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# Circulatory System Devices Panel

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P R O C E E D I N G S (8:10 AM)

DR. CURTIS: Good morning. I would like to go ahead and call this meeting to order. The first order of business will be reading the conflict of interest statement by Dr. Stuhmuller.

DR. STUHLMULLER: Conflict of interest statement. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. To determine if any conflict existed the agency reviewed the submitted agenda and all financial interests reported by the Committee participants.

The agency has no conflicts to report. In the event of the discussions involving any other products or firms not already on the agenda for which an FDA participant has a financial interest the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

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

comment upon.

Appointment to temporary voting status pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, as amended April 20, 1995, I appoint the following people as voting members of the Circulatory System Devices Panel for this meeting on June 29, 1998, Drs. Becker, Brinker, Domanski, Ferguson, Tracy and Wittes.

For the record these people are special government employees and are consultants to this Panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and reviewed the material to be considered at this meeting. It is signed Elizabeth D. Jacobson for D. Bruce Bryanton, Director, Center for Devices and Radiological Health, dated June 26, 1998.

DR. CURTIS: Dr. Callahan, do you want to make some remarks?.

DR. CALLAHAN: For those of you who don't know who I am, I am Tom Callahan, Director of the Cardiovascular, Respiratory and Neurologic Devices at FDA, and I wanted to clarify a few things before we start this morning.

This is one of the first meetings we have had since the new law, and there are, also, some issues associated with that that I would like to clarify, as well

as this particular session today.

The agency has fully embraced the FDA Modernization Act 1997, otherwise known as FDAMA and specifically Section 513(b)6 of the Federal, Food, Drug and Cosmetic Act as amended by Section 208 and has developed standard operating procedures to help advisory panel meetings.

As stipulated in the new Section 513(b)6(a)1 of the Act we have provided to the sponsor or its representative the same access to data, any information about the device as was submitted to the Panel.

Also, in according with Section 513(b)6(a)2 we have provided the sponsor the opportunity to submit information based on the data or information provided in the application to the Panel for its review, and under Section 513(b)6(a)3 we have allowed the sponsor the same opportunity as FDA to participate in the meetings of the Panel, and lastly under Section 513(b)6(b) of the act which requires that adequate time be provided for initial presentations, adequate time be provided for response to any differing views by persons whose devices are the subject of the Panel and free and open participation by all interested persons, we have encouraged this as well.

Today we have convened a meeting to obtain from you as members of the Circulatory System Devices Panel your

clinical and scientific review of and recommendations on a premarket approval application for the Ambu CardioPump, application No. P970041.

With this as a backdrop there have been a number of issues surrounding emergency use device research. One involved the harmonization of federal policies on the protection of human research subjects and resulted in the issuance of a rule in 1995 by FDA defining when and how human research can be conducted in this country without informed consent.

This issue, however, is not for deliberation at this Panel meeting. There have, also, been administrative and regulatory process issues associated with this submission. These are, also, not for deliberation at this Panel meeting.

Our mission is to assure that safe and effective products get to the patients in a timely fashion, that the product does what it is claimed to do and claims of significant results are supported by valid scientific evidence.

To aid us in this mission we ask you to focus on the data, the data before you and concentrate your efforts on the substantive review of the science and not get sidetracked with peripheral or regulatory process issues.

Thank you.

DR. CURTIS: We will move on now to the open public hearing. There have been two organizations that have requested time here. The first would be Dr. Jerry Potts representing the American Heart Association.

DR. POTTS: Thank you for offering to have us down or up as the case may be. I have with me some reprints that I would be happy to supply to anyone who hasn't seem them. I know a couple of you have, Dr. Ornato and Dr. Becker, and I may not actually have enough to go around. I would be happy to pass these around.

These reprints are of a recently published article that represents an exercise we undertook to tackle some of the difficult problems similar to what this Panel addresses in the applications such as the one before you, and we have a particular interest in getting this evidence evaluation process refined over the next couple of years as we move toward revamping our guidelines for emergency cardiovascular care, and in the year 2000.

Now, this morning I really just wanted to provide you with some insight into that process in hopes that some of the things that we have learned from that application of this process may help you in your consideration of these kinds of requests that you receive for approval of devices.

In the reprint that I gave you there are outlined three basic steps that we go through and it was surprising

as I looked at the handouts for this meeting how many of the questions that you formulated on these handouts fall right into a couple of steps of the process that we have been trying to refine.

The first step in our process as we have outlined it in this paper as we applied it toward a specific device that was brought to us sometime ago is to refine the question and gather the evidence and it is clear to me from your handouts, also, that you fully appreciate that this seemingly obvious step is actually quite complex, and in your own handout which says, "Questions on Future Development of CPR Assist Devices," it seems that Questions 3 and 4 fall well into the category of refining the question that you are asking.

So, it is interesting that some of the things that you are going through in this and other considerations parallel nicely what we have been doing.

Now, one of the problems in refining the question as we have learned is that it often requires determining a reference for comparing effectiveness of a device or a protocol or a drug, and in the resuscitation business that may mean comparison of outcomes to a standard practice for which there really is no good existing body of quality evidence, and that I will touch on in a second, again.

This places a tremendous burden on researchers, as

well as limitations on the reviewers of literature regarding that research. Gathering evidence is, also, crucial in shaping the outcome of the evidence evaluation process and this part of this part of that initial step may even serve as a first-pass filter to eliminate scientifically unacceptable types of reports, and if you look on the first figure in that handout, that would be Page 1655 of the paper, you can see a figure which sort of illustrates that filtering process in that figure as the question is refined and evidence is gathered.

The second step of the process in that figure refers to assessing the quality of the evidence, and that involves looking at the power of the methodology of different studies that are being evaluated and assigning a level of evidence to them.

Those various levels of evidence are shown on Table 1 on the next page, on the opposing page, and it is interesting, again, referring back to your own handouts that it seems on that same handout with the four questions I mentioned earlier, the first couple of questions and actually most of the other handout that has your header with the Circulatory System Devices Panel title is largely aimed at this second step, and again, at this point many studies filter out of the consideration because of these two issues once they are closely examined.

Now, it is at this stage that getting back to some of the lessons we have learned in looking at this, it is at this stage going from looking at the level of evidence to developing a class recommendation that we have made attempts to assign scores the studies, and in this way we hope that we might be able to weight the studies in support of a given intervention as compared to the weight of studies that might argue against a given intervention and come up with a net score that might actually direct us toward us toward a class of recommendation in an objective way.

This is, of course, very important because as we know in our particular committee structure many of the volunteers who come to us are intimately involved in research on some of these questions that come before us.

So we have to work pretty hard both to have full disclosure of any potential conflicts of interest and abstention where it is appropriate, but, also, in order to get as much participation as possible and objective evaluation as possible we are looking at ways in which we can better quantify this step from the second to third phase of our evidence evaluation process.

Now, earlier I mentioned that there is a problem inherent to the resuscitation business and all of you are well aware of that and that is basically a lack of quality data, and that comes mostly not from any reasons that the

researchers aren't doing good studies as best they can.

It is generally a small sample size that plagues most of the studies that come before us, and for that reason we have modified our current class of recommendations to place greater emphasis on the quality of the evidence rather than trying to state that an intervention is definitely, probably or possibly useful, and so, we simply have adopted the mode of recommendation in which all of the devices that have been shown to have some usefulness are either definitely recommended or fall into an acceptable and useful category and there from that point can be better broken down based on whether the evidence provides good support or fair to good support in support of those recommendations.

So, we have tried to address that problem as best we can. Now, I know that in working with the particular questions before you all of these things that I have mentioned will probably resonate for you, and I hope that although this may be a little late for this particular question, given that you are asked to make a determination today on the issue, I hope that as you look at other devices and protocols that are to be used in interventions as interventions in emergency cardiovascular care that some of the things that we have put together in this paper and lessons that I have described that we have learned from application of this process will be of some use to you in

the future, and I thank you for giving me some time today.

So, if you have any questions about what we have been through I can give you some information, and I can, also direct you to some other folks in the organization who have been a little more personally involved in digging through some of the data.

So, I will be happy to pass that on to you as well.

Thanks.

DR. CURTIS: Thank you.

Could you state whether or not you have any financial interest in the product?

DR. POTTS: No, I am an employee of the American Heart Association. I have no financial interest in the company that is before you today.

DR. CURTIS: The other comment I wanted to make is that the handout that we were given is included as part of the Panel pack, and we have all had a chance to see it before. So, this is not new information to the Panel.

DR. POTTS: Oh, thank you. I didn't know for sure if that had made it. Okay, thanks.

DR. CURTIS: Okay, thank you.

Next we have Sam Kazman from the Competitive Enterprise Institute.

Mr. Kazman?

(No response.)

DR. CURTIS: Okay, now we have several letters that will be read into the record.

DR. STUHLMULLER: We received some written correspondence from Ms. Terry Gisch from Regions Hospital in St. Paul, Minnesota, and this information will be incorporated into the public record.

The correspondence indicates that she was the Research Coordinator for the Ambu CardioPump study that occurred from July 1992 to May 1993, in St. Paul, Minnesota and attached to the cover letter is a series of letters written to her from a variety of fire department personnel in St. Paul, Minnesota in which they all recommend approval of the device.

DR. CURTIS: Is there any other member of the public who wanted to make a statement during this open public hearing? There is going to be another opportunity later on for further comments.

If not, then we will move into the formal presentation. What I would like to do before we get started is go around the table and have everybody introduce themselves just for the record.

I am Anne Curtis. I am the Chair of the Panel, and I am an electrophysiologist from the University of Florida.

DR. STUHLMULLER: I am the Executive Secretary for

the Panel. I am a cardiologist with FDA.

DR. BECKER: I am Lance Becker. I am an emergency department physician in Chicago and a member of the Panel.

DR. BRINKER: I am Jeff Brinker, interventional cardiologists from Johns Hopkins.

DR. FERGUSON: Tom Ferguson, cardiothoracic surgery, Washington University, St. Louis.

DR. DILLON: Roosevelt Dillon, electrophysiologist, private practice, Richmond, Virginia.

MS. WHELAN: Patricia Whelan. I am a clinical social worker at St. Vincent's Hospital, Manhattan, and I am a not-voting member and the consumer rep.

DR. DOMANSKI: I am Mike Domanski, a cardiologist at HOBI.

DR. SETHI: Gulshan Sethi, cardiothoracic surgeon, University of Arizona, Tucson.

DR. SIMMONS: Tony Simmons. I am a cardiologist, electrophysiologist at Wake Forest University.

DR. TRACY: Cindy Tracy. I am an electrophysiologist at Georgetown University.

DR. WITTES: Janet Wittes, a statistician with Statistics Collaborative.

DR. ORNATO: I am Joe Ornato. I am a cardiologist and an emergency physician from the Medical College of Virginia at Richmond.

DR. CURTIS: Thank you. Okay, we will move on to the company presentation premarket approval application P970041, Ambu International A/S, Ambu CardioPump.

Before you get started Dr. Stuhlmuller wants to make some clarifications.

DR. STUHLMULLER: I need to clarify one thing for the record. The sponsor has asked that the Panel be provided with a series of handouts this morning. They will be provided to the Panel for their review today. They have not been reviewed by FDA, and they need to be formally submitted to FDA for validation.

Any information in the handouts that is not a part of the official PMA record cannot be used in the evaluation of safety and effectiveness today.

DR. CURTIS: And as each speaker comes to the podium, please identify yourself and your financial interest.

DR. LANGE: Mrs. Chairman, members of the Panel, representatives from the FDA, audience, ladies and gentlemen. My name is Benedicta Lange, and I am a physician, and I am the Vice President of Ambu International.

I would like to thank the FDA for giving us this opportunity of presenting the PMA application on the Ambu CardioPump to the Panel today.

For my presentation I can say that it will be in English with a charming Danish accent. Present from Ambu today is V. V. Kerr President, Ola Kenga, Vice President of Research and Development, Paul Ottisman, quality manager and Mr. Frank Loma, President of Ambu, Inc., our American subsidiary.

To support us today is, also, Larry Pilot and Susan Manille from McKennon-Camille(?) and Dr. John Jennings, former Associate Commissioner of Medical Affairs with the FDA.

Ambu is a small Danish company located in the suburbs of Copenhagen, our capital famous for its queen, castles and the Little Mermaid. Ambu has for 60 years developed, produced and distributed unique, simple and safe products like the well-known Ambu bag for use all over the world in the field of emergency medicine.

This has been possible due to excellent cooperation with doctors, paramedics, EMTs and others with interests in the area of resuscitation. Our slogan is Ambu saves lives worldwide, and this something we are proud to work toward.

In 1991, the University of California applied for a patent for a CPR adjunct device. The idea came from a son who tried to resuscitate his father with an ordinary plunger, and he did so successfully. Two young doctors

became interested in this idea and named the concept active compression/decompression CPR, ACD-CPR and began hemodynamic testing on animals.

Because of promising results clinical trials were started in the US, as well as in the rest of the world. Ambu became licensee to this invention and developed what is today known as the Ambu CardioPump, and adjunct for external cardiocompression performed in accordance with the recommendation of the American Heart Association.

The Ambu CardioPump is designed to allow the operator to optimize chest compression according to the guidelines published by AHA, aid CPR effectiveness by adding an active chest expansion phase to the standard CPR procedure and help ensure consistency during the CPR attempt by use of a force gauge that allows the user to measure and monitor the compression/decompression forces applied.

So here we are 7 years later, in order to bring back this product to the American marketplace where it originally came from, a marketplace admired all over the world for its ability to develop inventions and create and support new ideas for the sake of mankind.

Indeed, in foreigners' minds America is the country to admire for its progressive thinking, but it is, also, a marketplace where until recently it has been very impossible or almost impossible to carry out research in the

field of CPR which is why most of the data we will present today is from abroad.

Outside US the Ambu CardioPump has been available for use in over 70 countries throughout the world. EMS systems in many countries, including France, Austria and Denmark have made the CardioPump a standard feature in ambulances and yes, in almost all countries you will find instances using the Ambu CardioPump.

In fact, in China the Minister of Health has recommended the product for use in all CPR situations. In some systems postmarket surveillance has been or is being carried out to assess the benefits of ACD-CPR on long-term survival.

The main concept in CPR is the chain of survival consisting of early access, early CPR, early defibrillation and early advanced care. CPR consists of well-known ABC, airway, breathing and circulation, and one could argue that there are many modelings, such as age and the underlying disease of the patient, EMS structure, response times, equipment available and treatment in the ER and in the ICUs just to mention a few.

A chain is never stronger than its weakest link. The link we are to discuss today is the circulation like, and I would like everybody to bear this in mind.

Another important thing to remember is the fact

that doing research in the prehospital setting is very complicated and resource demanding. The overall survival to discharge of neurologically intact patients is an average estimate throughout the world to be around 2 percent. So, in order to be able to show statistically significant changes in this outcome parameter more than 10,000 patients are needed.

Taking into consideration how many years this will take to do in just one system makes this almost impossible. So, multicenter trials would be the right solution but again having in mind that no two EMS systems are comparable this is, also, quite complicated.

Therefore much effort has been made to facilitate and standardize research and evidence-based recommendations in this important field as we heard this morning. Recommended guidelines for uniform recording of data from in and prehospital cardiac arrests recently has been published and AHA has published a template for evidence-based evaluation of emergency cardiovascular care guidelines recommendations.

The purpose of all these efforts is to facilitate innovations and research in this important area. As it is today no FDA regulations or guidance exist for this kind of device. All that is stated by law is that a product must demonstrate reasonable assurance of safety and effectiveness

for the proposed indicated use.

I would like to read to you the proposed indications for use of the Ambu CardioPump. The Ambu Cardiopump is indicated for us in the treatment in our patients with out-of-hospital cardiac arrest, absence of effective pulse and respiration to improve the overall efficiency of CPR and the chances for short and long-term survival.

The device is intended to be used as an adjunct to AHA protocols of basic life support in CPR. When used in accordance with the directions for use and proper training the device serves to strengthen the early PLS link in the AHA chain of survival.

As mentioned earlier, the Ambu CardioPump has been available all over the world except the US for many years. Today we are going to establish that there is a reasonable assurance of safety and effectiveness for the above indication by presenting the results of a combined analysis composed of individual patient data from seven prehospital controlled prospective studies from US, Canada, France, Germany, UK, Belgium and Greece.

The results of this combined analysis show a statistically significant improvement in overall survival with the use of the Ambu CardioPump.

The first five studies mentioned representing more

than 2000 out of 2866 patients included have been published in peer reviewed journals. Dr. D. Mauer, University Hospital of Mainz, Germany, Chairman of the Combined Analysis Group will present the methods and results of the combined analysis. Apart from paying all trial expenses for all members of our panel today, Dr. D. Mauer has, also, been paid as a consultant for the work of the combined analysis.

Dr. H. Sitter, biostatistician from the University Hospital of Marburg has worked as a statistician on this analysis together with Professor Kiting, University Hospital, Copenhagen for which they have both been paid.

Dr. Sitter will go through the statistical method used in this analysis. Dr. Patrick Plaisance, University Hospital of Paris, France will discuss the results of his exciting studies in Paris and will, also, briefly comment on why Paris was able to show such positive results.

Dr. Lars Wik, University Hospital of Oslo, Norway will give an overview of the hemodynamic studies and being the Chairman of the Working Group for Teaching and Training he will, also, highlight some important aspects to training including issues relating to fatigue, migration and use.

So, there will be more than Danish accents today, but to start up some people experienced in the use of the Ambu CardioPump here in the United States before studies were stopped by the FDA will share their experience with us

and I will, therefore, give over the podium to Ms. Terry Gisch, BA, EMTP and Dr. R. J. Frascone, St. Paul, Minnesota.

Thank you.

DR. CURTIS: Before you step away, if you would just clarify for us your financial interests? You said that you were Vice President?

DR. LANGE: Yes, I am employed by Ambu.

DR. CURTIS: So, you are an employee?

DR. LANGE: Yes.

DR. CURTIS: Okay, thank you.

Even though you all stood up and got introduced, as you step to the podium, if you could identify yourself and again state your financial interest before you start your talk, we would appreciate it.

MS. GISCH: Good morning. Madame Chair, members of the Panel, ladies and gentlemen, my name is Terry Gisch. I am the EMS Quality Adviser for the Emergency Medical Services Program at Regions Hospital in St. Paul, Minnesota. I have, also, been a paramedic for 16 years. I have no financial interests in the company.

DR. CURTIS: Were your expenses paid to come here?

MS. GISCH: My travel and lodging expenses were paid to come here.

DR. CURTIS: Thank you.

MS. GISCH: Our office contracts with ambulance

services to provide medical direction which is required by the State of Minnesota to be licensed in the state. One of our clients is the St. Paul Fire Department which provides paramedic ambulance service for the city of St. Paul.

The fire department has approximately 100 paramedics and 300 EMTs that respond to over 24,000 requests for emergency medical assistance each year.

In 1992, I was the research coordinator for the CardioPump study. I was responsible for coordinating the training and data collection for the study. When we first contacted the St. Paul Fire Department about whether they would be interested in studying the CardioPump they were extremely enthusiastic.

The theory behind the device made sense to them, and they were excited about playing a role in researching a device that had the potential to improve the dismal survival from prehospital cardiac arrest.

St. Paul was an ideal place to study the CardioPump because the essential elements of an effective EMS system such as rapid response times and automatic defibrillation were already in place.

St. Paul Fire was the first fire service in the United States to do CPR in the streets back in November 1963. Almost 30 years later they were the first rescue agency in the world to bring ACD-CPR to the prehospital

arena.

They remain frustrated that they are now excluded from the improved survival rates that other countries have experienced with the CardioPump. As with most medical devices training played a key role in the effectiveness of the device. We designed a training program for prehospital personnel that included a review of standard CPR and how it compared to ACD-CPR.

Training was easy for this group of students. Many were experienced rescuers who had performed standard CPR dozens of times. Emphasis was placed on device placement remembering to lift the chest with each decompression and to frequently refer to the gauge for guidance on compression depth.

We used their feedback, suggestions and comments to refine the training for other rescuers and hospital personnel. The training feedback included comments such as the following: They felt that the gauge was especially beneficial because it gave the rescuer a compression guide other than pulse perfusion that was based on patient weight and size.

It is very difficult when you are doing compression to estimate the one and one-half to two inches that you are supposed to be doing for compressions. The handle had a grip that they felt was easier on the hands

than standard CPR. They quickly realized, however, that ACD-CPR was more energy consuming than standard CPR, but this was resolved by frequent rotation of the compression duty amongst the rescuers.

We found that the current CPR manikins were not adequate training models because they did not permit the active decompression without tearing the manikin skin.

AmBu very quickly developed an ACD-CPR manikin that resolved that problem and permitted a very lifelike reproduction model for ACD-CPR.

In 1995, I was invited by AmBu to a meeting in Denmark where a group of international experts on ACD-CPR training met to network, provide training, feedback and make recommendations for a standardized ACD-CPR training program which included an instructor and student manual, student materials and a video.

Results of that meeting were published in Resuscitation in October 1996. Once the device was being studied in the field, we continued to get feedback. Firefighters are eager to share their opinions about things. EMTs and paramedics identified further issues that included the following: First, because both hands are required to hold the CardioPump handle during CPR it became difficult for the rescuers to themselves during transport to the hospital.

At times rescuers doing standard CPR will use a one-handed technique for compressions while they hang on to a support bar above their heads to steady themselves while the ambulance is moving.

The American Heart Association only recommends a one-handed technique for ages 1 through 8, and I know from personal experience that CPR in the back of a moving ambulance is poor at best regardless of what device or method one is using.

Most arrests that are not resuscitated in the field are not resuscitated once they get to the hospital anyway, and more and more areas around the country are discontinuing resuscitation in the field if several rounds of advanced cardiac life support have not been successful.

St. Paul Fire Department personnel resolved the problem by simply having one member of the crew steady the rescuer doing compressions. The device, therefore, actually encouraged the two-handed technique which is recommended by AHA.

Secondly, the device places the rescuer's hands about 5 to 7 inches above the victim's chest and requires the rescuer to lift during the decompression phase. This is not a problem if you are doing it at ground level, which is where most prehospital arrests are worked, but it can be difficult when you are trying to perform ACD-CPR with

someone who is on a bed.

I experienced this myself when using the CardioPump on an arrested patient who had been moved to an ER cart. The CardioPump on an arrested patient -- I am sorry, the American Heart Association recommends having the rescuer positioned directly over the patient, but I have witnessed many occasions where standard CPR is instead performed while standing next to a patient in a bed.

