attached by suture to a disposable loading system called the Qwik Loader. The Qwik Loader is utilized to collapse the umbrella and introduce it into the delivery sheath. The CardioSEAL delivery system is designed to facilitate attachment, loading, delivery, and deployment of the

CardioSEAL through a commercially available 10-French sheath.

One-size delivery system is compatible with the entire family of CardioSEAL implants. This particular version of the delivery system is a third-generation design with improvements and ease of use over prior generations.

The system is comprised of a control handle, a catheter shaft of pushing the implant through the sheath., a spring guide with a sleeve on the distal end for capturing the implant pin wire and the delivery system pin wire.

This video depicts the attachment and loading of the CardioSEAL implant. First the pin wire of the delivery system is advanced from the sleeve at the distal end of the spring guide. The implant pin is now placed within that sleeve and the two pins are locked in place.

The implant is then collapsed within the Qwik Loader. The occluder disc, which is a packaging aid, is disposed of. You can see the implant being pulled into the clear part of the Qwik Loader.

The catheter shaft is advanced to be adjacent to the implant. A Touhy-Borst is attached which will be used for flushing the system to remove air bubbles. Several of the loader components are now disposed of.

The suture is being removed there. The system is thorough flushed to remove air bubbles. This is easily visualized through the clear tube. Then the Qwik Loader is placed into a 10-French sheath in place across the defect.

Critical design features of the CardioSEAL implant include a design focused on long-term biocompatabilityincludingawell-characterizedtissue scaffold which promotes fast and thorough encapsulation. This photo of a sheep explant at 90 days demonstrates the complete endothelial coverage of the implant.

The spring arms are where the laser is pointing. This is the edges of the device. There is complete endothelial coverage of both the fabric and the spring arms including the device septum interface. The metallic framework has excellent corrosion

resistance and a low medal surface area to minimize leeching and it is MRI compatable.

The double-umbrella design gives the implant the ability to conform to variable anatomy and a low profile in the septum following implantation to minimize hemodynamic disturbances.

Now, I would like to introduce the next speaker, Dr. John Mayer of Boston Children's Hospital and Harvard Medical School. Dr. Mayer will speak on the INDICATIONS FOR USE of the CardioSEAL.

DR. MAYER: I have no interest in this company and have only been paid for travel and an honorarium. I am here to speak with you for, if you will, the surgeon's perspective about this device and its utilization. Hopefully I go in the right direction on the slides. And I didn't.

I apologize to my pediatric cardiology and cardiac surgery colleagues who are on the panel, but for the other members I would like to review a little bit about what the anatomy is that we're talking about.

Defects in the ventricular septum can occur

in a variety of locations, the most common one being here in what we call conoventricular or perimembranous area, but they can exist in any point in the right ventricle. This view is as though the interior wall of the right ventricle has been removed and one is then looking at the septum.

The defects in particular that we are talking about as applications for this device are those down here in the apical muscular area where there is a lot*of trabeculation in the right ventricle that can cover the right ventricular side of the defect and primarily those also in the anterior muscular area. We'll go into that in more detail.

This slide is simply to just give you an idea about the occurrence of these various sorts of defects in these locations. This is based on a review of a large number of cases over a 15-year period at children's hospital in Boston.

You can see the perimembranous VSDs are, in fact, far and away the most common defects, but there are a significant number of patients who have both muscular and multiple ventricular septal defects.

This is actually from a series from the University of Alabama in Birmingham and the only reason for showing all of this data is to point out that, in particular, if one looks at risk factors for mortality after surgical ventricular septal defect closure, the presence of multiple ventricular septal defects, particularly when they are in that trabeculated area of the ventricular septum, are the ones that are associated with the highest mortality, at least in that series.

And this is just an angiogram demonstrating the types of defects that we're talking about. You can see, in fact, here there are multiple holes, one in the perimembranous area but two down here in this more heavily trabeculated area of the right ventricle. These are, in fact, the defects that we're proposing and have gained experience with for device closure.

So one of the questions that clearly is germane to thjs issue is what would be a high-risk or complex VSD and I will provide you with my own viewpoint of that. There are two major criteria.

One is that the typical surgical approaches

would compromise ventricular function and, in particular, the use of left ventriculotomy. I'll show you some pictures of how that works from the surgical perspective.

Or a very extensive right ventriculotomy which might be necessary to close multiple holes. Or that there is a high probability of there being a significant hemodynamically significant' residual ventricular septal defect.

Some, cases in which that can occur are in patients who have failed a 'previous VSD closure, in those patients who have multiple apical or anterior muscular VSDs. A terminology has been used sometimes that this is a so-called Swiss cheese septum, multiple holes. And certain isolated posterior apical ventricular septal defects which are covered by the trabeculations as we showed in the previous slides.

I think certainly when I came to Boston a left ventricular approach was a standard approach to defects in 'this heavily trabeculated part of the septum. This is just an artist depiction of how this operation is performed so that one actually makes an

incision in the left ventricle.

The reason for doing this is because in many cases these defects are single and actually relatively easily identified from a left ventricular aspect, but from the right ventricular aspect they are much more difficult because of all of the crossing trabeculations. One can simply through this left ventriculotomy sew a patch in to occlude the defect.

When we looked, however, in the late 1980s at a group of patients who had undergone an apical left ventriculotomy for defects in this area, what we found is that fully half of the patients who had undergone that approach had a significant residua as a consequence of this approach.

Despite the fact that many times this seemed as though it was easy to close, there were a significant number of patients who had residual ventricular septal defects.

We had three patients or three episodes where an aneurysm formed at the site of the left ventriculotomy. A significant number of the patients had clinically significant left ventricular

dysfunction after this approach. Actually two of the patients either went on to die or had to be transplanted.

Now, as I think was already alluded to, this. device is not being proposed to be used to close every hole in the ventricular septum. Certainly we have evolved as an institution to take the following approaches, and that is that defects that are close to the atria1 ventricular valve leaflets or the chordae or defects that are close to the semilunar valves are ones that we have not employed this device to use clinically.

To remind you again, we are not talking about defects that are easily accessible from a surgical perspective, those in this so-called subpulmonary area, the perimembranous area, because of their proximities to the either semilunar or atria1 ventricular valves.

Defects in what we would call the inlet septum or AV canal type of defect are not ones that we would propose to use the device for. We are really talking about defects down here in this heavily

trabeculated part of the septum.

So, in summary, we would use conventional surgery for the conoventricular VSDs so that includes perimembranous VSDs now align the defects as occur in tetralogy. Inlet VSDs, we have used surgical approach for single large high anterior muscular VSDs and certainly those for the outlet VSDs.

Our current approach is, however, to use a transcatheter approach for multiple apical and anterior VSDs and posterior apical VSDs covered by trabeculations. We have utilized the device in certain post-repair residual VSDs.

Thank you. I'm going to introduce to you Dr. Peter Laussen from our cardiac anesthia group who is going to describe the procedure.

DR. LAUSSEN: Good afternoon, ladies and gentlemen. My name is Peter Laussen. I'm Co-Director of the Cardiac Anesthesia Service at Children's Hospital and Associate Director of the Cardiac Intensive Care Unit.

I have no financial relationship with NMT Medical. They are covering my expenses for this

presentation, however.

My presentation goals are to describe the technique initially with an animated video and some angiographic still frames. But as way of introduction, I think it's important to emphasize that in contrast to our experience with ASD and PDA device deployment, there may be hemodynamic events that occur during the placement of a VSD device across a complex VSD.

However, with appropriate anticipation and collaboration between our staff and the catheterization laboratory, patients are safety managed during this intervention.

Let me first start with the video produced by NMT.

(Whereupon, there was avideopresentation.)

DR. LAUSSEN: Next I would like to show a number of still antiographic frames that highlight aspects of this procedure because it's germane to discussion about adverse hemodynamic events.

In this particular still frame a petal catheter has been placed within the left ventricle and

on left ventricular angiography the muscular VSD is demonstrated.