Performing ACD-CPR requires the compressor to be over the patient by either standing on a stool next to the patient or by actually climbing up onto the bed with the patient.

Again, I think the CardioPump actually encourages the proper body position that is recommended by AHA.

Thirdly, many of the rescuers who used the CardioPump reported to us an unexpected ease with ventilating the patients. They felt that the device actively sucked in oxygen rather than simply having it forced in by the rescuer's positive pressure.

There were two cases of patients with severe bronchospasm in cardiac arrest that they reported they were unable to effectively ventilate the patient until the CardioPump was applied.

I know this is anecdotal experience, but they continue to talk to us about this even today.

Finally, performing ACD-CPR requires carrying an additional piece of equipment that is not needed for standard CPR. When we were doing the training we heard grumbling from them about having to carry another piece of equipment for arrest but once the device was out in the field we never heard that again.

Most felt that the benefits of the device greatly outweighed the hassle of carrying an additional piece of equipment. AmBu worked very hard on refining the original training device into a lightweight yet sturdy device. They designed a carrying case that made it easy to strap to other equipment and decontamination and clean-up was very simple.

In order for a device like this to be successful in this field it has to be simple, small and strong, and the CardioPump meets all those criteria.

Even today the firefighters continue to ask us, "When are we getting our CardioPumps back?" Firefighters are a difficult audience to impress, and you would think that after so many years they would have forgotten about it.

I have been stalling them for 5 years, and I hope to go back today with some good news for them.

Thank you for the opportunity to speak.

DR. FRASCONE: Madame Chair, members of the Panel, ladies and gentlemen, my name is R. J. Frascone. Other than having my accommodations paid for and travel expenses I have

no financial interest in AmBu.

I am the Medical Director of Regions Hospital Emergency Medical Services in St. Paul, Minnesota. In that capacity I serve as medical director for over 30 ambulance services and agencies including the St. Paul Fire Department.

The St. Paul Fire Department, as you know, conducted the research on the CardioPump that was published in the May 11, 1994, issue of the Journal of the American Medical Association.

I come to you today to relate to you my firsthand experience, as well as that of some of my paramedics who have used the device in the field. I am sure you are all aware of the data that were published in the JAMA paper. There are, however, numerous incidents that stand out which are not clearly reflected in that paper.

First, I was able to obtain radial pulses in every patient that I attended in the Emergency Department who was undergoing ACD-CPR. Never before nor since have I observed this with standard CPR. Second, on two occasions paramedics reported to me that patients became agitated during ACD-CPR. Because they were used to patients being flaccid during cardiac arrest, the patients would halt CPR to check monitor. The patients continued in the arrest rhythm but would go flaccid when the compressions were stopped. The

paramedics were convinced that the CardioPump perfused these patients so well that their level of consciousness improved enough for them to become agitated.

The activity actually interfered with the paramedics' ability to innovate and establish IVs. They joked about having to sedate patients with ACD-CPR and about how this improved level of consciousness was the closest thing to living through your own clinical death.

On another occasion paramedics had attempted numerous defibrillations on a patient that had a documented history of 10 minutes of ventricular fibrillation. The man continued to receive ACD-CPR and was ultimately successfully defibrillated.

Immediately after his defibrillation he abruptly sat up and told the medics to get this expletive deleted device off my chest. The paramedics were aghast.

Another patient who was successfully resuscitated with the CardioPump had arrested twice previously and reported that if he arrested again he wanted the CardioPump used because his chest hurt much less after ACD-CPR than it did after standard CPR.

Needless to say the paramedics of the St. Paul Fire Department were extremely upset when the study was halted as Ms. Gisch just mentioned. This was a device that they had come to believe in and have continued to inquire

about since its removal.

I hope you have had a chance to review some of the written comments that the members of the St. Paul Fire Department submitted prior to this hearing.

With your permission I would like to read a short letter from the EMS Chief of that Department, Dave Huisenga because it accurately summarizes his Department's opinions about the device. It was written to Dr. Stuhlmuller. Dear Dr. Stuhlmuller, I urge your approval of the Ambu CardioPump as an adjunct to CPR in the prehospital setting. I am the Chief of Emergency Medical Services for the city of St. Paul's Department of Fire and Safety Services. Our Department responds to over 25,000 911 medical calls for help annually.

Several years ago we had the opportunity to participate in a study of the CardioPump. Though our research was halted prematurely, our experience with the device was overwhelmingly positive. We had no greater incidence of complications with the device than with standard CPR.

More importantly, we had incredible success with cardiac arrest resuscitation. Had we been allowed to continue our research I am convinced our prehospital resuscitation rates would have exceeded any of those ever before experienced.

I am aware of other research projects that indicate the device may have little, if any impact on resuscitation rates. I am, also, aware of the EMS response times of the cities involved in the research including our own.

Perhaps because our response times are very rapid, the St. Paul fire experience with the device was much more positive. I continually receive requests from our crews for resumption of the CardioPump research. Many of our very senior paramedics, several with over 20 years' experience in emergency medicine have relayed remarkable stories about their experience with the device. Despite the lack of sufficient numbers in our research, these anecdotes have made a believer of me.

In my 26 years as a firefighter and paramedic I have never before or since heard of cardiac arrest patients suddenly and dramatically regaining consciousness and walking out of the hospital a week later. This has occurred while our crews were using the CardioPump.
I firmly believe from our limited experience using the CardioPump it is ethically and morally wrong to forbid the use of this device.

If permitted St. Paul Fire would welcome the opportunity to use it on our cardiac arrest patients.

Finally, I would like to express my own opinion as

an emergency medicine physician with over 20 years' experience when I say the CardioPump passes the mother test. That is when one asks oneself if my mother was in cardiac arrest in front of me, would I choose to use this device on her. There is no doubt in my mind the answer is yes.

I would like to express my gratitude for the opportunity to speak with you today, relate some of my real-life experiences, as well as that of my field personnel. I would be happy at the appropriate time to answer any questions.

Thank you.

DR. WIK: My name is Dr. Lars Wik. I am from Norway, University Hospital of Norway, National Hospital of Oslo, Norway.

My lodging and traveling have been paid by Ambu. The aim of CPR is to restart the heart. In most cases it is only a defibrillator that will be able to do this, but in real life a defibrillator is not available or we do not reach success with the three first countershocks. However, it is only early CPR and early defibrillation that has shown to increase survival.

In the prehospital setting more than 60 percent of the patients will need chest compressions to maintain their viability of the brain and simultaneously improve the likelihood for successful countershock later.

It still remains to prove that early advance care really increases outcome in the prehospital field.

We will now very, very shortly go through the hypotheses or theories behind what drives blood when we are doing chest compressions. By squeezing the heart between the sternum and the spine we are talking about a method which is called the heart pump mechanism. This theory operates particularly when the heart is large and the chest is compliant as in children, after long CPR time and small broad-chested dogs.

The other theory which is the overall intrathoracic pressure fluctuations demonstrated with chest pump mechanism operates particularly when the chest is large as in large-chested dogs and breast CPR is the ultimate chest pump method.

CPR is based on that a rise which is equal to the compression in intrathoracic pressure can force blood out of the heart, lungs and great vessels due to valving of the great veins at the thoracic inlet.

When sternal or chest cage pressure is released which we call decompression the elasticity of the chest wall causes the heart and thorax to expand and refill with blood.

So then how effective is this chest compression? Cardiac output, carotid artery blood flow and cerebral blood flow produced by standard CPR are usually less than 30

percent of normal flow and sometimes less than 10 percent, and without coronary and cerebral arteriovenous perfusion pressures of at least 30 millimeters of mercury the chances to sustain viability of the brain and restore the spontaneous heart action are small.

In other words, cerebral blood flow must be at least 20 percent of normal to maintain cell viability. Cerebral blood flow of 10 percent of normal which is, also called trickle flow may be worse than no flow demonstrated by the Pittsburgh group of Peter Saffer.

Cerebral blood flow during external CPR can sometimes be near zero at the rest times without CPR of 2 to 5 minutes or longer probably due to blood thickened by stasis or low pressure due to vasoparalysis, but most of us will not have problems with understanding that compression of the chest will generate a positive pressure inside the chest.

It may be more difficult to understand what happens when the compression is released because the release is performed first and the fact that the chest has a special configuration and the elasticity it has created a small negative intrathoracic pressure during the passive decompression phase which will enhance blood refilling of the chest.

This is the key to ACD and can be achieved in

principle by two methods. When you are sitting down here ventilating the thing you are really doing is lifting the thoracic cage every time, and when you are doing that you are developing a negative intrathoracic pressure, now, now, now and now. So, there is no hocus pocus with this.

The negative intrathoracic pressure can be achieved by suction through the airways if you have intubated the patient or by lifting up the thoracic cage. In principle, ACD-CPR is an aid to expand the chest actively and faster during decompression in order to refill heart and thorax with blood and not only to the steady state level which we will read during passive decompression but, also, above this level.

The potential positive effect of this is based on correctly performed compression and active decompression. Active decompression by means of an external negative force improves negative intrathoracic pressure during the decompression phase of CPR.

In other words, active decompression-compression more full exploits the potential of the thoracic cavity to improve blood flow.

So, let us look at the hemodynamic effects of decreasing intrathoracic pressure during decompression. Let us first look at this through the upper airways and I refer to the first study by Nisa Chandra in Circulation in 1979,

and remember that ACD was invented in 1987. Nisa Chandra doing so-called "new CPR" demonstrated that by suction during decompression phase through the endotracheal tube that improved carotid flow and new CPR is defined as simultaneous ventilation and compression.

So, during decompression she actually sucked air out and in of the patient, and that negative intrathoracic pressure which was generated then increased carotid flow. The other way to do this is of course, to lift up the chest, and I will now discuss what will influence intrathoracic pressure, decompression pressure if we aim to achieve negative pressure by lifting the thoracic cage.

Of course, chest elasticity is important, and the quality of passive decompression technique is, also very important, and we should be aware of that the quality will be worse if we have leaning on the chest, the quality of compression and then the filling of the heart and lung and of course the airways if they are open or not.

I will now demonstrate for you the hemodynamic effects this method achieves. I will start with looking at the heart. Echo doppler is a method which is used in cardiology, and I know that in the Panel there are cardiologists.

So, I am not a cardiologist. I am an anesthesiologist and emergency physician, but what this

slide shows is that more than 100 percent increase in transmitral valve velocity time integral and close to 100 percent increase in mean diastolic filling time, left ventricular stroke volume and a 10 percent increase in end decompression left ventricular volume.

In other words, the heart valves which I will call the doors of the heart function better with ACD-CPR and the mitral valve, the door between left atrium and left ventricle is important in this respect.

Several studies have shown that coronary blood flow increases by 37 to 114 percent, coronary blood flow, I mean the blood flow to the heart muscle. That must be important.

The coronary perfusion pressure, also, increased by 50 to 180 percent versus no increase, and the reason for the no increase was a study which didn't adjust how to perform ACD-CPR correctly.

The ET-CO2, also, increased by 50 to 180 percent versus no increase and a no increase I will demonstrate on another slide here and then I have to move over here. What this slide shows you is that partial pressure of CO2 which is a very good measurement of how blood flow goes into the thoracic cavity.

If you take this measure only during compression and decompression we will have the slide as presented here.

This is only during compression and decompression and not ventilation, and here you see the fluctuations during standard method and when we add decompression we see a significant increase in this ET-CO2, and we can, also, focus on the blood flow pressure which is inside the intrathoracic cavity and if you see at the three last bars it is clear that there is a negative intrathoracic pressure during decompression.

Cerebral blood flow is, also very important because what is the meaning of restarting the heart if we don't have a technique that can restart the brain, and cerebral blood flow has increased by 32 to 100 percent and as I mentioned the negative intrathoracic pressure measured in esophageal cavity has increased by 150 to about 500 percent during ACD-CPR.

So, the conclusion, ACD-CPR is based on the potential of the configuration and elasticity of the chest to generate blood flow during chest compression and decompression.

ACD-CPR supports the built-in mechanism of the chest and heart to generate blood flow when the chest is compressed and actively decompressed.

ACD-CPR improves hemodynamics significantly compared with standard CPR.

Thank you very much for letting me present this.

DR. MAUER: Madame Chair, members of the Panel, ladies and gentlemen. My name is Dietmar Mauer. I am from the University Hospital of Mainz in Germany. My travel expenses have been paid by Ambu. I am one of the consultants of Ambu, and the combined analysis has been supported in part by Ambu.

First slide, please?

I am the Chairman of the ACD-CPR Working Group and additionally I am responsible for the German ACD-CPR trial. My role in that meeting is to present the background, the protocol and the results of the combined analysis.

Let me start with the history. In 1994, at the end of 1994, I had the idea to bring together all study leaders from the European studies into a first European prehospital active compression-decompression cardiac resuscitation workshop in Copenhagen in February 1995. You can see the names of all people involved in the ACD-CPR trials in Europe.

During that meeting we tried to bring together all knowledge existing at that time as far as ACD-CPR is concerned.

We heard all the actual results of all ongoing studies. We heard the different study designs. We heard that there are different arrest times in all of these study centers. We heard that there are different time intervals,

for example, from CPR to first epinephrine medication and we heard about different first rhythm diagnosis in the different centers.

We saw that there were ongoing controlled prospective studies in Germany, in France, in United States, in Canada. One of these studies was blinded, the study from Ian Stiell in Canada, but we learned that most of the studies were, also, randomized but in different methods of randomization.

We learned during that first workshop that three studies had a power of more than 80 percent which means a power for short-term survival. None of the studies were calculated to have a sufficient power to prove discharge survival to be statistically significant.

Two studies were stopped before the intended sample size was noted, the study from Lurie and from Schwab from California.

During that workshop we concluded that we need two working groups, one working group for training and education. The Chairman of that working group is Dr. Wik from Norway and to have a working group for data analysis. All these results from that first workshop were published in our Resuscitation Journal group.

Then the first data analysis working group we decided to start a combined analysis using individual

patient data. The reason for that was to be able to get individual patient data to improve data quality compared to meta analysis to be able to look in subgroups and to be able to study a trend analysis, all that to try to examine where ACD and if ACD-CPR can be of benefit.

This combined analysis wants to study the effect of active compression-decompression resuscitation on survival rates and neurological prognosis compared to standard CPR. Prior to the beginning of that study we defined the study inclusion criteria and the study end points. All these inclusion criteria and end points were defined by the whole working group.

Our study inclusion criteria, first the study should be a prehospital study. The study type should be prospective and controlled. The study population should include adults older than 16 years with cardiac arrest when CPR was attempted.

Excluded were patients with trauma and patients with certain signs of long arrest time. The EMS system in that DCMS systems early defibrillation should be available and EMS personnel had to be retrained in standard CPR and trained in advance in ACD-CPR.

We found eight studies to be included in the combined analysis. We were able to include seven of these eight studies. To get, also, the San Francisco, Fresno data

I flew to San Francisco together with Dr. Lange from Ambu, and we started discussion with Professor Callaham from the University of California.

We presented the study protocol to him, and we discussed the study protocol with him, and he accepted the study protocol, but he was not able to give us the data from that trial. The reason for that remains unclear.

In addition, our statisticians, Professor Kiting and Dr. Sitter wrote several letters to the University of California in order to get these data, but we all failed.

Our study end points were the primary end points of 1-hour survival and discharge from hospital.

The secondary end points were neurological outcome defined as cerebral and overall performance category at time of discharge from hospital and the documented complication rate like rib and sternum fractures, aspiration, internal organ damage, pneumothorax, hematothorax and ecchymosis, subcutaneous bleeding.

To be able to do that analysis we found two statisticians. The first is Professor Kiting from the University of Copenhagen and Dr. Helmut Sitter from the University of Marburg, both experienced in meta analysis and combined analysis and both of them had never been involved in any of the prehospital ACD-CPR trials.

The data were collected in Marburg and the

statistical analysis was supervised by Professor Kiting from Copenhagen. All individual study centers sent their databases to Marburg and were not involved in the statistical analysis of these data.

The statistical analysis included combined analysis form of the individual patient data and intention to treat basis was the main interpretation based on the primary end points.

A logistic regression model was stepwise selection of rivals and alterations was 29 percent. Confidence intervals were calculated, but this will be presented by my colleague, Dr. Sitter now.

DR. SITTER: Madame Chair, peer members of the Panel, ladies and gentlemen my name is Helmut Sitter. I am coming from the University of Marburg in Germany and I am a mathematician and human biologist, and I have participated in the statistical analysis of the combined analysis here, and I am paid for this work and the travel expenses for this meeting here have been paid by Ambu for me.

Before we started with our combined analysis we set up a study protocol where we intended to include all qualitatively high-rated trials on the subject and to do a combined analysis.

Some criteria of quality for a clinical trial or a prehospital trial have been already mentioned by Dr. Mauer,

that is a prospective planning, that is that we have a control group and he pointed out that those criteria should be fulfilled for a trial to be included and of course, another quality criterion is randomization, but we realized at our first meeting that it is very difficult to do a genuine randomization in the emergency setting out of the hospital, and some trials call themselves randomized trials, but they are from the viewpoint of a statistician not a randomized trial, and that was the reason that we didn't impose the criterion of randomized for our inclusion criteria to this combined analysis.

We described the inclusion criteria which Dr. Mauer already cited, and one of the main reasons for this was to guarantee homogeneity of the trials so that we can compare the individual data provided by these trials to the combined analysis, and that we get varied results that the trials don't give up too much, and from the team doing the analysis we didn't know the results which were in preparation from the individual trials.

Then we decided to evaluate the studies on an intention-to-treat basis, and the three pillars on which our analysis rests are first chi square testing, second logistic regression analysis and third so-called "random effects modeling."

The first slide, please?

Here you see the result of a chi square test for trend. As Dr. Mauer already said, we had two main outcome variables. That was 1-hour survival and discharge survival in the trials, and there we wanted to use, also, the information that there was a natural ordering in these two outcomes so that we can have this ordering, that it is better to have a discharge survival, but it is, also, of some value to have a 1-hour survival, and with this ordering we can do a chi square test for trend and we see here in this comparison between ACD-CPR and standard CPR a statistically significant difference which favors ACD-CPR.

The next slide, please?

Then we did some logistic regression models, and I just want to show you a little bit the mathematics behind it. Here we modeled the probability of an event by exponential functions.

P is the probability and the outcome variable Y stands for dead or alive, and here we look at the probability of death under the condition that the variable X has a certain pattern, and the variable X symbolizes explanatory variables, for instance, the ECG rhythm or the age of the patient or the center where the patient was treated and so on, and then in our model we have the exponential function on the right hand side, and we want to achieve two goals.

First, we want to know from all our explanatory variables which are the important ones. So, which are the important X1, X2, 2XM and second in we know this, we want to know how have we to estimate the parameters better.

We did this with the so-called "stepwise selection of variables where we proceed in the following way. First we include into the model one explanatory variable and the variable with the highest predictive power. then the one with the next highest power and so on.

If we have already three variables in our model, we at every stage look also if we can increase our power of prediction by removing a variable which has been selected earlier. It might be the case that one variable which was selected early now hinders the good prediction because two, three or four variables which came in later on all together have a better prediction. That is a way of stepwise selection of variables.

Next transparency, please?

And when we applied this model we looked at our outcome variables of 1-hour survival and discharge survival. That was the variable Y in our model and we offered all the variables which we listed in our study protocol for stepwise selection. Then we saw that the important variables are for 1-hour survival center, ECG rhythm and time from call to start of CPR and for discharge survival nearly the same but

also, age is included, but we had here the data not from all 2866 patients. We had only data for about 2000 patients.

Next, please?

Now, we could, also, look at some models where we can increase the number of patients which we use for our analysis, but we have to put away some variables which didn't have all data points in it.

When, for instance, for 1-hour survival if we did not offer the variable center then we select ACD or standard CPR as an important variable and the ECG rhythm, and you see nearly the same for some other models which all have more patients in it than the previous models, and you see here that there might be an interaction between center and ACD treatment and we looked, also, at other models where we modeled these interactions by products and we saw that we have an interaction effect between center and ACD-CPR or standard CPR.

Next slide, please?

If we looked at some subgroups which we, also, specified in our protocol, that was, also, one of the advantages of a combined analysis instead of a meta analysis that we can look better at subgroups. We see here once more the group where the time from call to start is between 8 and 12 minutes, 1-hour survival, important variables center, age, ECG rhythm and discharge survival center ACD or

standard CPR and ECG rhythm; here once more ACD comes in.

Now, I want to make some comments on our random effects models model.

Next transparency, please?

These models are, also used in meta analysis and you usually have two different approaches, so-called "fixed effects models or random effects models."

In a fixed effect model you have the following perspective. You are gathering all studies relevant for your topic, and then you are analyzing these studies with the assumption that there is a common underlying effect.

When you use a random effects model, then you are having another approach. You say that the studies which you have identified can be regarded as a random sample of a whole population of trials on this subject, and you, also, account for the variation between the different studies, and your model assists variation in your random effects model and therefore you do not have to take such care of the assumption of a homogeneous effect, and we applied here this random effect model.

And the next transparency, please?

The results of this random effects model are derived by this formula. You have once more the effect Y and we describe here this effect as a combination of the effects from the individual studies. We have here case studies, in

our case seven studies.

We weight the effect Y by a weight, W, which is chosen as a retiprogal(?) of the variance and if we estimate this variance where we consider the variation in the study as well as the variation between the studies, then we arrive at the following results, and these results are depicted in a graphical way, and these graphics are Pitot(?) plot. You see here the odds ratio, that is a Y.

The effect is measured here by an odds ratio for the different centers and you will see the total and the odds ratio here for 1-hour survival in this model is less than one, where one signifies no difference, less than one favors ACD, and you see, also, this symbol is a little bit away from the one. It is lower than one. So, it is a 95 percent confidence in there while it excludes one which means a significant difference.

The next slide, please?

When we do the same for discharge survival we have once more an odds ratio of less than one favor ACD-CPR but the confidence interval now includes a one which means one means no difference.

So far the description of our statistical methods. Thank you for your attention.

DR. MAUER: In the second part of my presentation I would like to show you the study results 2866 patients in

that study. Fourteen hundred and 10 patients were resuscitated with ACD-CPR, 1456 patients with standard CPR method. No differences were found between the groups with respect to age, rates of witnessed arrests by standard CPR, first ECG rhythm.

In our analysis we found a significant 1-hour survival rate in favor to ACD-CPR. The hospital discharge rate was not statistically significant, and we found no discharge rate in between 5 and 7 percent.