As also shown in the video, this still frame demonstrates the antegrade passage (trans-atria1 septal) of an end hole balloon tip catheter from the left ventricle across the VSD into the right ventricle. It is generally easier to cross the VSD from within the left ventricle because of the trabeculations on the right ventricular septal surface.

This slide demonstrates the transvenous-transcardiac guidewire pathway. In this circumstance wire has been delivered through the femoral vein infera vena cava transeptally across the mitral valve to the left ventricle across the VSD into the right side of the circulation where it is being snipped and removed from an alternavenous access site which, in this case, is the internal jugular vein.

The importance of this is that undue pressure applied to this wire may directly injure the myocardium and cause acute atria1 ventricular vulvar regurgitation. It is the passage of this wire and

subsequent large sheaths that may result in homonymic adverse events during the procedure.

It is easier rather than to leave a large ll-French sheath within the atria1 system in the femoral artery and across the aortic valve, generally the VSD is crossed from the right ventricular side with a large ll-French sheath which in this circumstance has been passed from the internal jugular vein down across the VSD crossing from the right ventricle to the left ventricle.

The CardioSEAL delivery system is delivered through the.sheath. The distal arms are open within the left ventricle and the device is then removed back against the left ventricular side of the septum and then across the septum for deployment of the proximal arms. Also the transesophageal echo probe which is used to assist with deployment of the VSD device across the septum.

Following deployment of the device, the device is detached from the delivery system and an LV angiogram is performed to demonstrate appropriate position.

The reason for going through these angiographic slides is to highlight the transvenous-transcardiac pathway of the guidewires and sheaths because the hemodynamic adverse events that may occur during this procedure are primarily related to the technique.

Early in our experience we evaluated patients undergoing this procedure, the hemodynamic and potential cardiac complications during this procedure and determjned that the complications and adverse events were independent of the patient's diagnosis or indication for device deployment independent of the pre-catheterization clinical status as assessed by ASA classification and independent of patient size.

However, acute resuscitation may be necessary during the procedure despite the events are readily treatable and reversible. Hemodynamic instability, therefore, may relate to hypovolemia which primarily relates to frequent catheter changes through large sheaths because of arrhythmias which may be ventricular, super ventricular, and cardiac output

which commonly reflects acute vulvar insufficiency during the procedure and, in rare circumstances, cardiac arrest may occur.

However, with appropriate treatment with blood volume replacement, the use if inotropic, chronotropic and vasopressor agents, the occasional use of temporary trans-venous pacing and cardioversion, these complications are readily reversible.

Our strategies for management, therefore, include general anesthesia for all cases because of the risk for adverse events. Also because we share the airway with the echocardiographer during TEE and for vascular access issues.

Resuscitation drugs and equipment should be prepared and immediately available for every case, and we have ICU backup for every case.

In conclusion, the transcatheter device occlusion of a complex VSD is a challenging environment and a challenging intervention with potential for adverse effects. However, with appropriate anticipation, patients are safely managed

through this procedure.

Thank you. Next I would like Dr. Jenkins to come and talk regarding the clinical trial overview.

DR. JENKINS: My name is Kathy Jenkins. I have no financial interest in NMT Medical, Inc. I paid for my expenses to attend the session today.

What I would like to do now is to show you this source of the information that was presented to you in the Panel Packet and was presented for this PMA application.

There were five separate cohorts of information presented for the PMA application. These five cohorts were derived from two separate studies. The first cohort, and by far and away the most important, which is referred to as the pivotal cohort, includes patients undergoingventricular septaldefect closure using the CardioSEAL device as part of a study that I'll describe in detail known as the High Risk study. This information includes detailed information about device safety and efficacy.

In addition, there are four additional non-

pivotal cohorts. The one that we will describe in some detail includes patients that underwent closure of a ventricular septal defect using a prior generation of the device known as the Clamshell I.

All of the data from both studies used for indications other than VSDs are also presented as well as information in a , small number of prospective patients where the device was used to close post-infarction ventricular septal defects, although the focus of all of the non-pivotal cohorts is primarily to provide additional information about device safety as well as longer term follow-up.

As I mentioned previously, the pivotal cohort was derived from a study known as the CardioSEAL High Risk Study. This is a prospective multi-center study that began enrollment in 1996 for which the Children's Hospital in Boston is the study sponsor.

This study is overseen by a safety and data monitoring committee chaired by Dr. Thomas Haugen and is currently ongoing. Enrollment in the study through 2/1/00 was submitted as part of the PMA application.

As I mentioned previously, this study includes patients with ventricular septal defects as well as other types of cardiac defects. The safety data from this study were used to support HDE approvals for fenestrated Fontan closure, ventricle septal defect closure, and PFO closure in recurrent stoke patients.

The design of the CardioSEAL High Risk Study was to determine the safety and efficacy of the CardioSEAL device in patients with limited acceptable alternatives. The study is a prospective cohort of implants patients without a concurrent control group.

However, patients were entered into the study by an independent peer review process whereby an uninvolved, meaning uninvolved with the patient or the study, cardiologist and cardiac surgeon were required to approve the enrollment of patients in the trial.

The criteria that were used by peer review team to make the device determinations are shown on this slide. The peer review team had to ascertain that the patient had one or more cardiac defects of sufficient hemodynamic derangement to warrant

intervention and that the patient had either a type of defect that is technically difficult or impossible to close surgically, or an overall medical condition such that the surgical risks were sufficient to justify the known and potential unknown risks of the device.

The outcome evaluation was performed prospectively on an ongoing basis at baseline, discharge, 1, 6, 12, and 24 months following the procedure and included a clinical evaluation, chest x-ray, echocardiogram, and a fluoroscopy at 6 and 24 months after implantation.

A core laboratory was responsible for the final interpretation of all chest x-rays and echocardiograms in this study.

The efficacy assessments for patients enrolled in this trial was performed in three different ways that I will describe in detail. The first, which we call Clinical Status, by Lesion, uses a combination of information from two ordinal scales. The second Clinical Status by Patient, uses a combination of information from 8 scales. The third, Echo Closure Status, is defined more traditionally

categorically.

In all cases these efficacy assessments were evaluated as a change from a patient's preimplantation baseline to the six-month follow-up time point such that each patient served as his or her own control for this assessment.

The assessments include a degree of flow by echocardiography as well as other clinical information. As I mentioned previously, all echocardiograms were assessed by an independent core laboratory.

To apply the Clinical Status Scale, by Lesion Assessment, a scale value was assigned to the patient at each of the assessment time points using one of two applicable scales. Either an anatomically based scale, or a physiologically based scale.

The use of two parallel but equivalent scales allow longitudinal assessment of patients despite interim surgeries such as removal of a previously placed pulmonary artery band. A change by one category in the scale assessments is considered to be clinically meaningful.

This slide shows the actual scales that were used to make this assessment. I should mention that the point of this overall efficacy assessment was to determine the change in the patient's status that was specifically related to closure of the ventricular septal defect.

All patients for whom the hemodynamic consequences of the ventricular septal defect were a left-to-right shunt were made by assigning the patient a value of zero to five on this physiologically based scale.

Since quite a number of patients in this study have had prior placement of a pulmonary artery band, we created an anatomical but intended to be equivalent scale for those patients in whom the VSD no longer resulted in the left-to-right shunt. This assessment was based primarily on the actual diameter of the ventricle septal defect in relation to the aortic annulus diameter.

Patients who died or had the device explanted were categorized as -1 regardless of whether the death or the explant was due to the device or the

procedure.

So as an example, if a patient had a congenital muscular ventricular septal defect and had undergone prior placement of a pulmonary artery band, and then was enrolled in the study and had a VSD closed with the device, and then subsequently had the band removed two months later, the patient would have been assessed on the Anatomical Scale for the three assessments that were made prior to the band removal and on the physiologically based scale after the band had been successfully removed.

Two, go one step further and evaluate changes in the patient's status that went beyond the simple consequences of closure of the VSD. We also looked at efficacy using a Clinical Status Scale by patient.

This assessment 'was also made as a change from the patient's pre-implantation baseline at the six-month follow-up time point, but now included a status assessment based not only on the VSD but also on other clinical factors and, therefore, is a more global assessment of patient improvement or decline.

This slide shows the additional information that was included in this assessment. There's a total of eight scale that were used. The first right to left shunt was rarely applied to this population. The second two are the VSD scales I described previously.

In addition, patients were assessed as to their risk for systemic emboli, on hemodynamic compromise not due to shunt most usually either ventricular dysfunction or AV valve regurgitation, the presence of arrhythmia, elevated pulmonary vascular resistance, or additional medical illnesses.

This slide shows the possible assessments for the arrhythmia category, again where patients would be given a scale assignment according to the type of arrhythmias that they had at that time point.

So in each case a scale value was assigned to the patient in each of the eight categories but the overall assignment for the patient was the lowest value in any of the applicable categories.

To clarify with an example, if there was a patient with a medical illness of sufficient severity to be rated as a Category 2 as well as a ventricular

septal defect of sufficient severity to be rated as a Category 2, if this patient then underwent successful device closure such that the VSD categorization improved to a four but with no change in the medical condition, the patient would have been assigned a score of 2 at baseline based on the presence of both the VSD and the medical condition, but again would have received a score of 2 post-procedure based on the condition only.

The difference in the patient, therefore, would be rated as zero and the procedure would not have been considered successful on the clinical status by patient assignment. The same patient evaluated using the Clinical Status, by Lesion assignment would have improved by two categories and the procedure would be considered a success under that efficacy criteria.

We also used the much more traditional measure of efficacy for device trials., namely Echo Closure Status whereby residual flow was categorized as trivial to absent, small or more than small according to strict criteria used by the core

laboratory.

To assess safety for this group of patients, the safety assessment is primarily descriptive but did include a comprehensive definition of adverse events very similar to the definitions used in drug studies whereby all adverse events occurring at any point during follow-up in all patients in whom an implant was attempted were recorded.

Each of the events then underwent an independent assessment by the safety and data monitoring committee who was responsible for the final attributability and seriousness classifications.

The committee graded events as serious, moderately serious, or not serious using strict definitions that were shown in your protocol. And also categorized events as definitely, probably, or possibly related to initial device positioning, to device fraction, otherwise to the device specifically to the implantation part of the cath procedure or otherwise to the catheterization as well as using a variety of unrelated categories.

It's important to understand that the

committee used the possibly related category for these assignments very similar to the way that category is used in drug studies where the possibly related category was intended to mean plausibly related where the committee used probably or definitely related for events that they thought were likely to have been attributed to the device of the implant or whatever.

The primary measure of safety that we defined for this study was the proportion of patients with at least one moderately serious or serious device or implantation related event as assigned by the committee.

I would now like to switch and describe for you the second source of data that was presented as part of the PMA implication. This data comes from a different study that is known as the Clamshell I Follow-Up Study and is part of the non-pivotal part of the submission.

This particular data is a registry of all patients that were implanted with Clamshell devices.at the Children's Hospital during prior regulatory trials. The database was retrospectively created in

1994 and since that time patients have been following prospectively to screen for a device related and other major clinical events.

This study also includes patients with ventricle septal defects as well as other types of cardiac defects. These data are included primarily for ascertainment of late device related events.

In this study the information is solicited from all patients who consented to participate according to a recommended follow-up schedule. It's in the form of, a registry so the 'testing was recommended but not required but included annual evaluation for the first five years after implant and less frequently thereafter.

Adverse events are classified similarly to the CardioSEAL High Risk Study but were not reviewed by an independent safety and data monitoring committee. In the more recent prospective portion was included identification of device in fracture related events only.

An Echo Closure Status is also categorized similarly in the prior study but, once again, the Echo

Closure Status for this cohort has not been reviewed by an independent core laboratory.

I would now like to introduce you to Dr. Kim Gauvreau who is the biostatistician for both of these studies and she'll talk about the' sample size assumptions as well as review and show the actual data from the study.

DR. GAUVREAU: MY name is Kimberlee Gauvreau. I'm a biostatistician at Children's Hospital in Boston. I have no financial interest in NMT although they did reimburse me for my travel expenses today.

My portion of this presentation will focus on three things. I will first give a brief description of our sample size calculations. I will then summarize the efficacy and safety results from the VSD pivotal cohort which is part of the CardioSEAL High Risk Study. Finally, I'll present some efficacy and safety results from the VSD non-pivotal cohort that is part of the Clamshell I registry.

Beginningwiththe sample size calculations, for efficacy we wanted to have a sample size that

would be sufficient to detect a median improvement of two categories from baseline to the six-month follow-up time point on the Clinical Status Scale by lesion.

For example, we would want to be able to detect an improvement from category one, heart failure symptomatic to category three which represents a moderate shunt.

Since the data are measured on an ordinal scale and are paired each subject serving as his 'or her own control, we use the nonperimetric Wilcoxon signed-rank test to evaluate the null hypothesis of no improvement.

In order to achieve 90 percent power, we found that we would need a sample size of 35 patients. Given full information on our VSD pivotal cohort of 57 patients, we would have 99 percent power to detect a two category change.

Our safety analysis was primarily descriptive and here we wanted to be able to construct a 95 percent confidence interval for the primary safety outcome which is the proportion of patients experiencing moderately serious or serious device or

implantation related events with a specified degree of precision.

Using the normal approximation to the binomial distribution, we estimated that our sample of 57 patients in the VSD pivotal cohort would allow us to estimate a confidence interval with length of plus or minus 13 percent.

I'll now summarize the results from the VSD pivotal cohort. There were a total of 74 patients with a VSD enrolled in the CardioSEAL High Risk Study through February 1, 2000. Implant of a CardioSEAL device was attempted in 58 of these patients and successfully placed in 57. There were six patients who had multiple procedures and 26 who had more than one device placed. A total of 107 CardioSEAL devices were implanted.

The CardioSEAL device was not implanted in 17 patients. In 13 patients device implant was not attempted in most cases because the defect was smaller than anticipated. In one patient the implant was attempted but a device was not placed due to unfavorable anatomy.

Because the STARFlex device became available in the late phases of this study before February 2000, three patients with a VSD actually received a STARFlex device rather than a CardioSEAL device. These three patients are not included in any of our subsequent analyses.

For the 57 patients who actually received the CardioSEAL device, 46 percent had a congenital defect and 54 percent had a post-operative residual defect. Approximately,80 percent of the group were less than 10 years of age.

The cohort as a whole was quite sick. Eighteen percent had significant arrythmia, 35 percent elevated pulmonary vascular resistance, 25 percent significant medical illness, and 60 percent significant hemodynamic impairment not due to shunt. Seventeen patients had prior placement of a pulmonary artery band which was later removed in 16 patients. Approximately 83 percent of the 107 implanted devices were either size 17 mm or size 23 mm.

Just to remind you, we have three efficacy outcomes, Clinical Status Scale, by Lesion; Clinical

Status Scale, by Patient; and Echo Closure Status. I'll begin by looking at the Clinical Status Scale, by Lesion for the VSD pivotal cohort.

What you see in the top histogram are the values on this Clinical Status Scale prior to device implantation. Below that are the values of the six-month follow-up time point. You can see that the distribution shifts to the right indicating an improvement on this Clinical Status Scale.

There are six patients who have the value -1 at the six-month follow-up time point. These are the patients who either died or had their device explanted before the six-month follow-up. They were each assigned the value -1 on this scale regardless of whether their death or explant was due to the device or the procedure.

Note that the most common value that occurs prior to implantation or the mode of the distribution is the value 1 which represents heart failure symptomatic, while the value that occurs most frequently at the six-month follow-up is 5 which represents trivial or no shunt.

Fifty patients were measured on the Clinical Status Scale, by Lesion by prior to implantation and 47 at the six-month follow-up. There were 44 patients who had measures at both time points. These 44 patients had a median improvement of two categories on this scale. This improvement was statistically significant at the .0001 level.