The overall survival tested with chi square test for trend was presented by my colleague, Dr. Sitter. I would like to show you the odds ratios once again with the intention to focus your attention to Center 6 here. This is the odds ratios for 1-hour survival and the odds ratios for discharge survival. Also, Center 6 is the center which we know influenced the significance of the combined analysis very highly, and that center is Paris, and why that is so, this will be explained by my colleague, Dr. Plaisance.

In the subgroup analysis we did not find any differences between the group with the exception of asystole. In the asystole patients, patients with ACD-CPR had a better survival rate in 1-hour survival, and we found a good trend in these patients for a better hospital discharge survival after ACD-CPR.

As far as neurological outcome is concerned,

measured with CPC, cerebral performance category where CPC 1 is the best and CPRC 4 is the worst neurological outcome, we found that in both groups 80 or more than 80 percent of the patients were in a CPC 1 or 2 category, no significance between the groups as far as neurological outcome is concerned.

The complication rate, as far a severe complications are concerned we didn't find any differences in between ACD and standard CPR. We found a difference in ecchymosis which was found to be significantly higher in patients after ACD-PCR. Ecchymosis is small bruises, subcutaneous bleeding.

The major study limitation of the combined analysis is the decision by the principal investigators of the California trial not to participate in the combined analysis. I explained our procedure before. That is why we did a simple two by two table including the California, the published California data in our analysis, and we found no significant difference as far as discharge rate is concerned.

In conclusion, we found ACD or we knew that ACD-CPR improved cardiopulmonary hemodynamics. We found that prehospital and in-hospital studies showed both positive and no actual benefit on survival rates with ACD-CPR and a combined analysis using individual patient data demonstrated

the significant improvement in 1 hour and overall survival using ACD-CPR.

The conclusion of the ACD-CPR study group and that is not published, but written and signed by all the ACD-CPR study group authors is that in view of the results from the acute hemodynamic benefits observed with ACD-CPR and the results from the current combined analysis it seems reasonable to consider the use of the ACD-CPR to clinic and EMS systems when resources are available for adequate training and postimplementation surveillance, and it is, also, very important for me to add a little bit from our clinical life. I do resuscitations for nearly 10 years and I never have seen before the patients wake up during resuscitation, but I saw that in four cases using ACD-CPR. There was a need for sedation in these patients during resuscitation, and working in the intensive care unit if you change from standard CPR to ACD-CPR you see a huge increase in systolic arterial pressure also in cardiac output during ACD-CPR.

Putting that all together we concluded that we will use ACD-CPR in the prehospital and in-hospital setting despite the fact we did not find a significant difference in our own Mainz trial and we actually are in the process of retraining all our personnel in standard and in ACD-CPR.

I thank you very much for your attention in giving

me the possibility to explain our study results.

Thank you.

DR. PLAISANCE: Madame Chair, members of the Panel, ladies and gentlemen, good morning. My name is Patrick Plaisance. I am an anesthesiologist in the Department of Anesthesiology and Critical Care in Lariboisierere Hospital in Paris and specially in charge of the prehospital parts of the department. My trip was, also, paid by Ambu.

I would like to explain and describe our French experience of the ACD-CPR in the prehospital setting and, also, perhaps clarify some important points.

First of all, I think it is important to explain the specific structure EMS system. It is a two-tiered system. Emergency calls are received in dispatching centers by switchboard operators and physicians who are responsible for all medical actions. Concerning address the physician must send EMTs who provide BCLS CPR. They send some intensive care units which provide advanced cardiac collapse support CPR. That means defibrillation, systematic intubation and drug administration.

In Paris most of the EMTs are military firefighters of the fire brigades and they are specially trained to provide standard BCLS as well as ACD BCLS CPR.

It is the reason why doing the research phase of

our study we published last year in the Journal of Circulation standard and ECD CPR could be performed depending on the type of EMTs who were at the scene. For this study we had controlled more than 1000 EMTs coming from different organizations such as the military firefighters, professional firefighters, personnel of the Red Cross. Then in order to limit the risks of incorrect randomization we did not randomize this part of CPR but only the ACLS phase.

By contrast we made an important effort to seek and train all the personnel included in the ACLS phase. Concerning the military firefighters of Paris it was easy because they had used the device for 2 years before the beginning of the study and were already tested mostly by their monitors.

Then we did the training on the medical teams which are always composed of a physician, the nurse, one ambulance driver and sometimes a medical student. All the team of the MICUs concerned by CPR training especially CardioPump is used but we think that the ACD technique must be taught only to rescuers who already have experience of standard CPR.

It was mentioned in our study all the patients who need to be intubated are all ventilated with a portable volumetric ventilator. You see on the slide the ventilator we use for our study and we know that induced problems and

questions. I think it is easy to answer.

First of all, we never used any inspiratory impedance valve in our protocol study. We began our protocol at the end of 1993, and the first time we heard about this valve was in 1995, and we already had finished our study.

Keith Ruit was the only person to know this valve and when we discussed it for the first time, that is during one of the ECU workshops in Copenhagen we tried to understand why the Paris study had positive results as compared to the all the studies already published, and we thought that the use of the ventilator could have the same impedance of inspiratory gas that the valve was working on in animals but let me show you that is not the case at all.

May I have the diagram, please?

Here is the diagram of our ventilator which is an Airox built by MS in France, and you have here the arrival of gas oxygen or oxygen plus air coming to the patients here, and the only valve you have is this one-way valve. This one-way valve you have it in the other transparency. I will show you. It is this one, okay? This valve I have in my pocket because it is important to explain to you this valve, and when I occlude the expiratory part of the valve and here the pressure gauge and this here is the patient and here the gas coming from the ventilator and when I make an

inspiration it means when there is an active decompression there is no impedance at all.

Furthermore when you show the addition of air this is a security for the patient who is not well adapted to the machine and has inspiratory movements so he can have air coming from the tube even though the ventilator is not insufflating oxygen. It is not a ventilation used in intensive care units or in the operating rooms. This ventilation can impede inspiratory gas, not this one.

Another important point concerning our exclusion criteria, here are represented the number of patients excluded; 226 out of 738 emergency calls for cardiac arrest were excluded. We had three kinds of selection, first evidence selection done by the EMT corresponding to patients with irreversible death.

They used it as an issue of the well-known patient style, decapitation, incineration, decomposition, rigor mortis or definite cyanosis. The two others are made by the physician of the mobile intensive care units, that is patients who have at the time from collapse the beginning of any kind of CPR including bystander CPR longer than 30 minutes but you knew that this interval is not longer than all the population data shown by Silvas or Mulli who showed that duration of complete cardiac arrest of only 10 minutes was associated with CPR failure.

The last one is patients with terminal illness such as cancer. This represents less than 10 percent of the calls. I don't think our selection is actually more important than the one made by physicians in other countries.

Here are presented the outcome results of the study at different time intervals. You have from the left to the right return of circulation, 1-hour survival, ICU admission, 24-hour survival, survival at day 30 and hospital discharge rate at day 30 which is the percentage of patients returning home at that time and this in the start-up group in the open bars and in the ACD group in closed bars.

As you can see there is an improvement in survival rates at all time intervals excepts at day 30 with a P of 0.08 and a significant improvement in hospital discharge rates in the ACD group as compared to standard group.

As you know the didn't randomize the BCLS phase which is a limitation of our study we exposed in the articles and I explained why just before.

However, large differences in outcome were observed between patients receiving either standard or ACD procedure in both BCLS and ACLS CPR which means the first columns and the last one on the right, and since the odds ratio for these two groups was less than 0.35 for all the outcomes considered with upper limit of 95 percent

confidence interval always lower than one if it is possible I would like to show you as we did in the last European meeting this month two results of a study we have just finished and that is ready to send for publication.

This study concerns 1-year survival rates after the two techniques in 750 patients. This is nearly the same as I have just presented to you for the short-term survival. Everything is significant in favor in ACD and you have on the right the last histogram, the new one which is the 1-year survival rates with 4.6 percent from the ACD group versus, sorry, one of nine persons in this start-up group and it is, also, significant.

DR. CURTIS: Excuse me, was this information included in the pack we got for the Panel?

DR. PLAISANCE: No, it is not.

DR. CURTIS: All right. So, you can present this today, but it is something that we are not going to be able to consider later on in our deliberations.

DR. PLAISANCE: Okay. So, I will continue. So, I will just go to the conclusion. The conclusion for us is that the study, the first study showed an increase in short-term survival after ACD-CPR and there are several features that probably underline the improved outcomes associated with ACD-CPR. First, training of all EMS personnel is rigorous and frequent.

Two, rescuer fatigue is remediated because rescuers routinely rotate every 3 to 5 minutes. Three, there is supervision of the technique by the physician. Four, all resuscitation efforts are performed in the field at the site of the cardiac arrest. Five, CPR is performed for 30 minutes after endotracheal intubation even in patients in asystole, but the most important conclusion that all our inclusion and exclusion criteria meet the criteria enumerated in the combined protocol.

Even when we used a volumetric ventilator it didn't act as an impedance valve. We never used any impedance valve. Then it seems to be inappropriate to subjectively exclude our data from the combined analysis.

One of the comments regarding the limitations of our study was that we have a high level of field care. I don't know if it is a limitation. We try to educate every day all our medical student thinking that it is not a limitation but a plus. We are working a lot to improve our system by education of the population and the students because we are late on that point.

Even though the rate of survival after hospital discharge and after 1 year is allowed, I will say only after hospital charge increased survival from seven patients in a start up group to 17 patients with a good neurologic status so that they can go back working is a real progress. It is

the reason why ACD-CPR is now what is used in France by BCLS and BCLS teams.

I thank you for your attention.

DR. CURTIS: So, I will remind you that you have about 10 minutes left in your allotted time this morning.

DR. WIK: Thank you.

I will now finally try to loosen up the pressure, in other words decompress. As you are all aware of training is a key factor to success, also, in CPR. By presenting this manual I hope it demonstrates our willingness to focus on issues concerning ACD. I hope you understand our serious effort to standardize ACD-CPR training, teaching and performance.

All the studies we have heard about were finished or close to finishing when this manual was done. The manual was published in the official journal of the European Resuscitation Council, Resuscitation.

During experience with teaching, training and practice a group of people with the best capability and knowledge found out that we, the doers, should make a manual for teaching and training ACD-CPR. It was important for us to make a manual which was based on different experiences in training of the ACD's method, identification of problems with the method when using the CardioPump and eventually create a uniform course concept for training and teaching

ACD-CPR, and a questionnaire was used to reach these goals.

While reviewing the questionnaire it came clear that different training concepts have been used, and here I have listed a few of them. The training concepts which were different were some use a course manual. Some use a video. Some had formal instructor training and some had course duration limitation ratio theory:practice and things like that, and so there was a diversity so to speak on how people have conducted their training locally.

It was, also, important to learn from the issues observed when using the CardioPump and discuss them during the course, and these issues observed when using the CardioPump were very, very important, and I will, also, focus on what is happening in Paris. Remember that they did 2 years with practice before they included and started the study.

In traditional medicine if you have a good idea you start the study right away. So, we can ask with them testing the teaching capability of the new technique or are we really testing the new technique.

Adherence to the manikin, obese patients, women with large breasts, patients with chest abnormalities, patients with sweat, vomit or defibrillation gel/electrodes will make some problems with adhesion to the chest. We focused on that. We, also focused on fatigue. Fatigue is a

very important problem during CPR. During standard CPR it is important and we know also that it is certainly during ACD-CPR. We, also, focused on pulling up the pump for active decompression because it is very, very important to remember that a CardioPump should not be used as a tool to provide standard method.

The point with ACD-CPR is to use the suction capability and to lift up. Also, last but not least we focused on problems during transportation.

Based on the questionnaire general teaching experience and scientific evidence we created a manual for teaching and training ACD-CPR which has been peer reviewed and published in Resuscitation. It is built up in a certain way which has been approved by others before.

We start with an introduction which focuses on cardiac arrest epidemiology, early CPR and early defibrillation at the same time as a number of patients will need chest compressions. In other words, it is very important for us during this manual to teach the students how cardiac arrest occurs. It is, also, very important for us to teach them the principle of standard CPR and ACD and the differences between those.

We, also, focused on the ACD-CPR device, its construction and use the design and use of the ACD-CPR, how to perform a correct grip, the correct pressure point, the

correct working pressure and we even have some good advice how to improve the correct working posture. The use of the gauge is, also, very important for us.

We even have pedagogical advice for the instructor how to perceive the manual and teaching the students and motivation is a very, very important issue, and training, the training with hands-on training very important in ACD-CPR as well as standard CPR, and last but not least trouble shooting. Don't forget the troubles. Focus on them and discuss them with the students.

The authors may be aware of that fatigue is a problem during standard CPR and it is a fatigue doing ACD-CPR. Here are some results from standard CPR published in 1995. The provider of CPR had objective tiredness after 2 minutes of CPR but subjectively the subject didn't know it until 4 minutes.

In other words we do CPR thinking we are doing it correct, but if we evaluate it it is not correct. Those messages should also, be brought into teaching of standard CPR and teaching of ACD-CPR.

Very recently a group in the United Kingdom presented at the Resuscitation 1998 a guide to correctly performed chest compressions and that is a very easy guide which is put up on top of the chest and gives you feedback on how you perform CPR and once again this is standard CPR

and we see that the feedback tube which is here presented as CPR plus really guides you to provide better CPR. In the CardioPump there is a feedback tube.

This page which you probably cannot read but it clearly shows if you go in front of it the whole manual for ACD-CPR training. So we are not talking about a thick book. We are talking about a piece of material which is able to get down to the 1A4(?) paper.

So, my conclusions are a student and instructor manual has been developed. Development and preparation of the manual were based on sharing of practical experiences, identification of important issues and pedagogical advice.

Thank you very much.

DR. LANGE: Do I have any time for a conclusion?

DR. CURTIS: Sure.

DR. LANGE: Okay, thank you. I would like to close by thanking you all for your participation in this Panel. We at Ambu feel strongly about this product and its place among other tools available to first responders as an adjunct to CPR.

For many years the Ambu CardioPump has been available for CPR purposes in countries all over the world except for the US even though this is the country where it was first invented.

What you heard today is that hemodynamic studies

on ACD-CPR have shown improvement when compared to standard CPR. In some prehospital prospective controlled clinical studies these hemodynamic improvements have translated into significant short and long-term benefit whereas in other systems only trends toward benefit or equal effects have been shown.

That being said we recognize that this little device is no panacea. To be effective it must be used properly. Several facts are clear in this regard. First Ambu is dedicated to training and education to ensure that ACD-CPR is performed correctly. Together with world leaders we have written guidelines for use and training of ACD-PCR which have been published in a leading resuscitation journal.

Since there are many links in the chain of survival and many differences from EMS system to the other many explanations and suggestions for differences in outcome have been given.

Nevertheless, studies have demonstrated that the Ambu CardioPump is at least equivalent to and in some cases better than standard CPR and complications and side effects have been shown to be equal for the two methods.

Furthermore combined analysis of patient data for seven prospective prehospital studies including 2866 patients showed improved short-term survival and a

statistically significant improvement in overall survival, one center being most influential in this respect.

As a matter of fact, the Ambu CardioPump is one of the most investigated devices in the chain of survival. In the absence of FDA regulations or guidance on determination of effectiveness for therapeutic intervention of CPR it is important to consider the AHA classifications of these interventions as we heard it presented this morning by Jerry Potts.

The AHA uses a three-tier system. Sorry, the AHA uses a three-tier classification system based upon the strength or level of scientific evidence supporting the intervention.

This level of evidence approach is explained in great detail in Attachment B, Section 5 of the Panel pack.

Using the stated criteria the CardioPump could be classified as a Class II device based upon the animal and human mechanistic studies which demonstrated that ACD-CPR provides superior results when compared with standard CPR in terms of acutely increasing organ blood flow and increasing the coronary perfusion pressures.

This is not very readable but a Class IIA device is clinically defined by AHA as you can see on the enclosed material and here it says, "Class IIA interventions are acceptable, safe in usual clinical practice considering

interventions of choice. Generally high levels of evidence results are consistently positive.

If we exclude the not published combined analysis the data from prehospital clinical trials conducted to evaluate resuscitation and hospital discharge rates are not consistent.

In some clinical trials survival rates have doubled with ACD-CPR whereas other studies demonstrate equivalence to standard CPR.

While individuals in many of the trials lacked sufficient power to draw statistically significant conclusions regarding long-term survival no data suggest a poor clinical outcome with ACD-CPR.

Based on a combination of the hemodynamic, mechanistic and clinical studies excluding the results of the not-yet-published combined analysis the CardioPump could be considered as a Class IIB intervention which is defined as acceptable and useful, acceptable, safe and useful in clinical practice, considered optional or alternative intervention.

Required level of evidence is generally lower or intermediate levels of evidence. Results are generally but not consistently positive.

To summarize, at the present time ACD-CPR appears to be of benefit to some patients. We have, also, discussed

ACD-CPR with other resuscitation councils and the European Resuscitation Council when we presented the combined analysis to them, they said to us that they would agree that if we got this publication when it was published that they would consider it from a Class IIA to a Class IC device.

So, here we have some acute hemodynamic data suggesting that there is a measurable improvement in blood pressure with ACD-CPR compared to standard CPR. The individual prehospital studies evaluating the longer term survival in point of hospital admission and discharge rates are less consistent, but as you have seen combing the individual patient data of seven prehospital studies showed improved short-term survival and significant improvement in overall survival.

Based upon this evidence we believe a reasonable assurance of safety and effectiveness has been established for the listed indicated and that the Panel should recommend approval of the Ambu CardioPump.

We have met today not to discuss how FDA should define efficacy or effectiveness for therapeutic interventions in CPR or the appropriate methodology for assessing the overall risk/benefit of CPR assist devices. Even the admirable goals of increased hospital discharge or clinical utility are not at issue today, and we are not here to debate FDA's manipulation of data generated from a very

prospectively designed protocol.

Instead we are here to assess the evidence presented in support of the Ambu CardioPump and determine whether this is a reasonable assurance of safety and effectiveness of the device for the proposed indications for use.

According to FDA regulations this criteria is met when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended use under the listed conditions of use outweigh any probable risk.

We believe the answer to this question is clearly yes. This answer has been made in over 70 countries and licensed practitioners in the US should be allowed to make it. At issue is not only the status of the CardioPump but, also the advancement of emergency medicine in the United States.

We believe that all patients should receive the greatest opportunity for survival from cardiac arrest. When used correctly ACD-CPR affords that opportunity. We look forward to working with FDA and bringing ACD-CPR back to the American public.

Let me say this very spontaneously from the bottom of my heart, if the documentation we have today on the Ambu CardioPump is not enough for getting a device approved for

the American marketplace I must say I doubt that any company, any investors will put more effort or money in new inventions within the chain survival, the future of which one can only speculate on.

Do we want the chain of survival to survive in improving the future for the benefit of the Americans and people in the rest of the world or will the chain rust because the burden of evidence goes too far? This is, also on the agenda for today, and I thank you very much for your attention.

DR. CURTIS: We are going to take a 15-minute break now.

(Brief recess.)

DR. CURTIS: I want to make sure that all the members of the Panel have their lunch orders in. If anybody has forgotten to take care of that, please do so?

We are going to reconvene now and go on with the FDA presentation led by Carroll O'Neill.

MS. O'NEILL: Good morning. My name is Carroll. I am the lead reviewer for the Ambu CardioPump PME application and will present a summary of each study included in the PMA this morning. The rest of the review team is listed on this slide. Gary Kamer will present the statistical review of the application, and Dr. Dan Spyker will present the clinical review.

A premarket approval application or PMA was submitted to FDA in September 1997. The application relies on published information and a combined analysis of all of the data gathered from grouped studies.

As the slides are projected I will summarize the studies rather than go into the detail on the slides.

Next?

Studies were conducted on the Ambu CardioPump in St. Paul, Minnesota, California, Canada, United Kingdom, Germany, Paris, Belgium and Greece. These studies, with the exception of the California study form the basis for this premarket approval application, PMA.

The applicant explained that the California study qualified for inclusion in the combined analysis, but the principal investigator declined to participate.

Next?

The St. Paul, Minnesota study was conducted in 1992 and 1993. One hundred and thirty patients were enrolled in the study. The design was a systematic parallel group design where ACD-CPR was assigned to the ambulances on one side of the city and standard CPR was assigned to ambulances on the other side of the city. Planned crossover occurred every 75 days.

Return of spontaneous circulation and admission to ICU percentages were favorable to ACD-CPR. ACD-CPR was more

effective than standard CPR with less than 4 minutes of CPR.

The percentage of patients discharged from the hospital alert and oriented was 17 percent for the ACD group and 16 percent for the standard CPR group. The incidence of skin perforations(?) was higher in the ACD group compared to the standard CPR group but there was no significance found in other complications.

It is not clear the potential source of bias were minimized in this trial. Assessment of neurological status was performed using several different methods. Detailed information on neurological and cognitive function at discharge was not submitted. An independent safety committee was not utilized. During the first 5 months of the study investigators were not blinded to results.

Next?

The California study article was submitted in the PMA application, and the sponsor acknowledged that it met all of their criteria for inclusion in a combined analysis, but as I mentioned earlier the study was not included because the principal investigator declined to participate.

Inclusion of this in the combined analysis database required individual patient data which the analysis developers were unable to obtain without the investigator's consent.

This was a large study conducted in Fresno and San

Francisco in 1992, 1993 with 859 today prehospital cardiac arrest patients.

The study design for both cities was a crossover design in which prehospital personnel alternately performed ACD or standard CPR.

The crossover groups' intervals and randomization techniques varied at each site for logistical reasons. In both San Francisco and Fresno there were no differences between the ACD and standard CPR groups in return of spontaneous circulation, hospital admission, hospital discharge or cerebral performance category score at discharge.

There was no increase in complications with use of the ACD except for skin trauma to the chest. The estimated time of collapse to the time of arrival of EMS personnel in less 10 minutes was separately analyzed for both CPR methods. There were 77 patients in Fresno and 51 patients in San Francisco who qualified. The Fresno and the San Francisco data indicated no differences in return of spontaneous circulation, hospital admission or hospital discharge for the two methods.

The authors expressed concerns about conducting resuscitation studies out of hospital and recommended doing these studies in a controlled atmosphere such as the hospital because of the large number of variables inherent

in field trials.

Next?

The Canadian study included resuscitation in in-hospital and out-of-hospital arrests. This was a large study conducted from 1993 to 1995 with 773 in-hospital and 1011 out-of-hospital patients.

The devices were randomized to hospital arrest carts into ambulances according to a centralized randomization list. For both the in-hospital and prehospital patients there was no difference between ACD-CPR and the standard CPR groups in the proportions resuscitated to survival for 1 hour or survival to hospital discharge.

There was no difference in the neurologic status of the survivors as reflected by MMSE scores or cerebral performance categories.

The complication incidence did not differ between the two groups. In no clinically important subgroup either in or prehospital patients was there a difference in either the ACD-CPR or standard CPR group in survival for 1 hour or until hospital discharge.

The authors of this study reported difficulty in achieving adequate decompression for 15 percent or 61 in-hospital ACD-CPR patients and 17 percent or 85 out-of-hospital ACD-CPR patients. In addition, the providers rated the device as difficult or very difficult to use in 18

percent of cases.

Next?

The United Kingdom study was an out-of-hospital study conducted in 1994 and 1995, in three cities in the UK. Five hundred and seventy-six patients were enrolled.

This study implemented a planned treatment crossover every 2 months. Complications were not corrected in the study. The study showed no significant differences in any category of survival for either ACD-CPR or standard CPR.

The authors reported difficulty using the device when they transported the patients. They reported that they had to change from ACD-CPR to standard CPR during the trip to the hospital.

Next?

The German study was a prospective randomized controlled study which used a random number selective methodology. It took place over 3 years from June 1992 to July 1995. They have a two-tiered system using emergency medical technicians and paramedics in tier 1. Tier 2 consisted of two mobile intensive care units, MICUs staffed with a physician and two paramedics. Paramedics do basic life support, defibrillation, IVs and crystalloid infusion. ACLS was provided by the physicians.

There were no significant differences between

those treated with ACD-CPR and those treated with standard CPR in any category.

Complications were reported and there were no significant differences.

Next?

The Belgian study. Detailed data were unavailable for the Belgian study with respect to the study process and outcomes. The combined analysis included with the application indicated that there were no significant differences in survival or hospital discharge. Adverse event data were not supplied for this study.

Next?

The Greek study. An abstract was provided which described the Greek study. The abstract lacked detailed information about the study process and outcome. The data from Greece were included in the combined analysis and showed no significant differences in short-term survival or hospital discharge.

Next?

The Paris study was conducted in 1993 to 1995. There were 513 patients enrolled. The study used a parallel group design. Selection of CPR method was based on the calendar date. ACLS ACD-CPR was on the odd days and ACLS standard CPR was on even days.

The data from this study reflected a significant

improvement in favor of the CardioPump in all survival categories except for 1-month survival.

There were more complications using the CardioPump than in standard CPR, for example, hematomas at the contact point, pulmonary hemorrhages and sternal dislodgements.

It should be noted that this study as compared to other studies included variations in the treatment interventions and treatment assignment.

The French emergency medical system as you heard a little earlier is a two-tiered system in which there are two types of units dispatched to each cardiac arrest. One tier provides basic life support and is staffed with three emergency medical technicians and one chief EMT. The other tier consists of a fully equipped normal intensive care unit which provides ACLS and is staffed with a physician, nurse and two specially trained ambulance drivers.

Next?

ACLS in Paris consists of defibrillation, intubation, mechanical ventilation and administration of all drug therapies. Depending on which unit arrives first at the scene of the cardiac arrest determines the complexity of the initial treatment the patient receives. Enrollment does not occur until the MICU arrives on the scene and the physician determines whether or not to include the patient into the study. Therefore, all patients enrolled into the study

received ACLS and could potentially have six or more rescuers in attendance at the arrest.

Next?

If an ambulance at the arrest before the MICU ACD-CPR may be performed on a patient prior to enrollment because the emergency medical system in Paris established the use of this device in their cardiac arrest protocol for 2 years prior to the study. The added difficulties associated with transport of the patient during resuscitation were not present in the study since patients had been resuscitated and were stable or had expired prior to transport.

Next?

Several authors reported rescuers complained of fatigue and difficulty using the Ambu CardioPump. The articles from which this information was taken were included in the applicant's bibliography and are included in the Panel pack.

Schultz reported that approximately 25 to 30 percent more work was required to perform ACD-CPR compared to standard CPR.

Two German studies reported difficulty maintain adherence to the chest with the device in people with large breasts, hairy chests, patient who had vomited or has electrode gel on the chest.

Nolan reported inability to use the device while transporting the patients in ambulances to the hospital. He stated that standard CPR was necessarily substituted for ACD-CPR during transport in most cases.

Sundai reported decompression efforts with ACD-CPR were too weak particularly during transport on the stairs.

Next.

In summary I presented the highlights of each study. This slide and the next slide compare all eight studies for the end points of 1-hour survival and survival to discharge.

Next?

This is the 1-hour results and those are all percentages of the CardioPump compared to standard CPR.

Next?

To remind you the figures I presented from data i the published studies and unpublished information for the Greek and Belgian studies which the applicant has provided as the basis for this Panel.

Dr. Spyker will present the clinical review of these studies based on the data in the combined analysis. The data are different.

Thank you for your attention.

DR. SPYKER: Thanks, Carroll. My name is Dan Spyker. I am a medical officer in the Division of

Cardiovascular, Respiratory and Neurological Devices.

I want to thank you all for giving me this opportunity and for your help in this matter. I am going to comment briefly on primary outcome measures, combined analysis. Carroll has done a nice job of summarizing the individual studies as the sponsor has done, I think in the Panel pack you received.

We are going to talk about the summary of results and the clinical implications as my first vugraph.

When you think about primary outcome measures for any device, really or any intervention we think it ought to be meaningful to patients. So, the things we teach the medical students and think about ourselves are does it reduce pain and suffering; does it improve the quality of life or prolong life.

You have heard some nice discussions, I think, from both the sponsor and the AHA today about the chain of survival and early access, early CPR, early defibrillation and early advanced care. Each one of these represents a potential point for a primary end point, and I am sure we don't have any argument about that, but if you focus back as we think we might, should as a regulatory team on what matters to patients, we sort of wind of thinking that the primary end points for this kind of activity ought to be that people get out of the hospital alive and do they get

out of the hospital neurologically intact.

So, based on the recommendation of sponsors, this and other discussions of the agency clinicians in consultation with clinical experts, we have recommended consistently throughout this activity that primary end points ought to be survival to hospital discharge and survival to discharge neurologically intact.

Now, this procedure precisely agreeing with the sponsor's statistical analysis plan and their final report, and I am quoting directly from their report, the objective of the combined analysis, and by this I mean the seven studies, was to evaluate the effect of ACD-CPR long-term survival and neurological outcome in a large cohort of out-of-hospital cardiac arrest patients.

This doesn't seem to be quite consistent with their primary end points, but they state in both documents that the primary end points should be short-term survival and survival to discharge or long-term survival.

Now, I want to comment briefly on the safety results that have been pretty well presented by the sponsor, and we have some numerical summaries in our Section 4 of the Panel pack.

A lot of what I am going to present in the next couple of slides here reflects our analysis of the statistical data which was provided by the sponsor, the so-

called "combined analysis." So, we simply did some of the things that we didn't think were completely carried out by what was in that preprint.

So, the observations were 2866 patients and I am just trying to remind you here that we only had adverse event data on roughly half. So, the most that we had adverse event data on, I believe it was ecchymoses was in 61 percent of patients where we had that information, and the lowest we had was at 9 percent. So, in 9 percent of these cases we have information, I think it was on internal organ damage. So, I remind you that there is really not a lot of data in some of these situations, but aspiration was a common problem and that was in 29 percent of ACD patients versus 22 percent of the standard CPR patients.

Ecchymosis as you heard discussed in some detail, but I didn't know the percentages, but from the database 12 percent of the patients receiving ACD-CPR had ecchymoses or bruises on the chest versus 2 percent in standard CPR, and rib and sternal fractures was another one that occurred in sort of significant numbers, and that was 6 percent in ACD and actually numerically higher, 7 percent in standard CPR.

This summarizes the numbers that Carroll gave. We actually did these calculations before we received the sponsor's final submission. So, these are done as percentage change; the ones you have seen so far this morning are done

in odds ratios. There is no statistical difference in terms of whether you get a statistically significant result but these are slightly different.

So, 0 percent means, for example, this study in Germany had just a tad less than a beneficial effect. It was a bit below zero and numerically the largest difference was here with the Paris study we talked so much about, about a 12 percent difference between the success rate or the survival rate at 1 hour for ACD-CPR versus standard CPR.

Now, as the sponsor presented, these are means or point estimates and a confidence interval and in both cases we presented 95 percent confidence intervals.

So, this says that when you get down to the pooled and by pooled we mean engaged in talking about the pooled process and some analyses we have done, but the pooled data just needs a simple addition. I simply added up the number of successes in each of these seven studies and the number of trials and the pooled data as you can see from the graph just barely makes -- the difference is 3.2 percent more people survived ACD-CPR. The confidence interval is 0.2 percent to 6.3 percent. We are 95 percent sure it is in this range. That is exactly what this slide means.

Next slide?

This is just the identical results for in this case the out-of-hospital survival. Again, it is simply we

have quoted here with a percent difference a 95 percent confidence interval for each of the seven studies, added up the results, the simplest pooling you can possibly do, and again I get a difference of 1.2 percent. In this case the confidence interval from minus .6 to 3 percent does not exclude the zero here.

So, it means there is not a statistically significant result. Since really the intent was out-of-hospital survival, this line here and out-of-hospital survival neurologically intact I did this math for you. The numbers presented just showed the CCS category 1 and 2 you have seen so far.

So, overall the 1-hour survival, we saw 24 percent for ACD and 20 percent for standard, and this number we just showed you a moment ago, statistically different with the pooled data, a simple sum, if you will, discharge 7 versus 5 percent; confidence interval did not exclude zero.

Now, if we look at the patients who survived with either Class I or Class II, now, Class I in cerebral performance category is good, as good as you can get. Class II means a moderate impairment, so some measurable or substantial compromise in neurologic status but still better than III or IV.

So, CCS I and II we had 5.3 percent of people with ACD versus 4.9 make it out of the hospital and the

difference is .4 percent. The confidence interval is minus 1 to plus 2, so not statistically different. Likewise when you look at just CCS I which is where I would like to be if I am discharged from the hospital after an event like this, there is no numerical difference and the confidence limit as you can see, also, excludes or does not exclude zero.

So, the results across studies in the reported study methodology suggest there may be differences in the combination of ACD-CPR among studies. So, the things that Carroll told you, I mean you see those results I just showed you. Both of these kinds of results that you see and the methodology we have heard about suggest these studies might be different, and we tried to use the term "study" instead of center because these are not different centers in a single protocol study. These are different study sites, different countries.

The study effect is really examined by analysis. It is not a very complex thing. If you want to know whether there is a difference in gender, for example, there are simple statistical techniques to apply to that, and Gary is going to go through those in a moment.

Next slide, please?

So, the data submitted and from my analysis of it for individual patients in 386 patients, these data certainly permit to have individual data on every patient.

So, it permits the assessment of other important covariates. We can certainly without even having individual data we can assess the effect of center. In fact, the protocol mentioned that the data that would be included were a parcel with individual data. So these data permit assessment of other important covariates. You have heard about patient age, time of CPR assumed a critical variable and each was well known to be an important predictor of success. So, these can now be assessed with the combined data, and you have heard some of those results.

Study effect can be assessed without the individualized data as is typically done in a meta analysis. So, we wouldn't need individual data to see the study effect.

Next slide?

I want to mention that our comments on the seven individual studies with my analysis were not meant to be critical of individual investigators. These were very, very tough studies to do. There is no doubt about that, but our job, and what we are trying to do is comment on the combination to provide balance as to the evidence. That is what you are here to discuss for the intended use.

All the authors of these seven studies, in some form their comments pointed out the applicability of the results, that is the type of EMS system really has to be

fully considered and fully elucidated, and each study is different as you see in terms of the results and methodology. So, this is particularly important to cite.

So, the combined analysis certainly supports safety. The 1-hour survival difference was 3.2 percent for the pooled data. Typically the analysis was not done on these results, the results of ACD-CPR plus mechanical ventilation in the Paris study are certainly encouraging, and I would like to turn it over to Gary to comment on the statistical methods.

MR. KAMER: Good morning. I am Gary Kamer, and I have been the lead FDA statistician for the Ambu CardioPump since it first came to FDA's attention.

Ms. O'Neill has presented an overview of the submission as well as a summary of individual studies comprising the sponsor's analysis.

My comments will be limited to that analysis. Normally for cardiovascular devices a sponsor meets very early with the FDA to discuss the many scientific and administrative issues associated with obtaining an investigational device exemption. Then the FDA and the sponsor interact to assure the quality of clinical trial design and implementation.

Eventually a PMA application is submitted to FDA with intent to establish the safety and effectiveness of the

experimental device and to gain access to the market.

The current submission involved no IDA since it was an analysis of already completed clinical studies. Therefore, FDA interactive assistance and guidance was limited with much of the FDA consultation and veto process following the submission of the PMA.

First overhead?

First, I will briefly discuss the design and results of the sponsor's analysis. Then I will discuss several design limitations in the analysis of the issues. Finally, I will present an FDA summary of the results based on a review of the submission and the application of analysis more fully utilizing available data.

Conclusions will then be drawn from these findings.

Second overhead?

Both study and individual patient inclusion and exclusion criteria were developed before the study selection process began. These studies were identified as meeting the a priori requirements for inclusion and seven studies were eventually included in the primary analysis.

The California study was not included in the primary analysis mainly because of the inability to obtain individual patient data for that study, but some analyses were performed both with and without the California data.

Unless otherwise stated my comments will be on analysis excluding the California study.

Now, let us review the sponsor's results.

Third overhead, please?

No analysis with or without the California data established a significant treatment effect in survival to discharge. Therefore while survival to discharge rates were numerically better for the CardioPump than for conventional CPR this difference may be attributed to chance.

No analysis was performed on the important clinical end point of neurologically intact survival to discharge. Neurological outcome was not found to differ significantly between treatments. P equals 0.19 for cerebral performance category and P equals 0.23 for overall performance category.

However, the statistical power to detect an existing difference in CPC between the treatments was only .22 and the power for OBC was only .18. It was unlikely that any true differences would have been detected by these analyses. However, conventional CPR's success rates for neurological status were numerically better than those for the CardioPump.

A trend or Cochran-Armitage(?) analysis assuming equal weighting for survival to 1 hour and survival from 1 hour to discharge indicated that survival was greater for

those treated with the CardioPump. P equals 0.041.

This was an analysis of pooled data rather than a combined analysis. When I refer to pooled data or analysis I am indicating that the data from the component studies were simply added together without any adjustment for study.

I will refer to combined data or analysis when adjustment for study is performed. None of the sponsor's analysis adjusted for study. Therefore they may be considered pooled analysis. Finally a pooled analysis using logistic regression established that 1-hour survival differed significantly between treatments, a P of less than .05. The CardioPump's superiority being attributed primarily to the positive results of the Paris study.

While attributing this outcome primarily to one study, the analysis apparently did not adjust for the covariable study nor for any of the other covariables.

Fourth overhead, please?

Several design issues create limitations for evaluation of the CardioPump. Many of the component studies used systematic assignment of treatment instead of randomized assignment. This could introduce bias into the results.

Also some component studies reported survival to ICU admission rates and not 1-hour survival rates. The sponsor's analysis appeared to use 1-hour data from these

studies when reporting the 1-hour results. Is it truly 1-hour data or was it ICU admissions data used from these studies to represent 1-hour data?

If the data used are ICU data this would complicate the interpretation of the 1-hour survival results and perhaps would require revised analysis.

Finally, the inclusion of studies with major protocol differences complicates the evaluation of the CardioPump and raises concern over the generalizability of the results.

Now, let us consider analysis issues.

Overhead five, please?

Where results other than those presented by the sponsor are used they were based on a data set provided to FDA by the sponsor. Those alternative analyses have been performed to verify submitted analyses and to provide refined analyses as needed.

In a similar way to a meta analysis the results of any combined analysis are sensitive to the studies included in the analysis. Eight studies were identified for inclusion, but the sponsor has included only seven.

As discussed by Ms. O'Neill one of those seven studies may have used a treatment regimen differing substantially from the other studies. This table addresses the likely impact of two options of the results for 1-hour

survival and survival to discharge.

The first option is whether or not to include the California data in the analysis. Currently it is not included in our primary analysis.

The second option is whether or not to include the Paris data. Currently it is included. Reduces, as you can see on this table indicates a reduction in survival for the CardioPump relative to the conventional CPR while increases would indicate an increase. This table should not be interpreted as a suggestion that these options be implemented. Rather this table is presented to document these options and to provide insight into the likely impact on the results of the revised analysis.

The table indicates that either the inclusion of the California data leaving Paris in or the exclusion of the Paris data leaving California data out would most likely result in a reduction in survival for the CardioPump relative to conventional CPR. This reduction would occur for both 1-hour survival and survival to discharge.

Overhead six, please?

Similarly two analysis issues exist, not dealing with the composition of the data said to be analyzed but rather with the details, with the method of statistical analysis to be used. Unlike the previous discussion of which studies should be included the two analytic issues

require statistical comment.

All sponsor's analysis should have adjusted for both study, a suggestion by the previous discussion of the impact of the removing studies and similarly other statistically important covariables.

Some covariables which are eligible for the identification as important covariables and therefore for which adjustment may have been required are whether the arrest was witnessed, the patient's age and time to initiation of CPR.

As shown by this table such adjustments would have revealed a reduced importance of treatment on both 1-hour survival and survival to discharge.

Next overhead, please?

Not adjusting for study results in simple pooled analysis rather than a combined analysis. Again, a pooled analysis simply throws all the data together, treating them like they were from a single study. A combined analysis recognizes that the data came from several studies and permits an adjustment for differences in results from those studies.

This can be thought of as a refinement to simple pooling. For this summation adjustment for study may be made by including the covariable study in the logistic regression model. While study has been identified as an

important covariable even if it were not significant, its inclusion will provide a minimal adjustment such as would be provided by an analysis using Carpen(?) and Dohensil(?) chi square statistic which studies a stratification variable or by a meta analysis.

Similarly no other important covariables were included in the logistic regression model. Preliminary FDA analysis of one data set provided by the sponsor indicates the existence of one or more significant covariables in addition to study. Their inclusion would diminish the importance of treatment on outcome. Adjusting for study all these other important covariables could greatly impact the quantitative and qualitative results for all the clinical end points. Such adjustment is considered necessary from a statistical perspective.

Next overhead, please?

Up to this point 1-hour survival and survival to discharge have been the primary focus of my comments. The sponsor has suggested that some equally weighted combination of these end points should be considered in evaluating the CardioPump. I refer to this end point as overall survival for lack of a better term.

Here, overall should not infer that this is the primary end point. It is simply used as a convention. Analysis of singular survival end points remains crucial to

the evaluation of the CardioPump. This overall survival end point is sensitive to the weights assigned to each component.

Assignment of weights should always be blinded to outcome which will reflect the relative values of the end points. The Cochran-Armitage trend test takes both survival end points into consideration.

This table shows the percentage of patient survival less than 1 hour, the percent surviving at least 1 hour but dying before hospital discharge and the percent surviving to discharge. These are shown separately for each treatment.

The tendency for greater percent of CardioPump patients to survive longer is consistent with the results of the trend analysis done by the sponsor. However, stratification by study would result in a non-significant treatment effect. This adjustment was made by using a trend test stratified by study. This could have been accomplished by using logistic regression with ordered polychotomous dependent variable rather than the usual dichotomous dependent variable. The study would simply be a part of any resulting model, a covariate.

The individual patient data would contain values for the dependent variable representing died before 1 hour, died after 1 hour but before discharge ad survived to

discharge. The usual dichotomous dependent variable would have had values such as died before discharge and survived to discharge, for example. This approach should, also, permit the use of different combinations of weights for 1-hour survival and survival to discharge. Again, any assignment of weights should be blinded to outcome.

That brings us to the issue of how to identify and adjust for other important covariables in a trend analysis. While it may be theoretically possible to adjust for small numbers of important covariables via stratification it could be an unwieldy task.

Since the above ordered polychotomous logistic regression approach permits the inclusion of covariable study it may, also, be used to identify other important covariables such as possibly whether the arrest was witnessed, the patient's age or time to initiation of CPR.

As with the analysis of survival end points, the analysis of the end point overall survival may be refined by using logistic regression. The results of this analysis should better represent the true safety and effectiveness of the CardioPump.

Now, let us summarize what we believe the data indicate.

Next overhead?

First, the use of the Ambu CardioPump has not been

shown to result in a statistically significant difference in neurologically intact survival to discharge. The sponsor did not provide a comparison for this end point. Preliminary analyses by the FDA indicate that the results of such an analysis would have been even less likely to establish a treatment effect than would a comparison of survival to discharge alone.

Secondly, neither the sponsor's nor the FDA's analysis established treatment differences in survival to discharge.

Thirdly, while no difference in neurological outcome between treatments was found by the sponsor this may have been the result of insufficient sample size rather than the existence of no difference.

Fourthly, while the sponsor found a significant trend for overall survival using pooled data, an FDA trend analysis stratified by study resulted in a non-significant finding equals 0.0563. Further, the adjustment for other important covariables may tend to increase the P value even more indicating a reduced importance for the treatment effect.

Finally, while the sponsor found a difference in 1-hour survival favoring the CardioPump, FDA analysis indicates that the inclusion of study alone sufficiently increases the calculated P value to result in a finding of

non-significance. Adjustment for other important covariables might further increase the P value.

Overhead 10?

The stated aim of this combined analysis is to evaluate the effect of ACD-CPR on long-term survival and neurological outcome in a large cohort of out-of-hospital cardiac arrest patients. Statistical evaluation of the data did not support a finding of a significant treatment effect for either of these two end points.

Using covariate analysis no significant treatment effect was observed for 1-hour survival, neurologically intact survival to discharge or overall survival as defined in the trend analysis.

Thank you.

DR. SPYKER: That concludes the FDA presentation. Are there any questions for any of the team?

DR. CURTIS: Thank you. We will go ahead and start the Panel discussion now, and Dr. Becker will lead off.

DR. BECKER: Do I need to disclose my financial status?

DR. CURTIS: No, you do not.

DR. BECKER: I have none, but my way was paid here by probably everyone in the room.

I wanted to make some general comments to start

off with, and I would like to thank the sponsor for coming and for providing particularly a terrific group of experts to explain many of the aspects of the data.

I do have some specific questions for some of you, and I would like to use that time to explore some of the questions that I have.