Here you can see the changes in the Clinical Status Scale for the 44 patients measured at both time points. The positive changes from one to four represent improvements in clinical status on this scale.

The one patient with a value of zero did not change scale value prior to implantation to the six-month follow-up. The patients with negative values, the negative change all decreased on this scale. These include the patients who died or explanted before the six-month time point.

Defining a successful procedure as one in which Clinical Status Scale improved by one or more categories by the six-month follow-up, 84 percent of these procedures were successful.

I'm going to now turn to the Clinical Status Scale, by Patient which is a more global assessment of a patient's health status. Here again you can see the distribution of values prior to implementation and at the six-month follow-up time point. Once again, the distribution has shifted to the right suggesting an improvement in clinical status.

Here there were 53 patients who could be assessed on the Clinical Status Scale, by Patient at both time points. Again we saw a median improvement of two categories. Not only was this a clinically important improvement for the patients, it was also statistically significant.

These are the changes in Clinical Status Scale for the 53 patients who were measured at both time points. Again, a positive change represents a successful procedure. Here 72 percent of the procedures were successful by the six-month time point.

Our final measure of efficacy for the VSD pivotal cohort is Echo Closure Status. Prior to implementation 94 percent of the patients had a more

than small residual flow represented by Category 3. At the six-month follow-up time point only 9 percent of the patients had more than small flow.

This median decrease in the scale value from 3 to 2 is statistically significant or, in other words, for more than small residual flow to a median of small residual flow.

Summarizing the efficacy data for the VSD pivotal cohort there were successful defect closure and shunt reduction in 84 percent of patients by six months after device implantation.

Improved clinical status was observed in 72 percent of patients. While there was more than small residual flow in 94 percent of patients prior to implantation, only 9 percent had more than small flow at the six-month follow-up.

I'll now look at safety for the VSD pivotal cohort. Using the comprehensive definition of adverse events that was described earlier, 57 out of 58 patients with the device implant attempted experienced at least one adverse event through the most recent follow-up.

There were a total of 222 events. 32 of these were related to the device and include events which were definitely, probably, and also possibly related to the device. 35 events were related to the implementation procedure, 85 to the catheterization, and 70 were unrelated to the device implantation or the catheterization.

Our primary safety outcome was the proportion of patients with at least one serious or moderately serious device or implementation related event. 22 patients were found to have an event of this type which represents 38 percent of the VSD pivotal cohort. Again, we are including events that are definitely, probably, or possibly related to the device or procedure.

Here we can see of the moderately serious or serious device or implantation related events there were 16 device related events, 12 of which were detected within two days of the implementation procedure. Of the 17 moderately serious or serious implementation related events, 16 were detected within two days of the procedure.

I would like to take a moment to point out that there is an error in the data in the Panel Package which affects mainly Tables B7 and B9 in Section 5.D. If you look at those tables, we actually have one implantation related event in the one to six-month time frame and a second implantation related event in the greater than six month time frame. Both of those late events were mitral vulvar regurgitations.

What we discovered was that there was actually one patient who had ongoing mitral vulvar regurgitation. That patient we mistakenly recorded multiple events for that one patient. It really should have been just a single event.

Looking more specifically at the moderately serious or serious device related events, those that occurred within two days of the implantation procedure included four device embolizations. All four embolizations occurred in a single patient who is 70 years of age diagnosed with tetralogy of flow and had an AICD.

There was one device malposition which was

repositioned at the time of a planned surgery. There was one mitral vulvar regurgitation where the valve was stretched at procedure.

There was also one perforation of the heart which was detected between two days and one month after the implantation. That was an incidental finding at a planned surgery. There was one vessel dissection that occurred between one and six months after the implantation. That took place during device removal at a subsequent catheterization.

One more thing I would like to point out is that the events listed in white are either definitely or probably related to the device and those in yellow are only possibly related to the device.

Looking at the moderately serious or serious implantation related events, the events occurring are being detected within two days of the implantation procedure included five cases of third-degree heart block. Four of these cases resolved within one week of the procedure. The fifth case I will discuss in a minute.

There were three cases of ventricular

tachycardia two of which resolved with lidocaine and cardioversion. The third case was that same patient that we will come back to in a minute when we talk about the deaths.

There were two hypertensions requiring intervention. There was one event that was detected late, more than two days after the implementation procedure and what an aortic vulvar regurgitation.

Most moderately serious or serious device and implantation related events resolved as noted in the previous slides. However, there were ongoing device or implant related event present in two out of 58 patients or 3.4 percent.

These were mild to moderate mitral vulvar regurgitation. in one patient in mild to moderate aortic vulvar regurgitation in a second patient.

Device relatedeventswhichwere categorized as not serious by the safety and data monitoring committee including five device malphysicians, one device delivery system malfunction where there was a difficult release but it was ultimately successful, one kink in the delivery system or sheath.

There were four deaths in the VSD pivotal cohort and these deaths are described in detail in the Panel Package Section 5.D.1.2. Only one death was considered to be due to the catheterization procedure. This was in a three-and-a-half-month-old child with single ventricle misdiagnosed as Swiss cheese septum.

The patient has severe congestive heart failure, low output, and complete heart block after cath and died of multisystem organ failure at attempted PAB and pacemaker placement:

There were two additional death that were due to the underlying cardiac disease and one that was due to the underlying noncardiac medical condition.

There were four device explants. Again. these are described in more depth in your Panel Package. Two were at heart transplantation, one at a Fontan surgery after a failed septation, and one at catheterization due to device instability.

There were 17 device arm fractures among the 107 implanted devices. This represents 16 percent of the devices. No adverse events were attributed to device arm fractures in this VSD pivotal cohort.

We next looked at the VSD non-pivotal cohort which was part of the Clamshell I registry mainly to evaluate the long-term safety issues associated with device placement.

There were 87 patients in this cohort who received the device. There were a total of 140 devices implanted. In this cohort the median follow-up was 4.6 years and the maximum was 11.5 years.

There were a total of 25 device related adverse events, 10 of which were serious, eight moderately serious, six not serious, and one of unknown seriousness.

Looking at the 18 serious or moderately serious device. related events, eight were detected within one week of the implantation and included two device embolizations, one device malposition, and one new onset vulvar regurgitation. The events were quite similar to those noted in the VSD pivotal cohort from the CardioSEAL High Risk Study.

All events detected within one week to six months of the implantation procedure were only possibly related to the device. There were two device

malposition detected between one and two years after the implantation.

The efficacy data available for this cohort was echo closure status at the most recent follow-up. You can see that 82 percent of patients had either small or trivial or absent residual flow at most recent follow-up. Again, the median follow-up was 4.6 years.

Additional data which I am not presenting includes information from three non-pivotal cohorts. The first is the CardioSEAL High Risk Study, patients without a VSD. There were 271 such patients with a device implanted. The second non-pivotal cohort is from the Clamshell I registry, again non VSD patients. There were 414 patients who received the device.'

Finally, the CardioSEAL High Risk Study patients with acquired VSD following an infarction and there were five of those. Each of these cohorts is described in more detail in the Panel Package.

We would like to point out that in the entire series of 690 patients, only one device related adverse event led to device removal and that was in a

7-year-old with thrombus noted on the device nine years after PFO closure.

I would like to now reintroduce Dr. Kathy Jenkins who will summarize the conclusions.

DR. JENKINS: So in conclusion in patients at high risk for poor outcomes after surgery, VSD closure using a transcatheter CardioSEAL device resulted in successful defect closure and shunt reduction in over 80 percent of cases by six months after implantation.

Similarly, device closure resulted in an improved clinical status in 72 percent of patients. Device arm fractures were observed in 16 percent of implanted devices. However, all were identified incidentally. No clinical consequences have been attributed to fractures in CardioSEAL devices used to close VSDs.

Peri-procedure events occurred frequently but most were successfully treated. One infant death was directly attributed to the procedure. Only two patients have ongoing clinical impairment from moderately serious or serious device or implant

related events both with valve injuries.