First, I would like to say one thing. I am very sympathetic to the need for better ways of bringing devices to the market, and I am, also, very aware of the need for better ways of doing our research in the resuscitation field, and there is no question in my mind that some of this has been at least a frustration to this process and whatever kind of determination will come out of this Panel, I do agree that those issues with regard to research in the resuscitation field in the United States are exceptionally important and somehow we have got to do better than we are actually doing right now.

The other comment that I would like to make though is that I have seen that there is a danger in devices coming to the market, in my opinion, prematurely before there is really adequate data to support their full effectiveness and particularly when the claim is being made that they show better effectiveness than some other technique, and I am having difficulty in really supporting that aspect of what I have seen from the sponsor's application at this point in

the overall sense that in terms of better survival I see a number of problems with it, and I find it to not be compelling.

I don't have so much problem with the equivalence type of language, but I do have a problem with that, and so, I think that we will need to talk about that a bit, and so I think probably what I would like to do is ask a few questions fairly specifically to some of the panelists so that I can understand some of these issues, and I don't want to pick on our colleague from France, Dr. Plaisance particularly but I have to ask a few questions about that, and I very much appreciate you attending to be able to answer some of these questions, but a few questions that I have, I noticed that as I read the article over that approximately 10 percent of the patients were actually treated with the wrong treatment group, that is that patients that were labeled ACD actually received standard CPR and that about an equivalent number went back the other way, and I didn't see anything in terms of had you tested sort of the extremes of those two to see if there was any effect on the analysis had you analyzed it according to the actual treatment that they received, particularly since there was a 10 percent rate of that occurring and with a survival rate of, a relatively low survival rate, 3 percent or so, it wouldn't take very many patients to cause a bias

and so I am wondering if you might be able to address that.

Why don't I give you a few questions, and then if it is okay maybe you could get up and talk about that a little bit.

Another concern that I had in just understanding that data, and I think I want to say that I think there is some very important lesson to be learned within the study that you have published, and so, I am sure that it is very important and that is a piece of why I am trying to understand it and appreciate your help with that.

Another concern that I have is really why there is so little bystander CPR reported in the overall paper. It is approximately a rate of about 7 percent in both groups which would really be, I mean that is even low for Chicago is what I am trying to say, and so, what that means to me is that the groups, for example, that received no BLS probably received very little at all given the very low rate of bystander CPR.

I am wondering if you can kind of address that a little bit or if you have attempted to tease that out in any way as to what that effect is, and that kind of brings me to one of my real concerns with it that I think the thing that I don't understand the most about which is that it looks like, and I should probably refer you to a table here. I think it is perhaps Table 5 as I remember, the one with BLS,

yes, it is; it is Table 5. I mean I might have found -- I am sort of troubled by at least an aspect of this because what it looks like to me is your very best chance for long-term survival in Paris is to not get any kind of BLS intervention at all, and so, what I mean by that is that both for the standard group, the highest rate of survivals and the group that gets no BLS and for the group that gets ACD again it is in the group that gets no BLS, and it is really like 12 percent survival in that group compared to the other group if I have interpreted that right.

So, I guess my question is how do we understand that in terms of here are groups that were ostensibly receiving ACD-CPR and yet there is really very -- it looks like the group that gets no BLS does better than that group, and I guess I find that, I don't understand that. Most studies that I am familiar with consistently show a survival advantage for basic life support.

I am almost aware of none. This is an exceptional paper in that respect. I might have written it completely differently with a different headline as a matter of fact, you know, and so, I guess it makes me wonder especially given the sort of 10-minute time period as I went through the time periods it looked like that from the time that BLS was started until ACLS started was a full 10 minutes and that occurred after about 10 minutes or so of nothing. So,

ACLS kind of arrives on the scene at about 20 minutes into cardiac arrest and that is when the CardioPump in this study seems to show an effect, and I am just, you know, I am sort of, I cannot explain that.

I would have thought that you would have had kind of four groups, and they should have had the group that got ACD and BLS and got ACD and ACLS and they would have done really good and then there would have been an intermediate group and then the really bad group that didn't get BLS, and I am not seeing that here, and so, I don't want to put you on the hot seat here too much. I have already done more than is really polite, but you know, I was wondering if maybe you could address and help us to understand at least some of those differences because as I say, I do believe there is some very important information in this that we all need to learn from.

DR. PLAISANCE: Okay, I will try to answer the three questions if I can. First of all, I think that procedure as to the interpretation of this Table 5, when you see no BCLS it is because sometimes there was the ACLS team arriving just when the patient collapsed or when the BCLS team is coming simultaneously close to the patient with the ACLS team. So, we said and we wrote "No BCLS when the ACLS team began the CPR on the patients," okay? So, it is not an important number of patients with BCLS during a long time

but it used more BCLS because in some times the ACLS team was already there, for instance.

It is the reason why we were interested as you concerning these results. It is perhaps the reason why the no BCLS ACD-CPR is better than BCLS, for instance.

First question. The other one is what about the bystander CPR. It is France and it is true. I said at the end of my talk that we had to work a lot for the chain of survival, and the first ruling of teaching is very bad in France system because people are not educated. Less than 3 percent of the population is educated and people don't know yet what they have to do in front of cardiac arrest and especially to Code 15, and we are doing a big staff job with the requirement to educate those people. So, it is the reason why we have so low a percentage of bystander CPR.

We didn't perform any statistical analysis concerning the research issues while not, who hadn't done bystander CPR or who had. So, I cannot answer the second part of this question, and the third question is what about the patients who were correctly or non-correctly involved. Effectively it is 10 percent of the whole of the groups, yes, and I think it is usually under treatment those patients who received the one CPR technique were en route in this technique, okay? And we didn't analyze this subgroup of patients.

We only assumed that first of all we thought that it was not so important with regard to percentage. Ten percent, for us it is not very important, and I didn't note anything about the other studies concerning that point. In all of the studies it is not written, and we didn't analyze that. That is my third answer.

Did I answer all the questions?

DR. BECKER: Yes, thank you very much. Did you attempt to do any kind of logistic regression on this to see what the impact factors would be for survival in your system?

DR. PLAISANCE: No, we didn't.

DR. BECKER: Thank you.

That is all.

DR. CURTIS: We will start going around the table. I think I will move over to there to Dr. Ornato.

DR. ORNATO: Thank you. I have a couple of comments. The chain of survival is as the name suggests a paradigm or a concept that the Heart Association has put together to represent the fact that a person's survival odds from a cardiac arrest are dependent on a lot of chance things happening in sequence in a very rapid timely fashion.

The way they teach the concept at the Heart Association is that a community needs to have each link in the chain as strong as possible to maximize the patient's

chance for survival.

This particular device as our colleagues have pointed out focuses on one specific link in the chain. Personally although I think in the greater societal sense and really in the medical sense what really counts is how many people survive neurologically intact to go back into society I think it is important that we recognize that progress in the field of resuscitation is going to occur in tiny little steps.

It is very unlikely that any one intervention whether it is CPR or a particular drug that comes along is going to be so powerful that with the relatively modest numbers of patients that we can study we are going to be able to see this effect come out loud and clear.

Therefore, I guess from a reasonable standpoint I would like to I guess share with you what is my personal perspective that it may be unreasonable for us to expect that any single intervention alone is going to easily be noticeable as impacting survival even to something as short-term as hospital discharge.

Now, in the case of the specific device at hand, physiologically ACD-CPR in my humble opinion does appear to be superior to standard CPR when viewed physiologically in an animal model and when we look at the echocardiographic transmitral flows in the human cases where it has been

studied.

I guess one of the things that really surprises me is that I am, despite what may sound like a very positive feeling towards the technology, I am thus far completely unconvinced that the worldwide clinical data when analyzed critically as our colleagues at FDA have done yet demonstrates scientific proof of the device's superiority.

The one exception as we have seen is in Paris, and I guess the only thing I can conclude today is that if I am in Paris visiting and have a cardiac arrest and have asystole and have 20 minutes before ALS arrives, I am convinced that this is the device that I want to be used on me.

I am less convinced that in other settings, particularly settings such as we experience in North America where our response times to BLS and ACLS are substantially shorter than those experienced in Paris that there is yet adequate scientific evidence that this device really meaningfully improves survival beyond standard CPR.

So, to my way of thinking there really should be two issues that our voting members of the Panel should use to decide how to cast their votes.

First is is there evidence that the device is safe for use clinically in humans, and my own personal belief, analyzing the data is the answer to that question in my mind

is yes.

So, to me the issue is not safety so much as it is effectiveness. What standard should we use for effectiveness? My own personal belief is that it may not be unreasonable for us to ask the question of is this device effective when compared to standard CPR.

If in fact, that were the question at hand my personal vote would be absolutely yes. I don't see resounding evidence that this device is any less safe than standard CPR. I think the only question in my mind is whether it may be slightly better or may be slightly not as good as standard CPR.

My own conservative analysis is that at this point I am not convinced that I can really make a sound scientific judgment that it is better than or worse than, but I think it is reasonable from the data we have seen to say that it is probably at least equivalent.

If, in fact that were the question before this Panel, and if I were to have a vote I would humbly say that I would vote in favor of this device being equivalent to standard CPR and therefore effective at least as effective as what we consider to be the standard of care.

The concern that I have and the problem that I have and what I really think we ought to focus our attention on is the language that is being proposed by the

manufacturer which although they claim that it is a conservative claim from my way of reading the language that they have put into their document is, in effect, really claiming superiority of this device over standard CPR.

I am not convinced that we have data that would really firmly support that. So, I think the real question to me is if we must firmly stick to the language that the manufacturers have proposed.

I think they have placed the bar a bit higher than I think the science would really support at this point, and I think if the bar were placed slightly lower, that of being an equivalent device I think they have met the threshold.

I think I will stop there, and there may be some more comments I will have later.

DR. WITTES: Let me ask you something, Anne? I actually had prepared some slides for some statistical methods for the didactic thing. Would that be okay?

DR. CURTIS: Sure.

DR. WITTES: Because I think that --

DR. CURTIS: I think the Panel would all be strongly in favor of that. Go ahead.

DR. WITTES: All right. Remember the Saturday Night Live thing when Chevy Chase was Gerald Ford and somebody came in and presented some numbers, and he said, "But you promised me there would be no math."?

What I want to do just to get, I think, and this is really another thing in that direction is to present what I think are some of the statistical issues. They were really presented by the FDA, but I want to put them in another framework because I had to do this for myself as I was reading the Panel pack.

The first thing is what is the difference between meta analysis and the combined analysis. So, I would like to sort of change the language. I think what we have got is we have got a two-by-two table. You can either have individual patient data or published data, and I think it is a terrific thing that most of this analysis is on individual patient data, but then you can either stratify by study or lump the data and that has been called pooling, but I am going to call it lumping because it is just throwing them into one pile.

Now, if you think about all the meta analyses or overviews that come out of the Oxford group that is here where they take individual patient data, but they stratify by study.

What the Panel pack is referring to meta analysis I think is this category. You are stratified by study, but you only use the published data, and I think that is a misnomer. I don't think any of us who have done meta analysis would put this, would limit this to this cell, and

then there is what I think we see in the Panel pack, individual patient data but lumped, and there is no reason that this couldn't have been here and that is I think what the FDA was doing, was trying to take the individual patient data but make it as valid as could be by making sure to compare like with like.

So, that is the first thing. Now, the second thing is the logistic regression. I mean basically a logistic regression is like any kind of regression analysis where you have any kind of -- this should be a linear regression, and you are looking at the mean as a function of a bunch of variables in the data array, but logistic regression says, "Look, we need to come out, we need to be a probability at the end. So, we are going to transform in a way that makes this over this range from zero to one," and that is basically what it does. It makes a probability, but you can work within a logistic regression framework and still you have lots of choices.

You have lots of choices. These things are the covariables. You can choose lots of different covariables. You can choose lots of different ways of choosing the covariables, and the particular methods they used were step-up methods, but I think there are lots of people who say that it is much better to take all the variables first and step down.

So, one of the questions is what is the process by which the choice of covariables was made and one can stratify as the FDA did and say, "Let us think of each study and stratify by study." So, this is in a sense a family of models, some of which are better than others.

Now, let me just do a couple. The trend analysis, it took me actually a long time figure out what this meant, and I think this would be what is the trend. I think I have got this right. Here is the data. This dead is dead within a year, within an hour. Short term is within 1 hour to 24 hours, and this is more than 24 hours. Is that right?

PARTICIPANT: Discharge.

DR. WITTES: Discharge, okay. So, that is the data. Now, we normally think of this in these proportions as the FDA presented as among those people who are in each group what is the proportion who have died; what is the proportion short time; what is the proportion long term, but you don't see a trend there.

The way the trend analysis thinks of the data is in the other direction, the proportion of people who are dead who were in this group, the proportion of people short term who were in this group, the proportion of long term who where in this groups, and so, you see the trend 48, 52, 54. That is the trend that we are talking about, and statistically it is the same whether you look at this thing

or this thing. I mean you get the same chi square no matter what, but the point is that the trend is related to the proportions in the direction in which the denominators are down there.

Finally, one other little didactic thing. There has been some discussion about inclusion or exclusion of the study and I just think this is again a little off base. Suppose you say that the prior criteria for studies is any trial that includes people age 20 to 90, that is your prior stuff.

You then search the literature and you find seven studies, one of which has a group of people limited to 20 to 30 and all six of them, the other six have people 60 to 90, and then you discover a dramatic result in this group and no effect in that group. You cannot hide behind the fact that the prior thing said, "Twenty to 90," when in fact what you observed is something very dramatically different when you actually collect the data.

So, all I am saying is that while without prior inclusion, without prior guidelines it is really hard to say that you did an unbiased thing. You have to look at the data from a sensitive point of view and exclude things if they are different.

So, now, let me ask my questions? I just have a few questions. The first has to do with the reason for

stepwise forward. Can you describe why you chose stepwise forward and what you would have gotten had you chosen backward selection?

DR. SITTER: Yes, I would like to address the three or four points you have made in your presentation if this is allowed, and you started first with the wording of a combined analysis versus a meta analysis.

We wanted to stress the point that we used individual patient data and that is the reason why we called it combined analysis. So, we have a meta analysis relying only on published literature and here we have a combined analysis which may be, also, labeled as a meta analysis using individual patient data.

That is the reason for this, and we did this approach to have several advantages. For instance, we could get some data on the 1-hour survival results of the individual trials which were not published in the literature or which are not in the publications but we could include this because we asked the people responsible for the trial and they could provide this information.

We did, also, an analysis on the intention to treat basis which was not done in the individual trials, in all individual trials. So, we had the chance to do a standardization, for instance in these categories, and let me cite two sentences from a paper from Stewart and Palmer

written in the Lancet 1993, comparing meta analysis of the literature and of individual patient data and they conclude meta analysis based on collection and reanalysis of individual patient data provides the least biased and most reliable means of addressing questions not satisfactorily resolved by individual clinical trials.

They can, however, take considerable time and resources and usually involves worldwide collaboration. End of citation.

DR. WITTES: Can I say something?

DR. SITTER: Yes.

DR. WITTES: But I still think that is not directly germane to what I was saying. I agree with that completely. I think any one of us who has been involved in these analyses believes that it is much better to get the data, the raw data. It is much more flexible. You are much less likely to be biased and so forth, but the point is that having collected it you still may and should preserve the analysis within the study.

Just because you have collected the data per patient basis doesn't mean you should throw out -- it doesn't mean that the study is simply another covariate. The study is the fundamental unit of analysis still, and so that is really what I was trying to get it. You are not committed to disregarding the study.

DR. CURTIS: I would like to make a comment, too. If the Panel members have questions of the people who are in the audience, please try to address your comments to what the question was. I really don't want to get into extended comments based on what the Panel members are saying. If you have a question, that is great. Please answer the question, but we don't want to get into a debate back and forth here.

DR. SITTER: Then I will answer shortly. We have considered this study effect because we used the random effects model, also, called Desimoni and Layitt(?) method where this is recommended by the Cochran group for considering, also, the study effects, and we have done this in the random effects model in the logistic regression.

We, also, looked at the effect of center and of other covariates. We had one analysis that is a chi square test for trend where we put together the data irrespective of where they come from, but in all the other things that was considered, but all these analyses were complied to the protocol.

DR. CURTIS: Go ahead?

DR. WITTES: Okay. I still want to know why the decision was to go stepwise forward rather than --

DR. SITTER: We had --

DR. WITTES: And what the results would have been from the backwards.

DR. SITTER: We have not done it backwards. We have done it stepwise forward because if you do it backwards you usually just throw out the variables. You have no stepwise procedure. So, we built up a model that has a possibility of throwing out variables and adding other variables.

That was the reason why we included this method and it was specified and, also, carried out in this way.

DR. CURTIS: Janet, I don't understand what you are getting at, and maybe one other person here doesn't.

DR. WITTES: Okay, you have a bunch of variables, you know, age and all the variables that you want, and the question is when you are building a model do you say, "Let me take the variable that counts, that essentially reduces the variability the most, that counts the most, put that in the model, then pull the next, sort through all the variables, choose the next one, that is the next most powerful and build it up that way," and the method here is to take a variable, find the one that is the most powerful, take the next one, the next most powerful, then see whether if you took the first one out you still retain essentially all the explanatory variables. So, it is picking one at a time and building up.

The other approach is to take all the variables that you can consider potentially important and put them in

and get rid of them one at a time. You say, "Which is the one that doesn't contribute?" and then there is forward backwards where you pull them in and out, but there is usually -- and there are advantages and disadvantages of both, but often you would like to see that you get pretty much the same model no matter what selection method you use.

So, that is the import of the question.

DR. SITTER: So, it is the question how is the model building performed, and there are different ways of doing this.

DR. WITTES: And the relevance is that for the variable that is of most importance here if the choice of variables of covariates gives a different inference about the variable of most importance which is the treatment then you feel, oh, my goodness, I have got a model-dependent result.

If, however, no matter how you did the selection you get the same, the variable that matters which is treatment still shows up, then you feel more comfortable.

All right, let me ask you a question about the California data. Do you have, in the Panel pack it talked about that if the California data were in it doesn't change the results, but do you have the specific analyses that show that?

DR. PLAISANCE: We used the data that are

published and used it for chi square testing, and there was no change in the significance, but we have no access to further data.

DR. WITTES: No, I understand that, but do you have the set of analyses that did use the California data? Do you have them that we could see or --

DR. PLAISANCE: Yes, we have done it for chi square tables. We have done it because they give, also, the outcomes of 1-hour survival, and if we put it in there was no change, and the result of the chi square test doesn't change from significant or not significant.

DR. WITTES: Is it a chi square stratified by study or is it pooled?

DR. PLAISANCE: It is the pooled chi squared because we have from the California not the individual data.

DR. WITTES: So, there isn't like a match how Hansel's(?) test with the California data as a stratum; i that right?

DR. PLAISANCE: Yes, that is right.

DR. WITTES: Okay. Now, let me ask about Paris, and I think these are just sort of technical questions about the study because clearly the Paris study is the one that is the dominant study in terms of the inference.

The first question is just I don't think I quite understand the ones that were at, the patients that were

given the wrong treatment, the analysis was done. They were held in the treatment to which they were randomized or the treatment which they received?

DR. PLAISANCE: The treatment to which they were randomized, the intention to treat.

DR. WITTES: Okay, now, one of the worrisome things, and I appreciate how difficult this must be to do a real randomized study is whenever the randomization is done in some other way, in some predictable way, the question is could there have been some kind of bias induced, and I gather in the Paris study the randomization was odd/even day.

Is that right?

DR. PLAISANCE: Yes, that is right.

DR. WITTES: Can you describe how teams are set up in Paris? Do teams work for a week? Do they work for -- there aren't like Monday, Wednesday, Friday teams and Tuesday, Thursday teams or anything like that, are there?

DR. PLAISANCE: Let me say to the randomization procedure that, also, some other centers have similar randomization procedures, one even week versus odd week or some other kinds which are not generally randomized which I mentioned before, and generally randomized was for instance a month's trial, but a lot of the others not.

DR. WITTES: I know, but the reason I am asking --

DR. SITTER: Perhaps for the information of Paris may I hand the chair to Patrick Plaisance that he might answer this.

DR. PLAISANCE: To support the randomization of ECD in Paris studies written, I think clearly in the paper we randomized the patients when we arrived, and when I say, "When we," that is the ALS team and the physician randomized the patients, but first of all I want to answer another question or comment concerning the randomization and the inclusion of the patients in Paris.

The physician didn't want to include, not include or randomize or not randomize the patients. If the patient had the inclusion criteria we showed you he was included. That is it, but concerning those randomizations, effectively from 1 a.m., or 0 a.m., let us say until 25 p.m., midnight the patient was randomized on odd or even days.

DR. WITTES: The question is a little different from that. I think that I understand. The question has to do with is there some structural thing the way the Paris system worked that would make the odd and even, that would induce a bias in this odd/even day allocation.

An example that would do this, and I don't know anything about the system clearly, but if you had schedules in which some people worked Monday, Wednesday and Friday and other people worked Tuesday, Thursday, Saturday then an

alternating schedule would actually be testing the teams. The teams would be confounded with treatment. So, what I am asking is were there -- I am asking for kind of a description of how teams are set up or more fundamentally how do you know, I mean this is really the question, how do you know that odd/even, that going from odd to even, A to B, to A to B, to A to B that there is not something systematic going on in the system that confounds treatment with some systematic variable?

DR. PLAISANCE: It is difficult, I think, to answer this question. First, concerning the even and odd days it was, I think, perceived more because it was only physicians who made the decision. What about Paris and people working, sleeping or not sleeping? I think it is the same as other countries in the world. So, people, other people are working 5 days a week, and have rest on the weekends. I think it is -- I don't understand really your question corresponding to specific elements in the Paris study concerning this parameter.

DR. SITTER: Perhaps may I clarify? Was it the case that some people just worked on Monday and not --

DR. PLAISANCE: Concerning the teams, if it was the question, I apologize because I didn't understand that. Concerning the teams, we are a team 24 hours a day, and are working not only on Monday and some others on Tuesday, no.

They are working one day 24 hours and then they have 2 days of rest and then they come back to work. So, they are working during one year, they are working every day, let us say.

DR. WITTES: All right. It is an every 3-day cycle.

DR. PLAISANCE: They are working 1 day and rest 2 days and come back to work.

DR. WITTES: Did you consider, again, on a more general level because I take shift just because that is a variable that just jumps to mind, but are there, did you think about processes that could have alternated on days, that there was some systematic thing because another approach could have been to say that we are going to do everything, you know, today we are going to do all standard, but we will randomize the days? That could have been the approach rather than to have a systematic flipping.