Late onset adverse events attributed to the device were not observed in the pivotal cohort. Extended follow-up in a similar series of patients implanted with a predecessor device suggest that late device related events are rare.

Thank you very much.

DR. TRACY: Thank you very much.

We'll move on to the FDA presentation.

MS. BUCKLEY: Good afternoon. Again, my name is Donna Buckley and I'm a mechanical engineer in the Interventional Cardiology Devices Branch of the Office of Device Evaluation. I'm also the lead reviewer for the CardioSEAL Septal Occlusion System PMA submission, POOO049.

Dr. John Stuhlmuller, the medical officer for this submission, and I will present the FDA summary for the CardioSEAL System. This device is a transcatheter septal defect occlusion system used in the treatment of high risk ventricular septal defects (VSDs).

You're being asked to discuss and make

recommendations on the sponsor's PMA submission. Your points of discussion of the clinical study results and labeling recommendations will be taken in to consideration by FDA in the evaluation of the application. Finally, you'll be asked to vote on the approvability of this device.

The FDA summary will provide a brief overview of the following:

The FDA Review Team, the device description, HDE approval, nonclinical evaluation, clinical evaluation, and the questions to the panel.

Members of the FDA review team include myself, Donna Buckley, and Dr. John Stuhlmuller from the Office of Device Evaluation; Dr. Lakshmi Vishnuvajjala from the Office of Surveillance and Biometrics who served as the statistical reviewer; and Ms. Liliane Brown from the Office of Compliance who coordinated FDA inspection of the investigational sites.

The occluder is a double-umbrella design with a nitinol metal frame and attached polyester material. Four sizes are available ranging from 17 to

33 mm. The device size to stretched defect diameter ratio is generally 1.7 to 2.0 to 1. The implant is loaded into the 10F delivery catheter using the Qwik Load device. It is attached to the delivery system, tracked through the delivery catheter, and deployed across the defect.

The delivery catheter is 10F in size. The Qwik Load device, and I apologize for repeating, is attached to the delivery system. It is used to collapse and load the occluder into the delivery catheter.

A Humanitarian Device Exemption or HDE is an application that is similar to a premarket approval or PMA application, but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device where a Humanitarian Use Device is defined as a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States.

As previously indicated by the sponsor, the CardioSEAL device was approved under an HDE in

September of 1999 for the same intended use as proposed in this PMA application; HDE No. H9900005.

In vitro or bench testing as outlined in Section 1.4 of the FDA Summary was performed to evaluate the mechanical integrity and function of the CardioSEAL System.

Biocompatibility testing of the device components was conducted in accordance with IS0 Standard 10993. Studies in several different animal models were conducted with the CardioSEAL System. The results of the in vitro testing, biocompatibility and animal testing all demonstrate the integrity and functionality of the device for its intended use, There are no outstanding non-clinical testing issues at this time.

Now Dr. John Stuhlmuller will summarize the clinical evaluation of the device.

DR. STUHMULLER: Good afternoon. My name is John Stuhmuller. I'm a medical officer in the Interventional Cardiology Devices Branch in the Division of Cardiovascular and Respiratory devices. I am going to provide a brief overview of the clinical

information contained in the PMA.

The sponsor has provided information for five different clinical data sets. First is the pivotal cohort for VSD closure.

The non-pivotal clinical data sets include the following: Clamshell I follow-up for VSD closure, high-risk registry for non-VSD closure, Clamshell I follow-up for Non-VSD closure, and acquired VSD status-post myocardial infarction. Only the pivotal cohort for VSD closure will be reviewed at this time.

The pivotal cohort for VSD closure is a retrospectively derived patient subset. of the High-Risk Registry. "Complex" VSDs eligible for device closure included defects not accessible to closure through an atria1 or aortic approach, those associated with other cardiac pathology, patients with single or multiple defects, or patients at high surgical risk.

The registry is an open-label single-arm registry without a control group. Enrollment in the registry is consistent with the compassionate use criteria as outlined in the Expanded Access provisions of the Food and Drug Administration Modernization Act

of 1997.

The registry is also primarily a single-center study.

A total of 74 patients were identified for inclusion in the pivotal cohort for VSD closure. Devices were placed in 57 and 58 patients in which device placement was attempted. Multiple procedures were completed in 6 patients. Multiple devices were placed in 26 patients.

Patientoutcomeassessmentforeffectiveness was completed using the Clinical Status Scale. Patient outcome assessment for safety was by evaluation of potential anticipated and unanticipated adverse events.

The Clinical Status Scale was developed by the investigators at Boston Children's Hospital for use in evaluation of patients enrolled in the High-Risk Registry.

The scale consist of eight nominal variables each using an ordinal scale for patient outcome assessment. Each ordinal scale was developed so that change of one in either direction on the scale

represents a clinically meaningful change.

Effectiveness was determined at six-month follow-up using the Clinical Status Scale. Forty-four of 57 implanted patients completed follow-up. The Anatomical Scale was used pre-procedure and at six months in 14 patients. The Left-to-Right Shunt Scale was used pre-procedure and at six months in 22 patients.

Different scales were used in eight patients. The Anatomical Scale was used pre-procedure and the Left-to-Right Shunt Scale was used at six months in eight patients.

Based on the method of analysis provided by the sponsor, a median change of two categories was demonstrated and 84 percent of the procedures were considered successful at six months.

In terms of safety, patient evaluations were scheduled at one, six, 12, and 24 months. Adverse events by time of event are reported as with two days of implant, two days to one month, one month to six months, and six months to most recent follow-up.

Adverse events were characterized as device

related with a separate analysis for device arm fractures, implantation related and catheterization related.

Adverse events were noted in 57 of 58 patients in which device placement was attempted. A total of 222 adverse events were noted. At lunch we corrected a typographical error for device arm fractures.

On your handout I believe it's going to read 34 of 107 and it was corrected. There were a total of 32 device related events, 35 implantation related, 85 catheterization related, and device arm fractures were noted in 17 of 107 devices.

Next Donna Buckley will review the panel questions that we would like to receive input on.

MS. BUCKLEY: The sponsor has submitted data to support approval of the CardioSEAL device for closure of ventricular septal defects defined as complex. The data in support of this application has been provided from primarily a single-center, uncontrolled, registry study sponsored by Boston Children's Hospital.

The complexity of VSD in patients entered into this registry has been defined variously as VSD not accessible to closure through an atria1 or aortic approach, associated with other cardiac pathology, patients with single or multiple muscular septal defects, or simply patients at high risk for surgery.

Question la: Based on the information provided, please discuss the description "complex VSD" as the defining indication for use of the CardioSEAL device.

Question lb: In the absence of a control group, please discuss how to evaluate the safety and effectiveness of the CardioSEAL device.

A "Clinical Status Scale" was used to evaluate efficacy. The primary efficacy evaluation includes a comparison of the pre-procedure and six-month shunt using both the Left-to-Right and Anatomic Scales, also called the Clinical Status by Lesion Measure.

In order to evaluate safety, adverse events were recorded and categorized as serious, moderately serious, not serious, and unknown seriousness. Events

were also categorized as device related, implantation related, or catheterization related.

Question 2: Does the Clinical Status Scale allow for a clinically meaningful assessment of effectiveness for the device?

Question 3: Based on the data provided and your comments regarding questions 1 and 1, please discuss whether these data provide reasonable assurance of safety and effectiveness.

A summary of the Physician Training Program has been provided in Section 5 of the Panel Package.

Question 4a: Please discuss any improvements that could be made to the training program.

Question 4b: More than one device was placed in 26 patients. Please discuss training issues regarding the placement of multiple devices in a single patient.

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product

should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling.

Question 5a: Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations for treatment with this device.

Question 5b: Please comment on the CONTRAINDICATIONS section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

Question 5c: Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Question 5d: Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Question 5e: Please comment on the remainder of the device labeling as to whether it adequately

describe how the 'device should be used to maximize benefits and minimize adverse events.