DR. PLAISANCE: I think that this kind of randomization, first of all I think I showed you that people are working during all the protocol study one year and one-half, working let us say every day. I think I am talking about the BCLS teams and the ACLS teams.

So, there was not specific elements responding to that, but it was only, I repeat because I think it was only corresponding to the day the physician of the MRCU, when the

physician of the MRCU was a physician different every day, and it was, also, working 20 hours.

Did I answer everything?

DR. CURTIS: Yes.

DR. SITTER: And let me remark that this problem is, also, inherent to other centers where the treatment effect is not so prominent and that perhaps if it is not a genuine randomization there might be, also, a bias in the other direction in another center. We cannot say it is in this direction or in the other direction.

DR. CURTIS: Okay, thank you.

Dr. Tracy?

DR. TRACY: I have relatively few questions, and I think perhaps Dr. Lange would be the best person to answer most of these things.

Several of the study centers that used the device reported some difficulty, technical difficulties with it, either saying that it was difficult or extremely difficult to use. I think that was particularly true with the Canadian group. How many people in Canada are now using this device in preference to standard CPR technique?

DR. LANGE: Do you mean how many people in the center that actually has published the study?

DR. TRACY: Yes.

DR. LANGE: I don't think anybody, to my

knowledge, no.

DR. TRACY: So, that they did the study but then they abandoned the device afterwards?

DR. LANGE: That is my impression, yes.

DR. TRACY: Is that true with most of the study centers that were involved in the original data collection?

DR. LANGE: No, that is not true for most of the studies. You heard about Germany. You heard about Paris and in many other studies they are waiting for the publication of the combined analysis and for recommendations and different guidelines.

DR. TRACY: One thing since this is just a piece of the total picture of resuscitation, how does this device impact on the use of the defibrillator, an external defibrillator, particularly the automated defibrillators that are now in use? Do you have to keep removing patches and repositioning the patches after you have done CPR? Where on the chest does all this stuff go?

DR. LANGE: Maybe I should hand the question over to somebody with practical experience in this area.

DR. MAUER: We had that problem in two patients with very small thorax. We used AEDs with the detachable things, and we had this problem in two patients only out from now nearly 500 patients, and this exists in patients with very, very small thorax, but normally we don't have any

problems in using automatic external defibrillators and ACD-PCR.

DR. TRACY: Okay, it seems like one of the limitations, and I am not sure who can answer this question, but one of the limitations of use of the device is in transportation because it is difficult and it requires stabilization of the person who is delivering the compressions.

How in a system where there is limited personnel; you know, you don't happen to have somebody extra to just hold onto the person doing the chest compressions, how is that supposed to work out?

DR. MAUER: Resuscitation in a moving vehicle is not as effective as in a standing vehicle. We know that, and that is true for standard CPR and the same is true for ACD-CPR. We don't have, most of the European countries don't have any experience with resuscitation in a moving vehicle because we have doctors. We have emergency physicians in the out-of-hospital setting.

So, we resuscitate our patients until RUSC(?) and then we transport them or we leave them at home, but we know about this in UK. They had to change from ACD-CPR to transport from ACD to standard CPR and we know about problems in Canada. I think they had in Canada the most experience with ACD-CPR in a moving vehicle, but maybe we

have not ask Ian Stiell. I know that they had problems with that, but I think if you tried with standard CPR you, also, would have problems with standard CPR in a moving vehicle.

DR. TRACY: As the person fatigues who is doing the compressions, and the technique becomes a little bit sloppy compared to when they first start out how does that impact on the complications? The complication rates were not trivial, and that is, also, noted in the Paris study. It is not a trivial amount of complications. When you get sloppy is the effectiveness of the compression reduced and is the complication rate higher compared to standard CPR?

DR. MAUER: What we learned in our working group training and education where we brought all the opinions from the different centers together, we learned and we proclaim now that it is very important that the one who is doing the thorax compression with the ACD-CPR and standard CPR changes every 3 to 5 minutes.

DR. TRACY: That is not necessarily practical in many circumstances where there is a limited amount of personnel, but the final question I had with some of these complications, hematoma and pulmonary hemorrhages how does that impact on subsequent treatment? If you assume that many of these people are having these cardiac arrests in a setting with acute myocardial infarction you cannot give then a thrombolytic. You cannot heparinize somebody. How

does that impact? Is that perhaps why the 30-day survival was less because you couldn't do appropriate treatment because of complications relating to this device?

DR. MAUER: I can answer that question only for my center which is the Mainz center, and we didn't have any problems with that because our cardiologists are very impressive, and they do thrombolytic therapy if they have the impression that the patient has myocardial infarction, and only because of the little bruises over the sternum they didn't stop thrombolytic therapy.

In the other centers I am not very sure, but I don't think so, but I am sure for Mainz.

DR. SIMMONS: I don't really have very many questions. I guess I would like to address mine to Dr. Wik though. You presented a lot of very compelling animal and echo data that showed that this device improves perfusion 180 percent to the brain and 90 percent to the heart and yet the data show no significant neurologic benefit, and I am wondering how you resolved these issues in your own mind?

DR. WIK: I think we should go back to the basis of animal research and standardized research in the lab where we control all factors, every single factor we control in the lab. In a clinical setting it is almost impossible to control all the factors. In this specific ACD-CPR environment we have seen that training and practice is very,

very important.

What I think is that some of these data reflect that we should really consider the right training and right practice, and I think that one of the reasons for the Paris study really showing a beneficial effect is because they started the study after a time of training and practice.

So, what I am trying to say is that if you are providing the technique correctly you will have the beneficial effect and harvest the beneficial effect of the technique and that will then probably reflect increased outcome.

DR. SIMMONS: Are you aware of any data, I mean that you are actually really improving perfusion to the brain or the heart or the liver or the lungs or to the kidneys that there is less acute renal failure, less shocked liver or better left ventricular function and better -- I mean have you got anything at all to share that would indicate that this device actually does what it is supposed to do, because I haven't seen it here yet?

All I can say is that it is not worse than CPR, regular CPR.

DR. WIK: Are you thinking about the clinical setting and the lab setting?

DR. SIMMONS: The clinical setting.

DR. WIK: The clinical setting. The only thing we

can refer to is the data which are presented.

DR. SIMMONS: Okay, I really don't have any other questions.

DR. CURTIS: I think this would be a good time to break for lunch. We will reconvene at 1 o'clock, and I just wanted to announce that the Panel will not be in session during the lunch hour.

(Thereupon, at 12 noon, a recess was taken until 1:05 p.m., the same day.)

AFTERNOON SESSION 1:05 PM

DR. CURTIS: We will reconvene the meeting now. The next member of the Panel is Dr. Sethi.

DR. SETHI: I just have a few questions. One of the questions deals with the complication rate. We have noticed a significantly increased number of quote, unquote, contusions or hematomas or whatever it is. Could you tell me how significant were they, the contusions and hematomas of the chest wall?

DR. MAUER: What is very frequent with ACD-CPR is bruises, ecchymoses, hematomas due to the fact that the pump fits very exactly with the skin and if you decompress, you decompress, also, the skin, and there are some small blood vessels in the skin which are responsible for bleeding which is located subcutaneously.

This is not an intrathoracic bleeding. It is only a subcutaneous bleeding that is very frequent, particularly at the beginning, but the device has been modified a little bit so that is not so frequent now with this newer version of the device.

DR. SETHI: How about if the patient is anticoagulated? Does that make it worse? Those patients who are Coumadin and --

DR. MAUER: In the combined analysis we don't have a report about that. We found one patient dying because of

an intrathoracic bleeding in our hospital, but this was a patient with standard CPR.

DR. FRASCONE: We have just a bit of a language barrier here. What you actually see is a suction ecchymosis. It is a big hickey is what it is on the chest, and in the St. Paul study we did not have that insert that protects the plunger, and that is probably why we had a significant increase in those abrasions or hickeys.

DR. SETHI: I think every study you look at has significant increase in whether you want to call hickeys or hematomas, but if you look at the Paris study there are five patients with a pulmonary hemorrhage and can you tell me how bad were they or how did they diagnose that?

DR. PLAISANCE: The question of the patients with pulmonary hemorrhage, we had patients on the scene who had for 20 minutes, at least 20 minutes received ACD-CPR, and we saw in the infusion tube some blood coming out of the tube in those patients.

That is the reason that we wrote that they had sort of pulmonary hemorrhages, and when they came to the hospital they had x-ray and they had fibroscopy and the prognosis was not very serious because first of all concerning the x-ray review we had only one white lens on the x-ray, okay? That means just to show edema, pulmonary edema and then the tissues were put in peep(?) and they

survived. So, there was not a bad outcome with those patients.

DR. SETHI: In the Panel pack I don't see any autopsy data at all. I wonder if I missed it. Do you have any autopsy data of internal injuries that you could share with us?

DR. MAUER: In the combined analysis we took the documented complication rate which is the complication rate seen in chest x-ray or autopsies. So, it is a mixture of clinical examination complications and complications seen by autopsies.

DR. SETHI: You notice that a large number of patients, the data are missing regarding the complications dealing with internal bleeding.

DR. MAUER: I didn't get that.

DR. SETHI: In a large number of patients the incidence of internal organ injuries is missing. So, we don't know that.

DR. MAUER: Yes, that is clear.

DR. SETHI: Another question which I want to ask you is was about the Page 16 on the Panel pack, possible description of combined analysis of patients by study, 16. It is Section 4, Page 16. Look at the patient age. Is there a minimum age, 15 years, 16 years? It doesn't say how many of those patients were in this age group. Do you have that

data? Do you know what I am talking about?

DR. MAUER: Yes, and in the study from Ottawa from the Canadian study there were five patients coded with an age of zero years, and we asked them but didn't get an answer why this was coded in this way, and we took it in the analysis as being patients of this age, and there were 15 other patients from different centers younger than 18 years.

DR. SETHI: These patients were the complication rates any different than other patients? Did you analyze these patients differently? The question I am asking is this is a huge device to put on a small patient.

DR. MAUER: Yes, but these were altogether 20 patients, and the complication rate is too low numbers to do analysis.

DR. SETHI: That is all.

DR. DOMANSKI: I want to track through some data. I want to make sure. I know there is a real seriousness of purpose. People have come a long way, and they have done a lot of work, and I want to make sure that at least I go through this thing carefully and that I understand it fully.

I would like to begin by talking about a comment that actually one of the Panel members, Dr. Ornato made about the business of equivalence. I have a real problem with talking about this being equivalent to standard CPR, that being a basis for approval.

I don't think that is an appropriate basis for approval. The reason for mentioning it here is I think that it is not only a poor idea in this case to use that kind of approach, but I think it is a poor paradigm, and we were talking about this at lunch. I apologize, but I want to put it on the record. I think that you could imagine a towel manufacturer writing a carefully controlled, better controlled than what we have got trial of throwing a towel on somebody's chest and then showing that there is no difference between that and standard CPR, and there is a secondary end point. The quality of life is better for the resuscitator. I mean that is the obviously carried to its logical absurdity approach to doing an equivalence study.

When you say, "Equivalence," one usually thinks of equivalent to a device that is marketed that has been shown to be safe and effective for that. So, I don't think that it, for whatever indication one is doing it for, so that I think showing equivalence to standard CPR is not an appropriate basis for approval. Others may disagree, but I certainly would vote against that if I were given the opportunity.

Secondly, I would like to track through these trials for two reasons. One is I think that I am echoing, and I always want to echo the statisticians properly because I am really not a wonderful statistician and I really depend

on them, but I think that the combined analysis, just lumping together numbers the way this was done is hopelessly flawed methodology.

I mean I think if one were going to do it one would have to do a meta analysis. So, I think it is flawed on that basis, No. 1, and No. 2 is I think that it is flawed based on using non-randomized trials in it so that I would tend to reject combined analysis out of hand, and that is just me speaking, but I would like to track through the controlled trials that were done a little bit and make sure because some of them are randomized trials, and I would like to look at those and perhaps we could do that with the company whoever you think would be the best person to talk for your controlled trials.

You see I think there is a hint that the physiology that they are addressing makes sense. There are physiologic data, some of which have been presented that I think suggest that this may be a useful adjunct to physiology. There are some data in the literature, not with this device but that suggest that in a hospital setting this sort of decompression resuscitation may, in fact, be useful.

So, there is a genuine basis for studying this technique and thinking that it might be useful in an out-of-hospital setting, but I would like to track through with whomever again you think may be the most appropriate person

to come to the microphone and we could chat about each of these studies that are presented in the package starting on Page 44.

Who wants to pick up the gauntlet here?

DR. LANGE: I think it is going to be Dr. Mauer because he is actually the Chairman of the combined analysis and he is of course the one knowing each study the best, but we do not have each principal investigator here.

DR. DOMANSKI: I understand that. I just want to make sure. I want to bounce this off you all to give you a chance to respond because I may be wrong about something, and if I am I would like to know it.

DR. LANGE: I would just like to touch base a little bit on what you said and that is --

DR. DOMANSKI: Let me ask the other questions first because I really want to track through in particular order, and then I will give you a chance to respond to the comments at the end, and so I would like to track through these studies first, and I really will give you a chance to comment on what I have said.

I would like to start with the Paris study if I could because I guess the Paris study is the one that really you know, if you look at it the data or the result appears suggestive, and I am bothered by your randomization scheme. So, maybe I could ask you about that, and you could tell me

why I am wrong about it.

One way to have designed that study would have been truly to randomize it, that is when the people -- the way you would usually do that is to decide if a particular individual meets the inclusion criteria and is not excluded by exclusion criteria and then randomize and then treat them. In fact, what I understand happened was that as the crew arrives at the scene based on the day it is they knew what treatment they were going to give if the patient was entered into the trial. Is that true?

That being the case, I am very concerned about bias. I mean I can look at a patient and say, "Gosh, this guy really doesn't look good," and come up with a true bias, you know, maybe a very understandable bias. I don't mean intentional and say, "Gee, I am just not going to use the device on this guy," and have a completely unbalanced group based on how they were entered.

So, I don't think that trial was truly randomized, and I wonder if you want to comment on that because that is a key point. That is your biggest bullet in favor of this study, in favor of this device in my view.

DR. PLAISANCE: You are right about your comments, but I can ask another question. I think that when you are really forming a study which is not blinded you have a wealth of parameters which can play for bias, enthusiasm,

for instance. Even though there was a mystique on the, for instance on the device and then a mystique and you can see what kind of procedure will do, okay, but after you have seen the ACD-PCR and the CardioPump and if they don't want to play with the CardioPump they will not. So, okay, it is a possibility of bias, but when you are performing an open study it is always the case.

DR. DOMANSKI: I think that is a problem with an unblinded study that you cannot get away from in this case to be sure, but you could have randomized it. You could have done that, and maybe it was practically more difficult to do it that way.

DR. PLAISANCE: Yes. I tried to explain that when I spoke this morning. It was very difficult because when you are doing an emergency center, it was not the first one we were performing and it is very difficult to do that and have a randomization as you want because once more there are lots of people working around this technique, for instance, a lot of organization during defibrillation and so, it is very difficult.

DR. DOMANSKI: The reason for picking though on this study and being this, you know, putting it into focus is it is the real, if one were going to say that this thing is effective, this is the study you would have to use to do it, and I am concerned that the methodology in this study is

sufficiently flawed so that setting aside other studies or potentially flawed so that setting aside other studies is more difficult. If it were consistent with all other studies, you know, if everything were kind of pointing in the same direction, then one's concern about it would perhaps be or at least my concern about it would be less.

Maybe we could look, also, at some of these other studies. It seems to me that in the St. Paul study the people were not truly randomized. I guess the same is true of the California study and again please correct me because I could be wrong.

DR. PLAISANCE: Yes, that is true.

DR. DOMANSKI: The Canadian study is indeed randomized.

DR. SITTER: The only genuinely randomized studies are the German and the Greek one.

DR. DOMANSKI: What about the Canadian?

DR. SITTER: The Canadian, I am sorry, was, also, randomized, these three, sorry. There were three studies that there was a genuine randomization, that is Canadian, German and the Greek one and in another there was assignment odd and even days like in Paris or odd and even weeks or a change after a month.

DR. DOMANSKI: So, the ones that are not bad, if one looks at the Canadian study which was truly randomized,

the German study which was clearly randomized, I am kind of looking at the results in these studies, too, and just to make sure I do it right and the Greek study. I wonder if either the FDA folks or the company took those three and combined them as a meta analysis?

DR. SITTER: We discussed it during the development of the protocol and there we decided that we will not insist on such a genuine randomization process because of the reasons we displayed earlier.

DR. DOMANSKI: But I would note that I think that if you, and maybe the statisticians could help me because the room has certainly got some very good ones in it. I think if you look at the data from those trials it would clearly not, just from first principles it would clearly not show a favorable effect for this device.

So, if you used the truly randomized studies I think that this device would not show any increased efficacy compared to standard CPR.

DR. SITTER: In the majority of the individual trials you will see a trend towards ACD which is not statistically significant, but --

DR. DOMANSKI: I don't know about that. Let us look at those three for a second then. If you look at the Greek study, there is a 2 percent difference in favor of the device.

Now, let us go back to the German study, admittedly not significant and all that, but if you look at the German study it is actually the other way around, at least the way I am reading it. I am looking at just return of spontaneous circulation, but if you want to look at something else I am happy to do that, too, and I do sign on to the business by the way that there are multiple links in this chain and that you cannot necessarily expect one of those links to drive the whole process, and I understand that, but I guess I am a little concerned that I would like return of spontaneous circulation, something simple. So, that goes the other way and in the case of -- now, I lost my place, I guess, but at any rate those two. Somehow I am not sure it does trend clearly in favor of the device. I don't know if you want to comment on that?

DR. SITTER: Sorry, I did not --

DR. DOMANSKI: It is just that you said that they all trend in the same direction, and they don't trend in the same direction if you take those three and those are the ones at least that I would like to focus on because they are randomized trials and if you look at return of spontaneous circulation, and they in fact don't all trend in the same direction. The Greek study what little trend there is I mean --

DR. SITTER: You have in the Greek study a little

trend in one direction, in the German it is a little bit in the other.

DR. DOMANSKI: Well, again, the German study -- where is the German one? All right, the German study I am looking at return of spontaneous circulation in 51 percent. It is on Page 49 in the packet I have, 51 percent in the ACD-CPR group and 60 percent in standard CPR group. Here again, even on ICU admission and hospital discharge trend a little bit in favor of the ACD.

I actually don't see compelling trend. So, I guess summing it up and I don't want to belabor it but I guess summing it up I think that the methodology in the combined, and I am going to let you comment now on the methodology of the combined studies is flawed. It is not a meta analysis, as a matter of fact.

It is throwing a bunch of things together, many of which were not randomized trials, and the one trial that shows a clear benefit is the Paris trial, and the Paris trial really is not a randomized trial in the sense that one would like to use that term and I apologize for interrupting you before. Would you like to respond to my comments?

DR. SITTER: May I come back to the comment that the analysis is flawed? That is not true because we did apply the methods which are recommended, for instance, by the Cochran collaboration. We did a random effects model

with the Desimoni and Layitt method. We did logistic regression modeling where we looked at interaction, where we looked, also at the covariates and the factors and so on.

DR. DOMANSKI: Please understand I want to make clear what I mean by flawed. I think that the business of just lumping the thing together flaws it.

DR. SITTER: We haven't lumped it together. We have taken into account variations between the different studies and that is not just lumped together.

DR. DOMANSKI: Janet, maybe you could comment on that for me.

DR. WITTES: I don't understand because that is exactly the question I was getting at. What I see, you certainly talk about logistic regression. You talk about keeping things separate, and yet the data that you present is a lumped analysis. It is just throwing them all together into a trend analysis, and what we are both sort of asking for is can you show us the analysis that shows the final logistic regression with the covariates that were in that and the estimated betas for that model?

I think that would at least for me would give me --

DR. SITTER: Yes, I can show it to you. I can tell it to you that we have in the logistic regression models in the resulting model there were many inferential --

there is the ECG rhythm at the beginning, the time of arrival and the center in which center it was, and there was an interaction between center and between treatment if we included interaction terms and if we did not look at the interaction with the centers then the treatment effect was the most powerful effect, and if we looked at subgroups then in several subgroups the treatment effect was powerful in the logistic regression models, and was selected and came in there, and the conclusion from the random effects model I showed you two Pitot plots where the odds ratios are calculated according to the Desimoni and Layitt method where you look at the odds ratios, where you look at the confidence intervals and for the 1-hour survival the confidence interval is lower than one.

DR. WITTES: I guess I need to see numbers. I am hearing words describing them, but I need to see what those numbers are, and I need to see how specifically, how the effect size, the estimate of effect size is influenced by variables going in now, and I appreciate that you have done that, but we haven't seen it.

DR. SITTER: If you haven't seen it, I have displayed the logistic regression models during the talk today where there is stated which variables are selected, and the odds ratios calculated are, I can present them once more for 0.8 for the 1-hour survival favoring ACD-CPR with a

confidence interval from 0.65 to 0.99 and the confidence interval for the discharge survival includes one.

DR. DOMANSKI: Janet, let me just say that the concern, my single concern is the use of non-randomized trials as opposed to the exact methodology, and that is what I meant when I said, "Flawed," but in any event maybe the other is a problem as well. It may be that you want to re-present those data. Perhaps I could let them respond to the initial comments because I cut them off in the beginning because I wanted to make sure I got all the questions on the table, but I felt badly about that. So, I want to make sure they get a chance to respond.

DR. LANGE: Your remarks concerning the studies which was a background for us letting specialists come together back 2-1/2 years ago discussing --

PARTICIPANT: I cannot hear you over here.

DR. LANGE: Oh, I am sorry. What I said was that I totally agree with the fact, I mean this is a fact that all the studies are not randomized and most of the studies do not show any significant differences in terms of outcome which was why we gathered together these people back then 2-1/2 years ago in order to get some experience and get some discussions on how to proceed.

Now, there were two kinds of answers. One was in making a new controlled blinded, as blinded as it can be

randomized prospective study with the power analysis saying that we should include more than 10,000 patients or something in order to show if the change is relevant, change in discharge from hospital but the experience of the doctors and you might comment on that, Dr. Mauer was that that was very burdensome, and we, also, have to remember as far as I know, and I might be wrong here, but no device has been able to translate hemodynamic findings or benefits into clinical outcome, not anyone in the chain of survival.

So, that is when we decided to go for the combined analysis to see what can we get out of it.

DR. DOMANSKI: Do you know what the sample size would have been if you just used return of spontaneous circulation or 1-hour survival because I share your concern about having to show discharge from the hospital. That may be too heavy an oar to ask any one device in that chain to pull. You ought to be able to show something that it maybe did something that benefitted the individual, at least initially.