The Panel Package includes the available two-year data for the CardioSEAL device in the pivotal cohort. In addition, data were provided from the Clamshell I follow-up study for some patients followed out to 12 years. Long-term adverse effects that may be associated with device implantation include late thrombosis formation, the risk of endocarditis, problems with late operation, and arrhythmias.

Question 6: Do you believe that additional follow-up data or post-market studies are necessary to evaluate the chronic effects of the implantation of the CardioSEAL device? If so, how long should patients be followed and what endpoints and adverse events should be measured?

Thank you.

DR. TRACY: Thank you. We'll move on to the open committee discussion. Dr. David.Skorton was the lead reviewer. We'll ask him to begin.

DR. SKORTON: Thank you and thanks for the presentations. Before I start my questions, I just

want to take a moment to commend the sponsor and the researchers for tackling a very, very difficult clinical problem which doesn't have any easy answers.

However, having said that, I have a few questions to ask. Philosophically what we're looking at is an uncontrolled study where the efficacy measures are largely semi-quantitative. The leap of faith is that you really cannot do surgery on these patients.

I have a question for the surgeon who spoke earlier. I apologize, I forgot the gentleman's name. The data that we're shown for the bad outcomes of ventriculotomy incisions were from the '70s and '80s. Of course, we don't see ventriculotomy incisions as much anymore because of those data. Please help me to understand what are the data for those few patients nowadays that do have to have ventriculotomy incisions:

Obviously, all of us occasionally do have to send patients for ventriculotomy. Maybe not for congenital heart disease but sometimes to close peri-infarction VSDs. Can you help us to understand what

those data look like today?

DR. MAYER: That's a little bit difficult to answer actually. I will answer it the following way. Based on that information, we as an institution sort of went away from what had been the previous approach of doing a left ventriculotomy for patients with defects in this area.

We have a little bit of clinical experience with maybe seven or eight patients -- I can't remember the number exactly -- which we have approached through a lower sort of periseptal, if you will, incision but that is a subset of apical VSDs. I chose the words relatively carefully that the ones that are further back that are more posterior are ones that we continue to have problems with.

I don't have the data to tell you how many of those patients have been approached surgically, although I would say the numbers are relatively small at this point. Clearly it depends a little bit on the size of the defect and the location.

Clearly there are a number of muscular VSDs that we can approach transatrially or through a

limited anterior ventriculotomy. That's why in particular those patients who would require a left ventriculotomy or an extensive right ventriculotomy are the ones that we are sending to the cath lab basically.

The other subset of patients, and there are a significant number in this series, are ones in which previous surgical attempts have failed typically in those areas. I guess that is one indicator that you have is that prior surgeons both in our own institution and elsewhere have failed to close the VSD because it was difficult to access surgically. A significant chunk of the total pivotal cohort are, in fact, post-operative VSDs with residua.

DR. SKORTON: Fair enough. Thanks. My next couple questions are truly like one big question. It has to do with a part Clinical Status Scale. It's probably a statistical question and partly clinical question.

I saw that you used a non-parametric rank test which I think is admirable because who knows what the distribution of these factors are.

I'm assuming that your assumption using a rank test across all of these is that one category in each row of the scale has equivalent clinical significance.

DR. GAUVREAU: By using a non-parametric rank test it's only assuming that the categories have a certain order to them but not that the difference between a two and a three is the same as the difference between a three and a four, but just that a three is better than a two and a four is better than a three.

DR. SKORTON: Let me restate it. It's a point well taken. The definition was, as I understand it, for each scale that one step is supposed to indicate something of clinical significance. Is that fair?

DR. JENKINS: Yes. Your statement the way you first made it is correct. When we tried to design the efficacy outcome for the trial, initially we proposed echo closure status for the complex cohort that included VSDs and other indications.

Actually, the FDA required us to create a

more quantitative method to follow patients. It was a complex cohort with multiple indications. We actually did some consulting and one of the biostatisticians at the Harvard School of Public Health helped us construct the parallel but equivalent scales exactly with the assumption that you propose so that we could say something about the cohort overall.

When you carve out the subgroups, for example, in the clinical status by lesion assessment or some of the other subgroups, that problem falls away. In the clinical status by patient assessment, your assumption is exactly correct.

DR. SKORTON: Thank you. So following up on that, I just have a couple questions. I don't mean for these to be cheap shots. I'm really asking because I'm trying to understand how they were used.

The anatomic scale that measures VSD diameter as a percentage of aortic root diameter, I'm assuming some of these VSDs were multiple holes near the septum near the apex or anterior septum.

How do you figure out in a multiple hole VSD what the diameter is that you have a single number to

compare against aortic root diameter if there were, say four holes?

DR. JENKINS: I think that you might have noticed that the sample size dropped for the six-month efficacy assessment. The reason for that is that there were substantial number of assessments. It wasn't that only 44 patients achieved the six-month follow-up.

Actually, the follow-up is 100 percent in this study. It's that the assessments were considered to be inadequate to make a complete determination of VSD diameter or lesion shunt size.

The multiple jets that were greater than two were quoted as more than small. There were quite a number of cases where people didn't feel comfortable making an assignment and that's where the missing data comes from.

DR. SKORTON: Okay. Thanks. You just answered the next question, too. I appreciate that.

Could you review for me one more time in the assessment of clinical status by lesion? My understanding, and I apologize if I got this wrong, is

that you use different measures for the initial assessment than for the follow-up assessment. Is that right?

DR. JENKINS: Not in all cases and not in most. Only in patients who had initially a placement of a pulmonary artery band so that they couldn't be -- our attempt was to create the entire scale with the physiological consequences of the whole. That was the intent.

Unfortunately for banded patients, that broke down because they might have known that shunt and still have a big hole in their heart. They would be neither "blue" nor have a right left shunt. We tried to formalize an anatomically based assessment that we felt would be equivalent to the shunt based scale.

In other words, what size hole would have resulted in what size shunt if you could do what you couldn't do which is take the band off and measure it. That was the numbers that we came up with there.

DR. SKORTON: Okay. The last question, which I've been told is fair game to the sponsor and

not to the investigators, is it looks to me like the application is aimed at a relatively small number of the sickest of the sick, difficult to operate patients. I'm just curious what the motivation is to convert this from an HDE to a PMA? It's a question for the sponsor.

MS. KULIS: My name is Anne Kulis and I'm with Regulatory Affairs and NMT Medical. I would say that the primary motivation was that with an HDE there are significant administrative requirements such that IRB approvals are required for each institution before the site can receive devices. Our hope in converting this from an HDE to a full PMA approval was to reduce the burden both for the institutions as well as for the company.

DR. SKORTON: My understanding, and I could have this wrong, but I'm in charge of the IRBs for our university and my understanding on HDEs is that you go through IRB approval of the protocol but you don't need to take informed consent on each patient. You don't need to get IRB approval of every single case but of the protocol.

I agree it's certainly more of a burden than not doing it but it's not the same as a research protocol as I understand it where you have to get approval and informed consent of each patient.

DR. JENKINS: If I could just answer that because we've gotten quite -- when we got our original HDE approvals I was actually the recipient of multiple phone calls from all over the United States about this. It's very IRB dependent. It's very institutional dependent.

There are some institutions in our high-risk trial that chose to stay as part of the high-risk trial because they couldn't get the HD approved at their sites. It was actually more burdensome than having our trial approved.

There were some that treated it almost like it was an approved device that was on the shelf and it was an off-label use. Some of the academic centers who were maybe more fearful or more conservative really did place quite a few hurdles to investigators. We also have two investigators here who have enrolled VSD patients under HD approvals who might be able to

talk about the issues at their center.

DR. SKORTON: That's okay. I'll take your word for it. I'm done.

DR. TRACY: I guess we started at that end of the table last time so I'll shift over and ask Dr. Crittenden to raise questions.

DR. CRITTENDEN: I, too, enjoyed reading the Panel Pack. I thought it was very interesting and I agree this is a cohort 'of patients who need a lot of help and surgery is probably not a good answer.

I, too, like Dr. Skorton, have some concerns. Not so much concerns but questions about this Clinical Status Scale. Have you done anything to look at the validity of this to see whether or not if you take a second group of patients and look at it whether or not this really makes any sense whether it's valid?