DR. LANGE: Like 1-hour survival?

DR. DOMANSKI: For instance, what sort of sample size would you have generated?

DR. MAUER: When this working group came together we had a calculation that we didn't even know what is the survival rate. What is the survival rate in Chicago, 3

percent, 7 percent, perhaps? In Mainz it is 12 percent. In Iowa I don't know. In Germany in other parts it is 2 percent. So, we don't know the exact survival rate. Assuming that we wanted improved survival, discharge survival, we talked about this. We talked at that time about discharge survival and to improve survival from 3 to 4 percent and to think that that is statistically significant outcome, we needed nearly 10,000 patients. To increase survival from 18 percent to 25 percent you need 2300 patients per arm or something like that. I don't know. We didn't do a calculation as far as 1-hour survival is concerned, but you can take all studies. All studies did a calculation but on the basis of RUSC or 1-hour survival. That is why all the studies are underpowered as far as discharge survival is concerned.

DR. DOMANSKI: Yes, I wasn't trying to push on the discharge survival. I understand the problem with that, and I wouldn't have, if you had shown the return of spontaneous circulation and shown the 1-hour survival I would have thought that quite compelling as a link in the chain, but I guess you know what that sample size would have been. You have a sense of that. I understand the difficult with calculating. I am not sure how I would go about it frankly in terms of making assumptions.

DR. MAUER: If you take, for example, 1-hour

survival and take a basis of 30 percent and you double your survival rate from 30 to 60 percent with a 100 percent effect then I think you would need in between three and four hundred patients per arm, something around that. I didn't do that calculation. We did it for our study, but it is now 4 years ago.

DR. DOMANSKI: Would you regard that as a reasonably heavy order? I mean would you have regarded that as unreasonable in terms of asking someone to do that study for instance?

DR. MAUER: Okay, we had that workshop and the decision was made by nearly everybody in that workshop not to do a new study because there were so many ongoing studies at that time that we tried to get all these data, and it seems to be the easiest way to come to a lot of patients, a large patient cohort to be able perhaps to show any benefit or not in discharge survival. That was our plan to do, and it was a clear decision by the whole working group not to do a new study.

DR. DOMANSKI: Did you know the design of the studies, of these studies that are today laid out before us at the time when you had the workshop?

DR. MAUER: Yes, this was presented during that workshop. We knew everything about the study design. We knew that it is, and it is very difficult to do a randomized

study. In Paris, for example, they have, I think 7 million or how many inhabitants --

PARTICIPANT: Twelve.

DR. MAUER: Twelve. This is nearly impossible to do a randomized study in such a huge city. We can do it in ours. We have 200,000 inhabitants.

DR. DOMANSKI: Could I ask you a question about that? You know, I have heard that mentioned before. We were talking about it briefly over lunch how difficult it is to do randomized trials in this setting. Why would it have been so difficult to simply pull a randomization number as you arrived at the scene or as the call came in or something like that?

Well, actually it couldn't have been done that way. You would have to have looked at the patient first.

DR. MAUER: We discussed that with our statisticians, and they told us the best randomization is a randomization with a list, and if you take a randomization list, one randomization list and you have 100 ambulance cars in one city it is impossible to do that with a randomization list. We tried it in Mainz in our system, and I can tell you this made if very difficult.

We had a 24-hour supervision of one doctor who was only responsible for that randomization list. He needed to know where all these ambulances were and what they did at

that time because when they resuscitated they had to give him the randomization number and when the other ambulance car went to another resuscitation they needed the randomization number. It is difficult.

DR. WITTES: You can always stratify by ambulance.

DR. MAUER: Yes, this was not accepted by --

DR. DOMANSKI: It is probably not easy to do is the take home.

All right, those are the questions that I have. Do you have any other comments in response to what I have said or asked?

DR. MAUER: No, you are right with your comments, but the question is if we did the right thing. That is, also, for me a question, what we discussed now. We decided, and it was a decision by a lot of preclinical, practical people doing studies all over Europe. We did the decision to do that analysis and not to do a new study, and I think it was not bad to do it especially with the combined analysis because I think a meta analysis is easy to do, but the quality of combined analysis with individual data is very much more higher than a meta analysis I think.

DR. DOMANSKI: I would hesitate. The second we start to do that I would defer to the statisticians and let them argue the meta analysis. I mean I could try it as an amateur. My concern about the meta analysis was actually

perhaps even a simple one and that is the studies that went into it weren't randomized. I recognize and sympathize with the problem of making a decision and having somebody retrospectively come back and look at it.

The problem that we are faced with, at least I am faced with and the whole Panel is faced with is trying to decide whether or not this thing has really been demonstrated to be effective and we are kind of stuck considering the data that are there and asking ourselves whether it really demonstrates it in a reasonable way so we want to put this out.

You know there are things that could go wrong, too. If you fiddled around with a device that really wasn't very useful in our setting and then delayed the CPR in some way or compromised it in some way we don't know that one might not. So, one would want to have good data.

I think the preclinical stuff, you know, the animal stuff is good data and I think some of the stuff that has been done before in hospitals is. It is just that it would be nice to be able to see something here that is compelling, and I am worried that we don't.

So, let me finish there and move on because I am taking too much time.

DR. CURTIS: Mr. Jarvis?

MR. JARVIS: I have no questions at this time.

DR. CURTIS: Ms. Whelan?

MS. WHELAN: The Minnesota folks began the presentation with some anecdotal reports from the firefighters I think who are eager to use the device again, and yet later in her presentation Dr. Lange spoke about the Canada group choosing not to use the device. Could you tell me why?

DR. LANGE: I am not 100 percent sure since I am not Ian Stiell, but I have discussed it with him, and he said, "What we showed in our study is that we see no difference," which is I mean postmarket surveillance. I mean that would be something that if the product was on the market these people could try it out and see does it work in my system. So, that was his explanation as to why, but he was very open, very cooperative in the whole combined analysis study, also, seeing the limits that there are in any study. Does that answer your question?

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: I have a couple of questions about some things that we really haven't touched on yet. I didn't see, and I am not sure who to ask this question of, but I did not see in our package or maybe I missed it, any description of the durability of the device and how reliable. Do you ever have them break?

MS. GISCH: We did not in the St. Paul study.

There was a device that we had that had a ring inside of it, and that has since been refined, but that ring would sometimes pop out, but they changed that model, and we did not have any.

MR. ROCHESON(?): Maybe I should comment, also. I am the quality manager.

DR. CURTIS: Could you identify yourself, please?

MR. ROCHESON: My name is Paul Rocheson. I am from Ambu. We have had almost no complaints on this device, and I think we have never had a complaint for a device which has broken.

DR. GILLIAM: That is pretty impressive. You have never had anything break. If you give it to me for a month, I would probably break something.

(Laughter.)

DR. GILLIAM: But did you test it on bench testing, and how long do you anticipate the device to last? I mean how many compressions does it take to wear out the spring gauge, any idea?

MR. ROCHESON: I have some idea about maybe the spring gauge in the printout.

DR. GILLIAM: You might want to speak to the accuracy of the spring gauge at the extremes of use?

MR. CURNAN(?): I am Warner Curnan, the Vice President of Research and Development for Ambu and have been

chief for the development of the CardioPump. As to the endurance of the spring inside the spring gauge it is calculated and I mentioned for more than 1 million cycles of fluctuations between the extremes of the CardioPump gauge which is from approximately 590 and up to 150 at the other extreme approximately. We have never seen any failures so far from the market, and the other question?

DR. GILLIAM: And the other question stemmed to the accuracy of the spring gauge in measurement and how often do you have to -- we looked at the instructions for adjusting it using the screwdriver to adjust it, and how often do you have to do that and is there any idea of the reliability of people, for instance, not doing it, how good is the device if the readjustment were not correct?

MR. CURNAN: You will notice that in our directions for use we indicate a single measure of keeping on line the pressure gauge calibration, that is to say it is like a floating zero-point instrument where the pointer if it is located at the zero line it is most likely in calibration because the rest is mechanical linkages, and it is locked up to the characteristics of the spring.

If it goes off for some reason because of wear, for example, you would see it immediately as a drift away from zero as an indication for recalibration, and we give the directions so the user people can actually go in and do

it themselves, reset it to zero, and that would be it.

DR. GILLIAM: I have no further questions at this time.

DR. FERGUSON: I would like to thank the members that have given such a very complete and detailed description of the device. I have four questions for you. The first one relates to the crossovers, if I can call them that, people who -- there were several of the studies, and the one that sticks in my mind is the one that said that they have 20 percent of the time an inability to get the device to adhere properly to the chest wall. So, that is one patient in five. Am I quoting that correctly?

DR. LANGE: Which study?

DR. FERGUSON: I don't remember which study it is. It is probably not the right word to use, crossover, but --

DR. SITTER: They received ACD instead of standard?

DR. FERGUSON: No. They start with the device, and they have to give it up because of perspiration, vomitus sweat and all the things we know happen to people who have had an arrest, and so, some of those people I presume you have to give up using the device and go back to regular CPR. Is that correct? And that figure quoted in one of the papers I know was 20 percent. I don't know what it was for all because I didn't take the time to look that up in the

others, but let us assume that it is 20 percent even. There are a certain number of people that are going to be crossed over in any kind of study you do, if you have to give up the use of the device because of this problem, and that is what I am trying to get at.

DR. SITTER: This figure was about 7 percent. I first thought you were talking about another thing.

DR. FERGUSON: So, in 7 percent of the time you start using the device, and you have to stop using it because of these conditions. Is that correct, and go to regular CPR?

MS. GISCH: We addressed that problem in St. Paul by telling the paramedics that in the event that the suction cub did not stick they should continue using it because at that point all you lost was the active decompression phase of it. You still got a compression and a passive relaxation. You just didn't get the active decompression.

We, I believe, ended up excluding patients that originally got ACD-CPR and then because of the device failure the crew decided to discontinue it and switch to standard CPR. So, the patients that got both methods got excluded.

DR. FERGUSON: I appreciate that description. That is helpful to me. The point I am getting at here I guess yo understand is the fact that if people cannot get the device

to stick then it is counterproductive in terms of saving the patient's life if they fuss with that a long time. Do you understand what I am saying?

MS. GISCH: They still get the benefit of the gauge.

DR. FERGUSON: If they continue to do that, but there are some people who might use the device and not be aware that they should continue to use the device that doesn't stick is what I am getting at.

MS. GISCH: We addressed that in training.

DR. FERGUSON: That is a training issue.

MS. GISCH: That we addressed.

DR. FERGUSON: Okay, so that everybody has to be trained to understand that?

MS. GISCH: That was part of the trouble-shooting training that we did.

DR. FERGUSON: Okay, and they are warned to either continue to use the device without the decompression or to abandon it right away and go to --

MS. GISCH: We suggested that they continue with the device. Some of them elected when they had problems with it sticking to just discontinue it and go with standard CPR. So, those patients that got both methods ended up being excluded.

DR. FERGUSON: Good. Thank you.

A question for Dr. Plaisance, if I am not mistaken and I am not an intensivist in the sense that I deal with CPR every day, but as I look through these studies yours is the only one that uses a respirator routinely. Is that a fact?

DR. PLAISANCE: Yes.

DR. FERGUSON: Because I know that the area from which I come and so forth and a lot of other areas I know the ventilation part is carried on in the standard CPR-AHA format. So, my question to you is did that have an effect possibly, the fact that you use mechanical respirators on every patient in that series, did that have an effect which could have changed the results in any way?

DR. PLAISANCE: It is very difficult to answer the question. I think it counts. I must say that effectively we use routinely for many years a ventilator but this kind of ventilator I showed you this morning is a volumetric one. It means that it is has the same impact as a bag because you inflate volume and the only difference is that when you have a bag you have a two-hands bag. When you have the ventilator and the volumetric ventilator you have your hands free to do something else, but I don't know whether there is a difference of not using a ventilator or using a bag.

DR. FERGUSON: You would agree that adequate ventilation is as important as the compression?

DR. PLAISANCE: Yes, of course, but I think that adequate ventilation can have it with the ventilator and it is much more difficult with the bag.

DR. FERGUSON: Thank you.

DR. PLAISANCE: And it is the way I think everybody who has performed CPR in hospitals with the ventilator, I suspect.

DR. FERGUSON: In a hospital?

DR. PLAISANCE: Yes, of course. So, it is the same way.

DR. FERGUSON: Thank you.

DR. WIK: May I comment, please? Regarding the ventilation issue, you should remember that both groups received the same ventilator treatment. So, the potential positive effect of the ventilator which has a valve, this is very, very comparable to a manually driven bag. It would be the same. So, I really don't think that the ventilator did influence in any way in favor of ACD-CPR in the Paris study.

DR. FERGUSON: I am sure you are right. I am just looking for reasons why that study is so aberrant compared to the rest of them, and that is one thing that stuck in my mind as a difference.

The third thing is the totality of studies with the Ambu device have all been included. Is that not correct? In other words, there are no studies out there when you talk

about -- we have talked about seven studies today that have been done. There are no studies that have been excluded, correct?

DR. MAUER: San Francisco did not want to participate. There are other small studies. There is one study in Germany. They published their pilot case, and they wanted to start the study, but then they stopped. They did not continue to do the study, and when we discussed to include this German study they told me, and there were several discussions about that, that the data collection in that study would not be ready.

We had at the time the end of December 1995. This was the time to have the data ready for the combined analysis, and that study was not ready at that time. That is why we did not include that study, and there is another study in Salzburg, but this was not a controlled study. These two studies were really excluded from the combined analysis.

DR. FERGUSON: Thank you, and one last question. It relates to the fact that I have a problem with the fact that I think from a physiologic standpoint there seems to be no question but what the principle is an excellent one, not a good one, an excellent one, and so, I am trying to figure out why we haven't been able to translate this into usable data.

I was impressed when Dr. Frascone made several observations, and the one I guess that impressed me the most was when you said that during the time you used the instrument you could get radial pulses on all those patients. Now, to get a radial pulse on a patient that has cardiac arrest for anybody that has actually done that, that has got to be very impressive because you are usually looking for a femoral or carotid pulse and then you cannot feel it very well.

Why was that simple observation not translated into a study? I mean that would be a perfect way, it seems to me to combine the physiologic data which we know is there and correct into a clinical setting.

DR. FRASCONE: It wasn't isolated as a study, but it has been reported that systolic blood pressures can be as high as 160 with this device, and I believe the mean was 80 in one of the papers. So, it is not surprising that you would get radial pulses.

Similar to that, of course, is the anecdotal evidence regarding cerebral perfusion with patients struggling and the gentleman that sat bolt upright immediately after defibrillation. Obviously the brain was being perfused throughout that time.

DR. FERGUSON: That is impressive, but that is episodic, I am sure in your experience, but if you were able

to feel a radial pulse on every patient that you attended that had this device and you know what the percent of patients that you can feel a radial pulse in with regular CPR, that would seem to me to be a very important clinical observation which goes back to the animal studies. That is just a comment.

DR. FRASCONE: Yes. I think if we were to do that same study today we would be putting lines in all these patients and reporting that data out as well.

DR. FERGUSON: That is all I have. Thank you very much.

DR. BRINKER: One of the virtues or benefits of being one of the last people to ask questions is that most of the important questions have already been asked. Therefore I don't have a whole lot to say but just a couple of comments. In my experience most of the people I resuscitate actually do very transiently get some sort of spontaneous rhythm and/or blood pressure but then require multiple episodes of resuscitation, and I am sure this is the case with many of the patients in this group, and I am wondering as a function of survival since that was a different end point than resumed spontaneous activity for an hour whether patients requiring multiple episodes of CPR after the first episode will continue to be treated with the assigned methodology of CPR.

That is if you resuscitated a person with this device, and a day later he arrested in hospital was he resuscitated with this device or with standard care? If it was with standard care and he turned out to die over a couple of days, then while the index result of the procedure was rightfully assigned to successful, the subsequent outcome of the patient might have been adversely influenced by him not getting the same kind of therapy.

So, my question is in patients with multiple arrests who received CPR more than the index, was there any attempt to treat him with the same sort of CPR?

DR. MAUER: That is very, very difficult to answer that question, but this question shows us the main problem that existed in all the studies that the in-hospital therapy is in nearly all studies not standardized. So, if you resuscitate a patient after 3 weeks, he is in another unit. He is not in a coronary care unit.

He is in a different clinic, I am sure that he will not, in our system he will not be resuscitated with the CardioPump because we introduced the CardioPumps in the intensive care unit and the prehospital setting and that is true for nearly all studies, and that is, also, true for all other alternative methods examined in the prehospital setting.

DR. BRINKER: I am just saying that --

DR. MAUER: Did they all get the same method of CPR during the whole process of treatment? That is our problem. The problem in doing these studies and taking discharge survival as an end point, a study end point is that that study end point is influenced by in-hospital therapy and that in-hospital therapy is not standardized.

DR. BRINKER: I agree. That is why I am pointing out this issue.

Let me go to --

DR. FRASCONE: May I interrupt for a second? We went as far as the EDs all of the emergency medicine departments in the city were trained in ACD, and if the patient had ACD-CPR en route and arrested again in the ED, that was continued until admission.

DR. BRINKER: Let me address the Paris study, just two quick questions? One is that many of these patients got basic cardio life support for CPR with the device before randomization. Is that correct?

DR. PLAISANCE: Yes.

DR. BRINKER: And in that case the device failed to work. Otherwise they would have never been randomized. Is that correct?

DR. PLAISANCE: Yes.

DR. BRINKER: Is there any idea, do you have any sense of the bigger picture here in out of the general

population how many people who got the basic life support CPR with the device prior to randomization actually were resuscitated and never reached the site?

DR. PLAISANCE: Yes, I think we had a slide this morning showing people who were excluded because they were resuscitated before the arrival of the ACLS team. Is that the question?

DR. BRINKER: No, you need both numbers. You need how many actually survived because they were resuscitated with the device and how many actually died or ended up getting randomized because they weren't resuscitated with the device.

DR. PLAISANCE: Patients who have received ACD-CPR during the BCLS phase and who were resuscitated before the ACLS phase I think it was only five, and all the patients died. All the patients died rapidly. I don't remember exactly, but they died.

DR. BRINKER: Let me ask the other question I have for you, and that is that unlike any of the other studies, and this may have an important influence on your data, 80 percent of your patients the first EKG showed asystole. Only 12 percent showed defib, and that may be a function of the delay it took for CPR or at least an EKG to be obtained. I am not quite sure, but this is a marked difference to any of the others and presumably defib is easier to resuscitate

although it might not be the case.

So, the question is do you think that the high incidence of asystole in your group is a function of delayed response, delayed CPR or do you think that you are dealing with a different patient population, and then some of the other things, and I think this is important as this device may be beneficial in a certain subgroup of people that are hitherto undefined. Certainly if you could tease out what subgroup would be best approached with this device it would be easiest to study this device in that subgroup and get a whiz bang result, and you wouldn't have to go through this process, but since we have a general population we have to look at everything that we have got, and one thing that does tease out is that you have a different group.

So, why do you have 80 percent asystole?

DR. PLAISANCE: We had 80 percent asystole because effectively the delay is very long. To know whether people, somebody is in systole or not you must have L2 cavascope. So, it was only in Paris at that time. It is only the ACLS team which has this kind of device. So, I think that perhaps if, and we are working on the suitable(?) defibrillators given to the firefighters for instance in Paris, and we showed that when they had the device we had obviously more ventricle fibrillation on the scene. So, it means that the delay to have systole is 20 minutes because

the ACLS team arrives after 20 minutes. We think that the percentage will be less if the firefighters, for instance or EMTs had defibrillators.

So, the delay is important in Paris and the delay to have the defibrillator is important because it is the ACLS team who is equipped with this.

DR. BRINKER: That could be a critical issue because you are taking worst case patients and finding some benefit. On the other hand, there may not be very many worst case patients if everybody got defibrillated right off the bat.

DR. PLAISANCE: The second part of the question that I can answer perhaps is concerning perhaps the benefits of this kind of device on systole patients, patients in systole. It is possible because we think that perhaps what one explanation should be that we have a high percentage of systole in our study and it is positive.

So, it is possible that in the systole we had we must have, and modalamex(?) is very important to achieve and if you have modalamex with drugs or without but with drugs suddenly it is better for the patients, and it is I think the same issue or the same results in the conclusion as all the studies in animals for instance where everybody knows that modalamex is improved with ACD-CPR, and it is the case, too, in a subgroup of patients I think in Germany where they

looked at the patients in systole. There was a trend of significant improvement with ACD-CPR in the same kind of patients, the systole patients.

DR. SITTER: May I comment further on this? When we did the analysis that was, also, one idea which came up, and if you look at all centers then the systolic, patients in systole may benefit more from an ACD treatment but if you looked especially to the Paris center it was very interesting that in the BF patients there the device worked as good as in the other patients concerning the odds ratios. They had the same odds ratios. That was very astonishing for us. So, it is no different in the Paris study from the patients in asystole and non-asystolic patients.

DR. BRINKER: That is an interesting piece of information.

Just a word to the St. Paul group. I think that you mentioned that if a patient got crossed over to the other form you excluded those patients. That is probably inappropriate. They should have been included as intention to treat and kept in the study, and so, I don't know what you meant by excluding them.

MS. GISCH: I need to clarify that. If they were randomized to receive standard they wouldn't have been able to have ACD because they wouldn't have had the device with them. However, if they got ACD and the medics forgot that

they had it and by mistake the patient received standard then they were randomized to that group. It was only in the patients that got both methods; they got 10 minutes of ACD and 15 minutes of standard CPR that got excluded.

DR. BRINKER: They shouldn't be excluded. They should be included as to whatever they were supposed to be randomized to, and that is an important issue with differences between the site protocolization and -- okay.

Just a couple or three more questions. One is did you look at how long CPR was carried out between conventional therapy and this device, and one of my thoughts is that one kind of sneaky mode of bias is that everybody that has this device at least at first thinks it is going to be better, and there may be an issue of carrying on CPR longer in people that get the device as opposed to people in the non-device group, and while I don't think that would have made a difference in terms of absolute survival at discharge, it might have made a difference with 1-hour survival. So, the question is do you know whether people in both groups got CPR for the same duration with their assigned therapy?

DR. PLAISANCE: I think it is in our first paper that the patients -- we have the time in travel between the collapse and the non-resuscitated CPR and in the two groups it is I think 55 minutes in the two groups.

So, patients had the same time.