DR. JENKINS: No, we haven't done any interater or other types of validity checks. What we did do, though, is that the echo closure status was reviewed by the core laboratory and we did revise the clinical status assessments afterwards. This is a

scale that was really designed specifically for this study. It doesn't really have any external validity beyond this other than face validity.

DR. CRITTENDEN: So the FDA didn't ask you to do it, you would have just presented the echo data, I presume, for efficacy?

DR. JENKINS: That's probably right.

DR. CRITTENDEN: The other question I had is there are a number of device fractures. Is there anything to be done about that or you just watch them over time?

DR. JENKINS: The rate of device fractures in this study is about half what it was with the predecessor Clamshell device. In the entire high-risk trial to date, we've actually scrupulously screened for fractures with out chest x-ray core lab review and with fluoroscopies.

We found them as an incidental finding in about 16 percent of this group of patients and in the cohort overall. As of yet, we haven't found any events that were definitely or probably related by the safety committee to the fractures.

There were three instances in the non-pivotal cohort, the non-VSD cohort where a patient experienced palpitations at the time or around the time that a fracture was detected at the same endpoint. In those three cases the committee quoted those events as possibly or plausibly related to a fracture but there was nothing else.

There had been a rare number of events in the original Clamshell I cohort that were attributed to fractures with masses in the heart or minor shifting of the device. We haven't observed that with the new CardioSEAL device.

DR. CRITTENDEN: Does this affect the endothelization of the device? Does it change that at all?

DR. JENKINS: I don't know for the CardioSEAL device but we did recently, and I think it's imminently about to come out in the literature, presenting a paper on the explant data from the Clamshell I cohort. In that analysis where we had really very good pathological information in all the explants, there seemed to be no association at all

with endothelization in the presence of a fracture.

DR. CRITTENDEN: That's all I have.

DR. TRACY: Dr. Wittes.

DR. WITTES: I have very little also. It was very hard for me to calibrate the results against what one would have expected because there was not only no control but nothing that described what you would have expected. Not being a cardiologist I didn't know what to expect. That was very hard for me.

I also struggled with the very same issue that you brought up about making the assumption that changing from one to two on one row is the same as changing from one to two in another row. I would have been nicer obviously if you had been able to have everybody in one row or the other because then at least you would see -- then you would know whether you have improvement or not.

I am particularly uncomfortable about those people who changed rows and whether the improvement that you see is truly a clinical improvement. I mean, the improvement that you code is truly a clinical

improvement.

DR. JENKINS: I think that the clinicians answer but not the data person's answer to that would be that most of the patients who changed rows on the primary assessment did so because they had a pulmonary artery band actually removed.

In general, that's not possible to do if you haven't successfully closed a VSD because you can take the pulmonary artery band off and the patient goes into congestive heart failure.

The fact that the patients were able to subsequently undergo pulmonary artery band removal is not quantitative but it is sort of a sign that the VSD was being at least partially successfully treated.

DR. WITTES: I actually was asking that clinical question. I guess the other issue then would be is if this moved into a different center, how center dependent. Again, it's an unanswerable question but it's a question that as I read I wonder.

DR. JENKINS: There were multiple interventionalists involved at one center but the bulk of the data was from one center. I think I would like

to ask Dr. Hoyer or Dr. Boucek to talk about their experience under the HDE approval.

DR. HOYER: Hi. I'm Mark Hoyer from Riley Hospital in Indianapolis. I have no financial interest in NMT Medical. I was asked to come here today and my expenses are being reimbursed today.

To answer, I think, Dr. Skorton's question as well and then moving on, the HDE approval is very different than the PMA. I've actually had experience in two locations. I have been in Florida and had to get approval.

Fortunately, somebody had paved the way already with the HDE category of approval which allowed me to kind of get in much more easily. We still required informed consent for every patient. In Indianapolis the exact same thing has held true. It is indeed an IRB approval.

Actually, although the IRB approval was easier in Florida, it's been more difficult and there was an entire full review board there in Indianapolis. In fact, we still get informed consent for every one of those patients.

We've been involved in closing a few of these complex VSDs. Obviously not the 57 patients that have been reported in the high-risk protocol already. We actually have been involved with three closures in two patients so obviously one of those had multiple defects.

I think the logistics of that has actually worked out pretty well. It requires some training clearly. I was proctored initially in Florida for fenestrated Fontans so I had some device experience and then came to Indianapolis and was able to carry that forward. That's basically been my experience thus far. I'll let Dr. Boucek answer some more unless there is anything else specifically.

DR. BOUCEK: I would basically support what Dr. Hoyer said. I also have no financial interest in N-MT. My travel arrangements were provided for.

We've done more like eight or so infants under the HDE. Frequently they are extremely ill children like you've heard about. Often they are referred to our institution for consideration of transplantation because they've had previous surgical

attempts to close the VSD which have been unsuccessful in children who are quite symptomatic.

It would be virtually impossible to resubmit them to another operation to try to close residual VSDs. These are very sick children and I think because of the experience that we've learned from what the group at Boston Children's has done, we've actually not had near what appears to be the difficulty placing these as reported here.

I think there has been a learning curve which has been communicated to the community. We've not had the problems with heart block and things like that. I think we've learned from other's experience.

This is certainly something I think can be done in an institution where there is an active interventional laboratory. I think we usually have the capability for surgical backup but we've never had to utilize it.

I think with appropriate anesthesia preparation and training, most of the adverse events that you've heard about can be anticipated. Now, in fact, we actually prevent them or prophylax them

through anticipation rather than responding to them when they occur.

DR. TRACY: Dr. McDaniel.

DR. McDANIEL: Thank you for those comments. I had a couple of questions when reading through this in kind of a general -- let me figure out what the heading is here. Under CONTRAINDICATIONS I was just curious. It says, "Anatomy which the CardioSEAL size required would interfere with intercardiac or intravascular structure such as valves or pulmonary veins."

I guess the pulmonary vein is the part I don't understand. I know you have to do a trans-septal cath to get there but is it the whole procedure you are referring to so there may be injury to the pulmonary veins in that sense? Because the CardioSEAL sitting in a VSD position shouldn't interfere. It's in a couple of places and I'm just -- or is that more related to its use?

DR. TRACY: That doesn't correct for the VSD indication.

DR. McDANIEL: Okay. It's probably related

to the ASD closure. I thought that.

Then a couple of comments on the patient's guide to device and the closure. Again, I read these fairly carefully. In the first sentence it's referred to as a ventricular septal hole. 'Most patients who by this time are pretty much -- they know it's a VSD or you could spell it out.

I think that is kind of unusual language. On the second page where you're talking about the use of TEE, it should probably say TEE involves using -- putting an ultrasound probe to a patient. I'm not sure what they would think that might be.

My only other comment on the patient or family information is that you don't at all refer to the trans-septal part of the procedure passing all the wires in and out of the body. I'm not making any comment whether it should be in there.

It's a very complex procedure but the illustrations really imply that it's a fairly simple procedure. You go from the neck, pop this thing through, and then you're done. I don't know if that needs further explanation or not but it was just

something that I initially was confused because I knew they had to come from the left side. This was a bit confusing to me.

I have a couple more questions. I think that's it.

DR. TRACY: Dr. Laskey.

DR. LASKEY: I really have only congratulatory comments so I'll be brief. These are critically ill kids and, I guess, at some point adults, too. Anything you do for them that a surgeon doesn't want to tackle has to be respected.

I think that the clinical outcome measure that you struggled with is really overkill. I think the data kind of speak for themselves in terms of the unbanding, as you said, and just general clinical improvement.

There are so many more questions with the methodology that is so limited, as you said, that they almost had to do better. You started out by giving them the worse possible rank they could have had by giving them the minimum number and so forth, not just by reverse regression to the mean but the way it's set

up they had to do better.

My question to you is you had a few people in your histograms who did worse. Is there something that you now know about how to tell who is going to do worse with this assuming it's a technically successful implant? Who should you not approach with this device?

DR. JENKINS: I guess I'll answer as well as anyone else in the room. I think that the technique needs to be very cautious in **small** infants as indicated by the infant who died directly as a result of the procedure. I also think that several of the failures were attempts at septation where septation was probably not possible.

I think that's a clinician learning curve as opposed to something technical. Hopefully we will eventually be able to refine our understanding of what is septable and what isn't. Those would be my main comments.

DR. BOUCEK: If I could just add frequently you are doing these in situations where there is nothing else to offer and the families are obviously

quite interested in trying to avoid heroic therapy like transplantation. If you could effectively septate a child that the surgeons had refused to operate on for standard repair, then that would have a significant impact on that child.

There may be a child who you can't effectively septate but because the damage to the myocardium from previous surgery or such things will still go on to need a transplant or may not survive. I'm not sure that is a contraindication they are trying to help those children.

I think the children that probably should be excluded are the ones that they have in the panel where it's likely that the act of closing the defect is going to predictably result in damage to the myocardium such as the AV valves or the semilunar valves.

I think ultimately we would hope that many of the children whose hearts are damaged by attempts to close complex VSDs at surgery could be done primarily with catheter techniques and avoid some of the children who right now actually get damaged trying

to do a standard surgical closure.

DR. LASKEY: Yes. These patients are beyond the pale so there are no rules here really. I think you are to be congratulated on what you have done.

I just have one other question. Is it an 11 French upper --

DR. BOUCEK: Ten French.

DR. LASKEY: No problems in kids?

DR. BOUCEK: I think size is an issue as has been indicated that if you get down to very small infants that's an issue but we put them in infants to six kilograms and it has been well tolerated and been able to go back through the internal jugular vein.

Of course, if we do procedures like ecmo where we put canulas into the internal jugular vein, they are much bigger than even that 10 French so there is precedent for putting large structures like that into the internal jugular vein.

DR. LASKEY: Thank you.

DR. TRACY: Thank you. This is obviously just a very incredible patient population. It must be just extraordinarily difficult to get consent for a

procedure that has a 99 percent chance of an adverse event occurring, a 16 percent chance of a device failure occurring, and a 7 percent chance of death, that offers an 80 percent chance of closure and a 72 percent chance of clinical improvement.

It sounds like a very difficult thing to walk into somebody's room and explain that to them. I think this would have to be part of the physician training to tell people how they can deal with that.

DR. JENKINS: I think it really has to do with Dr. Boucek was just suggesting which is whether the alternatives that you're offering the family of this doesn't work.

The way that we normally approach it in Boston is by explaining to them that the cardiac anesthesiologists are going to be at their side and are going to walk them through the procedure and be there to hopefully take care of anything that comes up.

We don't send people into this procedure with a rosy hope that everything will be absolutely perfect but with the hopefulness that if the

procedures are successful, that they may avoid needed to go through something that would be even worse or just not making it.

DR. HOYER: If I could say another thing. Mark Hoyer. That brings you to the issue that you're faced with a complex patient problem and options that you want to discuss with a family, whether that be surgery.

We've already heard that the surgery may be extremely high risk. Then we bring into this that we have the possibility of maybe using a device to close a defect in the cath lab, albeit at somewhat higher risk than a normal diagnostic procedure would be.

Then we have to kind of think about the issues of what the burden might\ be of the administrative aspects of an HD approval versus a PMA and more widespread application of the device.

Occasionally what happens is we get lots of questions about insurance issues. It's extremely frustrating or disheartening, I guess, to see a family that might be faced with a decision of a financial burden versus a soul and heartfelt decision for their

child.

I think that makes it a difficult thing. Obviously most situations they will opt for doing what they possibly can for their child. It does not -- it still enters into the equation and becomes a consideration in their minds and they do ask about it.

DR. BOUCEK: I agree with you completely. If I had to hear this list of potential adverse events from the procedure, I think I would run as fast as I could from the hospital.

What we usually do actually is put a side-by-side consent with surgical and device and try to compare the relative incidence of these complications or adverse events with either procedure since that is really their only two options since these children don't have the option of saying, "I'm just going to leave and pick my battle another day."

They really need something done and they have to make that decision. We go through each one, what is the incidence of an air embolus being on bypass, what is the incidence with this type of procedure, and try to give them what we think is the

fairest comparison we can.

Then we have some parents that because this is still considered "investigation," they will say, "I'll stick with surgery." I think that is one of the reasons that this sort of onus may have an impact on a patient's decision about what may be best for them.

DR. TRACY: I think that the patient education material, I agree, I like the idea of having something to give but it just looks like you're going to pop that thing in there and pull that little thing back.

I think it needs to be redone to show the complexity of the trans-septal snaring, etc., etc. That may actually help with the consent because the patients can -- the family then can understand the complexity of the procedure that the child is about to undergo.

Just a couple others for my own curiosity. Why do upsize to a 1.7 to 2 to 1 size on the size of the occluder that's used? Do you stretch it out intentionally? That seems like you would be increasing the risk of mechanical problems or

arrhythmic problems. Is that because they are sort of genestrated areas or why is that thing so big?

DR. BOUCEK: Well, you don't really stretch out the area with this type of device. With a sizing balloon you try to get an indentation in the balloon so you know what the size of the balloon is. Of course, the center pin on this device does not impinge upon the edges of the VSD.

The flanges tend to reach around the edges of the VSD so you don't expand the size of the defect the way that some other types of devices do when they are designed to fill the defect from the inside. I think that is a fundamental different.

We found actually that those criteria which were based primarily on closing an atria1 septal defect, I think that 1.7 to 2, are probably very conservative when it comes to a ventricular septal defect since the muscle tends to construct down and actually become smaller during the time when the heart would be generating the most pressure which would like result in the device moving.

I think those are very conservative. When

you size these VSDs most end up being a relatively small. Some of the sizing choice in the defect ends up being can you cover adjacent VSDs when there are multiple -- excuse me, VSDs in the same location.

DR. TRACY: One other thing. In several places I see that the ACT is 200 milliseconds. You might want to go through and change that.

Dr. Aziz.

DR. AZIZ: Again, I think I would like to commend the investigators for tackling a difficult problem in these young infants and kids. I want to sort of focus my comments on the adult population, the post-VSD. At least, those are the patients that I have some experience with.

This is a group of patients who can be very difficult to manage. I think the management surgically of that condition has evolved over the years with people saying you should wait for a while before you operate on them because hopefully the tissue had sort of scarified so the sutures would stay there.

I think the contraindication to that is if

you wait, the guys who really need it most die early. Most people have been forced to operate on these patients earlier.

I see that you have a small subset of patients who have had post-infarct VSDs. My comments are going to be directed to these patients. A lot of these elderly patients also have concurrent coronary artery disease. In the patients who you propose or think of doing this VSD closure, what is the thought process about handling the coronary artery disease that is present at the same time? Anybody on the panel?

DR. BOUCEK: I would imagine Dr. Lock has probably the most experience with the post-MI VSD. I have no experience with it.

DR. JENKINS: I'd like to say that post-infarction VSD was not considered as part of the labeling indication for this submission. Primarily because of the small amount of data that we had, we really didn't think it was sufficient to show safety and efficacy in that small group.

DR. LOCK: I have two comments on the post-

infarction VSD patients. Most of the patients that have been successfully managed using the entire series of devices that we used have all been post-operative patients.

MS. MOYNAHAN: Could you please introduce yourself?

DR. LOCK: I'm sorry. My name is Jim Lock and I'm from the Children's Hospital in Boston.

MS. MOYNAHAN: And any conflict of interests?

DR. LOCK: I'm on the Board of Trustees of -- Board of Directors, actually, of Nitinol Medical Technologies. I don't own any stock in the company, although I do -- I am assigned options. I receive compensation for serving on the board which I donate to the Children's Hospital.

My institution receives royalties for the commercial sales of a series of different devices that were developed at the Children's Hospital. As an individual I'm assigned some of those royalties from the Children's Hospital.