DR. BRINKER: Excellent. Two more questions. One is there seems to be an increased incidence of respiration with, at least that is the suggestion with the device and one question is there somehow some physiologic means by applying suction to the chest that might favor aspiration of gastric contents? I am not sure what statistically but a trend would be different.

DR. SITTER: There is no statistical significance. The difference in the aspiration was not statistically significant.

DR. BRINKER: Finally, I guess a sort of final question is that it obviously takes training to use this device, and I would hope that if the device was approved it would be more than that couple of pages or one major page manual that you got up because I think that this would require a lot of hands-on experience and maybe visual aids, etc., and I am concerned about the fact that normally when one gives CPR, one has got a leveraged position by which to apply pressure and despite the suggestion that people tire out pretty quickly if they can do it a lot more easily I think than if they have to pull up against what could be a large patient and presumably a lot more pressure to expand the chest to any degree.

So, one issue may be if you buy the Paris data and

if you think that aside from possible differences in patient population that some of the benefit achieved might be the intense training that these people had previously it would be No. 1 important to replicate that training in the markets that you go into, and No. 2, if you were to do another study making the assumption that you would be strongly encouraged to do that, it would be important to do that study in an environment in which all the operators were totally well trained and fully capable of doing this, and if you were to do another study I would agree with Dr. Ferguson that you should, No. 1, pick your study population as carefully as you can and No. 2, look for surrogate end points that could be surrogate end points.

In other words, you know, intra-arterial pressure or something that you could get that would reflect a better CPR and maybe the claim might not be longer life but improved hemodynamics for this CPR which might be a valuable claim for you.

Finally, do you have a CE mark for this device? Thank you.

DR. CURTIS: We are going to be taking a 10-minute recess now.

(Brief recess.)

DR. CURTIS: As we get started again, I wanted to make one clarification. A comment that Dr. Domanski made

earlier might have suggested that there was a generalized discussion at lunch over the safety and effectiveness of this device, and I want to assure everybody here that that did not happen and remind the Panel members that that is the way it is supposed to be, that generalized discussions are held in public here in the room.

We have gone around the table once, and I want to make a couple of comments, and then we will go around and if anybody else has any other questions or concerns this last time around will be the time to get any of those last question out of the company members or people from the FDA if you want any answers.

One of the things I was impressed about looking back on this is the fact that if you look at the studies that are truly randomized there are really only three of them. Most of the studies had some sort of a systematic approach to whether the patients got the device or not, side of the city, day of the week, odd or even, first 75 days here, 75 days there, and it was the Canadian, German and Greek studies if I read them correctly that did not do that and were randomized, and those three all did not show any appreciable effect of the device over standard CPR.

Let me see if there is anything else I wanted to say in there. The problem with those kinds of systematic approaches, odd/even day or anything like that is the fact

that there is always that potential for some bias introduction not intentional but excluding the patient who looks bad enough that they are probably not going to make it, and there may be some biases there. So, I suppose one of the studies I am most impressed with is the Canadian study being as large as it was and truly randomized, and not being able to come up with an effect.

I was, also, impressed with the issue of the number of covariates. It was mentioned in the FDA executive summary and commented on by Dr. Wittes several times about the fact that there are study effects, initial rhythm on EKG, whether or not the arrest is witnessed or not and unless you include all of those and account for those in a combined analysis then you are probably not going to come up with accurate results.

There was the table that was discussed earlier. It is in the FDA summary, the table 4-16. I imagine it must be the way it was written out here, but in several cases the bottom of the table talks about minutes to CPR and minutes to EMS, and for example, in the Paris studies, it says, "Minutes to CPR 19.2, minutes to EMS 12.3."

If you read that the way it is written there it looks like EMS got there and waited 7 minutes before anybody initiated CPR. I am wondering if that is an error in the way the table was put together? Is anybody still here who

could clarify that?

It is the FDA table 4-16, and if you look at the bottom of that table I am just wondering if it would be more accurate to say, "Minutes to CPR and minutes from initiation of CPR to when the EMS got there," for example. I don't know.

DR. SPYKER: In fairness to the sponsor I guess I had better try to respond to that. There were two continuous variables measured, and it looked fairly clear that the first one was minutes to CPR, but the second one it is my impression from reading some of the individual studies they had somewhat different definitions. So, they are welcome to comment, but it is clear as you pointed out that those numbers don't make sense in the usual --

DR. CURTIS: In the usual way of thinking.

DR. SPYKER: So, I assume there are different definitions applied among different studies. That was specifically what they said when they explained why it was they did not use this as a covariate.

DR. CURTIS: That is something that just doesn't make sense, and I am sure the FDA put together the numbers that they had available. I am sure they did the best they could with it, and I am not sure there is going to be an answer you can come up with from that.

The other thing, too, is one of the things that is

really impressive is that it is impressive that in a situation where there was the longest time to beginning of CPR, namely, the Paris study that the short-term results were as good as all the other studies, where most of the other studies had response times in the range of 5 to 6 minutes or so, and yet the outcomes were just the same, and again I think this is peculiar. That whole study is a real outlier.

In most cases in the US the way we usually think about it, if it takes 20 minutes for somebody to get there an initiate CPR there is really no hope of resuscitating a patient, not one chance in three of getting 1-hour survival. So, it seems a little bit odd, and I am not sure that you could come up with a good explanation for that.

Those are the only other comments I wanted to make. Dr. Ornato has an emergency back where he is coming from. He is going to need to leave us soon. So, I am going to let him speak again right now.

DR. ORNATO: Thank you. I really appreciate your indulgence. A couple of points I would like to make. One is to follow up on the last point that was just made. The time at which ACLS was arriving in Paris is at about the time where resuscitation is being ceased in most typical US and Canadian systems. If you look at the St. Paul time of total duration of CPR it is at about the same minute or two

as the Paris ACLS game is actually beginning. That to me is a startling statistic because I think it sets the tone for these really are two very dissimilar systems and two very dissimilar questions.

Second is a point I would like to elaborate on that Dr. Domanski and I may agree to disagree on. I would like to further clarify what I meant before when I said that we may wish to make a distinction and perhaps the manufacturer may at a future date wish to make a distinction between trying to convince a panel such as this that this device is superior to standard CPR versus equivalent.

I agree, Michael, that if a device costs money, and this device or any other device is going to cost money - -

DR. STUHLMULLER: Excuse me. I need to make one clarification in terms of what the Panel needs to do is look at this in terms of what the indications for use are and whether the device is safe and effective in terms of indication for use and not to debate superiority versus equivalence. So, what you need to do is look at and focus the discussion on is it safe and effective for the proposed intended use.

DR. ORNATO: All right. Then let me go on to a third issue which really has to do specifically with the Parisian study and how it differs from other studies, and

perhaps to try to shed some light on why there may be a seeming improvement with the use of ACD-CPR as opposed to standard if you look very carefully at tables 1 and 2 in Patrick, Dr. Plaisance's study on Page 957 of Circulation there is a couple of interesting elements that I think are at the very least food for thought.

This is a prospective study. It is a pseudo-random design but it is clearly not blinded. We have all had some concerns expressed today about whether bias could have been introduced into the conduct of the study even though that bias if it were introduced certainly would have been innocent and not intentional.

I, therefore, have looked very carefully at tables 1 and 2 to see if there might be any hint that might support a hypothesis that there could be some perhaps subtle bias here, and if there is a hint I think it would go along the following lines.

If you look at the odd/even day randomization at the number of cases that were excluded due to terminal illness or time from collapse to initiation of CPR being greater than 30 minutes as judged by the ACLS team, you see that in fact more cases, a trend, there is no statistic here, and it probably is not statistically significant but the trend clearly appears to be in favor of the odd day which is the day in which ACD-CPR was apparently provided,

more cases with apparent or judged to be terminal illness or time greater than 30 minutes were excluded.

Perhaps more of importance even than that is table 2. If you look at the total duration of ACLS CPR you see that it is shorter for the group that received ACD as opposed to standard CPR. You, also, see in the column below it in the row below it that the total amount of epinephrine administered was higher, 15.2 versus 13.9 milligrams. Now, although neither of those variables is very striking in and of itself if you then ask the question in a slightly different fashion which is what is the dose of epinephrine given per minute of the ACLS resuscitation you find that in fact epinephrine was dosed more rapidly in the group that got ACD-CPR, on the average of 1 milligram every 1.7 minutes versus on average epinephrine every 2.2 minutes.

That is about 26 percent faster rate of administration of epinephrine. If you calculate it based on mgs per minute you are, also, looking at about 26 or 27 percent greater epinephrine per minute. Now, I obviously on the fly cannot do nor would it necessarily be appropriate to do on a variable like this, to do a statistic on it to see whether it reaches a level of significance, but I think at the very least it raises a question in my mind that there could have been some subtle biases here that their data may in fact support.

I guess the final point is that if you look at the total amount of epinephrine that was administered it is clear that it is higher than that which we during this time interval typically were administering in North America. The rate of administration of epinephrine in the Parisian study was varying between .46 and .58 milligrams per minute and if you look at the, for example, the St. Paul study the rate was about four times lower, 0.1 mg per minute.

Now, whether that is of any significance in terms of the physiology of this device I think is a totally open question, but I think it is very important to recognize that when we have got one study that seems to be coming up with a totally different answer than others there may be some subtleties that are at least worth exploring that might help us to at least somewhat account scientifically for why the differences are appearing.

DR. WIK: May I make a comment, please?

DR. ORNATO: Of course.

DR. WIK: Referring to the epinephrine use in the ACD group in the Paris study and indicating that the ACD-CPR group got more epinephrine than the standard group per minute if we recall the studies by Lintler who did the same in animal studies, Carl Lintler showed that epinephrine didn't have any positive effect together with ACD-CPR which counteracts your --

DR. PLAISANCE: Just to answer you concerning the doses of epinephrine per minute it was higher in the ACD group but not significant. We did study this.

DR. CURTIS: We will continue to go around. If anyone has any other comments or questions at this time at the far table?

DR. WITTES: I think I will try once more. I think what you are hearing from all of us is an understanding that it is very hard to do randomized studies in this setting, but, also, that places the burden, the analytic burden much higher. The hurdle becomes much higher because the analysis has to be extremely rigorous and actually kind of exploratory to see what the effects are.

So, I will ask once more for the following data, and it can come either from you or from FDA. I would like to see the logistic regression that led to the final analysis which is an odds ratio of .83 statistically significantly different from 1. I mean that would at least let me see what are the variables in there, how these interplay and so forth.

No. 2, I would like to see that same analysis or as best you could have done given that you don't have the individual data for California the analysis including the California data and that is what I need in order to at least understand the numbers in front of me.

MR. KAMER: Janet, I would like to answer that. In that we did not have the full analysis there we used some exploratory analysis done very quickly. Again, it is not our data set or our responsibility to do the analyses except to check but what happened was in putting in Newease(?) in jump, jump does not allow the process as was done by the sponsor of analyzing in a stepwise or any other wise. You choose what you want to put in and you put it in. So, we could not replicate that.

The problem was when we did work with it we put in no covariables whatsoever. We got the answer provided by the sponsor with covariables in it supposedly, and that was a problem.

We then entered I believe a few different, in an exploratory manner covariables they did enter. They were significant. So, it would be appropriate to enter them at least initially and of course as expected the P value or the -- let me put it this way, the P value associated with the treatment increased and no longer was the treatment really -- it was no longer indicated that the treatment was significantly affecting outcome at all or in a significant way, I am sorry, not at all, but in a significant manner.

DR. WITTES: And in the odds ratio did that group move closer to one at the same time?

MR. KAMER: The odds ratio in that case, I am not

sure that we did -- it would have. It should have because the upper confidence interval was already at .99 and doesn't have to go too much closer to one. It was over, and I think the P value becomes, even with just study alone entered, becomes .06 something. I read the number off. It becomes .05 something.

DR. BRINKER: Point 63 which is worrisome to me. I don't want to jump in here. It is hard for me to say that it is not significant because it .0563 and say that it might be worse if we put in the other factors. The .0563 to me is as close as you can get to being significant. I don't feel comfortable with saying that the data are no longer statistically significant because it is .0563.

MR. KAMER: The questions isn't that. The question is there is more. That is a tip of an iceberg perhaps if no other covariables were entered. How much of an iceberg there is I have no idea.

DR. BRINKER: I think it is important that we get something more than just, oh, it is .0563, therefore it is not --

MR. KAMER: We cannot do the correct analysis immediately. Now, we can go back and do that.

DR. BRINKER: It is hard for me to buy that I should ignore this as being statistically significant because it is zero point decimal places.

MR. KAMER: I think your question as to what the P value should be addressed to the sponsor not FDA.

DR. WITTES: But I think it does speak to my question because what I am hearing is that if you, what I read in this paper is that the estimate is .83, the odds ratio estimate and the confidence limit goes up to .99. I interpreted the language around it meaning that that included all the covariates that were chosen, and one of the covariates was the study.

Now, what I am hearing is if you put the study in alone you get not .83. You get something higher with a confidence interval what is wider. So, I, also, don't care whether it is .046 or .053. I don't think that matters. The question is is the .83 and that confidence interval that we heard is that the result of the analysis with all the covariates and what are those covariates. To me that is the question that I am trying to get the answer to. This is one step toward that.

MR. KAMER: Sure. I wasn't making the point that .056 is, you know, because it still leaves it up to the clinical decision. It is not just statistical but the point was Janet Wittes and I were, I think, agreeing on this that from what she said that we need to know what that number is. It might be .03, I am sorry, .3 or .28 and that is a big difference from .03.

DR. WITTES: Or it might be 024.

MR. KAMER: Exactly. It could go either way although our preliminary analysis didn't -- it went the other way.

DR. SITTER: For 1 hour survival the odds ratio from the random effects model was addressing Monulaip(?) methods which is described in this pack. It is demonstrated here and you see that we have here 0.8 a the odds ratio and the confidence interval where the left limit is here and the right limit is here and this confidence interval is away from the one. So, it is 20.999(?) that is away from the one and in this method we have all the factors as covariates considered.

DR. WITTES: Do you have the output with the numbers? That is really all I am asking.

DR. SITTER: I have just the graphical form with me, not the numbers now here for our system but we designed this graphic in the usual way to present it, for instance, Cochran collaboration recommendations to put it in such a form.

DR. BECKER: May I try one time? Is this adjusted data?

DR. SITTER: Yes, this is adjusted data.

DR. BECKER: What was it adjusted for?

DR. SITTER: That is adjusted for the centers

where we looked at the variations and take this into account. It is adjusted for the centers.

DR. BECKER: So, those are the only variables in the logistic regression? In other words, I think where I am confused is what I am trying to figure out is witnessed cardiac arrest taken into account. Is initial rhythm taken into account? Is age taken into account, and so, is that the question that you are asking, and so, that is where I am confused right there.

DR. SITTER: Yes, we did logistical regression modeling where we have, also, ECG and so on, ECG, age and, also, center in it. Here in this one where we looked at these odds ratios and did it according to the Desimoni-Layitt method that is the center effect. The center was covariates.

DR. WITTES: But do you have the final model that has the center, all the variables that you included in the model and the Dersimoni(?) and Laird? I mean that was the final analysis.

DR. SITTER: The final analysis from this with the model I showed it here which was selected. That was first the centers and it was when we looked at the centers and we modeled the centers as dummy variables for this logistic regression because you have to do this because you have not just the center zero and center one, it goes up to seven

different centers, and if you do this we have, also, faults that all the centers come into the model and then the final model is that the centers are in and that the ECG rhythm is in and that the age is in on the priority for discharge survival and ACD standard is not in for discharge survival but it is in for 1-hour survival with an odds ratio where the confidence interval for this odds ratio is from 0.8 to 1.05 for this category.

DR. WITTES: Okay. So, if you include all those variables this is not the picture that you see. You see a picture with crossing the one. If you do that and added the Dersimoni and Laird random effects would that widen it still? I mean what is actually kind of surprising is that this, the Dersimoni and Laird usually widens the confidence but not narrows it. So, it is surprising to me that this is narrower than yours, but I don't think, I mean I think we could go on and on forever.

What I need to see is the results, those numbers, each of those covariates and each one's estimated coefficient and the estimated confidence interval for the overall effect. Otherwise it is very hard for me to go the first step, and that is really all it is because then we have to think about what are the effects of the bias, but at least that puts down on the table this is the best estimate that we can get out of this set of data.

DR. SITTER: If we look at the centers that is here in this graphic form, and I have it not with me in a form where you say that the odds ratio as written down there and the confidence interval is written down from this and it is depicted here.

DR. WITTES: Thank you.

DR. CURTIS: Let us move on. Any other comments over there?

DR. SETHI: When you look at the study published by Carl Curant(?) University of Arizona he showed no difference between ACD-PCR compared to the standard CPR in pigs. Could you explain to me why they did not show the difference? Did you have discussion with the investigators why they could not show any improvement? This is especially when you are looking at six or seven out of eight studies, there is no clinical improvement, and it, also, correlated with the animal studies. It kind of bothers me a lot.

DR. WIK: It is very difficult to comment on studies which have not been brought to the Panel here.

DR. SETHI: This is in the Panel pack here. It is a study in the Panel pack.

DR. WIK: I cannot speak on behalf of Carl Curant actually.

DR. SETHI: I am just asking the question that you know here you are presenting the data saying that this

device is superior in human beings.

DR. WIK: What we have done --

DR. SETHI: Let me just finish? But even in the animal studies we did not see any difference. So, I am asking the question why is that. You must have seen this abstract and gone over this Panel pack. Any idea why we don't see the difference?

DR. WIK: Are you referring to the from Circulation in 1995?

DR. SETHI: That is right, yes.

DR. WIK: The comment I can make is that it is very important to know how you adjust the mechanical device when you are performing both standard and ACD-CPR, and if you are not doing that the correct way you can get into problems with showing differences. These studies and another thing which is not measured here is intrathoracic pressure. So, in other words how do we know that they have performed ACD-CPR but then not referring to intrathoracic pressure measurement.

The other studies which we have referred to have measured the intrathoracic pressure, and I think that is a very, very important thing to focus on that when we are discussing animal studies and maybe also clinical studies you should really know what we are discussing that we are comparing apples with apples and that we are really knowing

that ACD-CPR is performed.

DR. SETHI: And that is kind of a surrogate for your intrathoracic patients?

DR. WIK: No, no.

DR. SETHI: Or the effectiveness of your device?

DR. WIK: ET-CO2 is not, reflects, of course, not the intrathoracic pressure. ET-CO2 reflects blood flow.

DR. SETHI: It is a surrogate for your blood flow. As I understand you are saying that your ACD-CPR does increase the blood flow, and your ET-CO2, also, is a surrogate for similar --

DR. WIK: What we say and others have said is that ET-CO2 correlates well with coronary diffusion pressure and blood flow. It doesn't correlate necessarily with intrathoracic pressure. That is totally different.

DR. SETHI: Yes, but what means the same thing to me is that your proper blood flow which is to the brain and to the body is to me, is reflected by your ET-CO2 and when you look at the experiment which is nicely done and you don't see the difference in survival, when you don't see a survival difference in seven out of eight studies it is bothersome to me to say the device is really effective.

DR. WIK: Then I am asking the question how do we know that they really had a negative intrathoracic pressure?

DR. SETHI: That is not my responsibility. That is

your responsibility to find out.

DR. CURTIS: Dr. Domanski, any other comments?

DR. DOMANSKI: I don't think so. I think I have really said what I had.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: I don't have any questions.

DR. CURTIS: Dr. Ferguson?

DR. FERGUSON: I just have one question that relates to product liability and safety. The device has been introduced into 70 countries you said, and I don't know how many have been sold nor do I care to know, but I would like to know if the company would recount their experiences in terms of whether they have had product returns, whether they have had problems with people writing in and saying that the device doesn't work properly, etc., like you would have with any product.

DR. LANGE: No.

DR. FERGUSON: Thank you. You don't need to be so verbose about it.

(Laughter.)

DR. CURTIS: Dr. Brinker?

DR. BRINKER: I have one question for John, actually, and I think this may be an important question. You suggested a few minutes ago that we were not here to determine whether this was equivalent or superior to option

alternatives. We are here to decide whether this was safe and effective as a therapy for CPR. Is that correct?

DR. STUHLMULLER: Yes. I will answer and then Dr. Callahan might want to elaborate. My understanding is based under FDAMA the evaluation of safety and effectiveness has to be in terms of what the proposed intended use for the device is, and so if we make a recommendation it has to be based on the indications for use as to whether you feel it is safe and effective for its intended use.

DR. BRINKER: I think this is an exceedingly important question, and here is the reason I am putting this into context. If I feel that CPR the standard way with just my two hands at least for cardiac compression or chest compression is relatively safe and relatively effective, and I think that the data that is submitted here, and there will be discussion about that, probably shows at least that there is no difference between this device and regular CPR; it might be better, but there is no real evidence in my eyes that it is clinically, but it certainly seems as good, the question I have, however, is that usually we would say that a device, that I could say that regular CPR is done with an invisible device like this, if I had an invisible device and just used my hands, I would have the same results, and now I have this device.

It isn't invisible, but it enables me to use my

hands in a different transducer way, gives me the same results, is there an implication there that this -- that is all I have to say is using this device as a transducer for my hands gives me the same effect as my hands alone and that is effective, and it is safe, and this device will be approvable? That is a key question for me, and you have to answer that.

DR. STUHLMULLER: I defer to Dr. Callahan. My point was to make sure that the Panel discussion stays focused and for the policy I defer to Dr. Callahan.

DR. CALLAHAN: I think what you hit on is the exact issue before us and that is in your clinical opinion for this device what is the appropriate control for this device to compare it to. Can you compare it to conventional CPR and if you can compare it to conventional CPR it doesn't have to be better than CPR necessarily, but perhaps is there a subpopulation that it is more benefit for, but the question is one of it has got an intended use; do you think that there is real assurance in some significant population that the use of this device under conditions of use will provide clinically significant results and part of that is the underlying question. What do you think is the device to compare it to, if you had as you said, CPR with in your analogy an invisible device and now you have something else that does the same thing are you doing any more than

conventional CPR. That is the question before the Panel.

DR. DOMANSKI: You know, that actually clarifies it, makes it easier, but I am not so sure that this does show equivalence with standard CPR, and maybe I could ask the statisticians whether this is an adequate equivalence study even if you were comparing it? That would seem silly, but, Janet is this powers of equivalence study?

DR. WITTES: First of all, I don't think it is power. They weren't designed as equivalence studies but also, if there are biases I don't think the fact that we see mostly the studies on the good side means equivalence. I think we still have to have the analysis, the really critical analysis to see whether in fact the estimates stay comfortable and furthermore the confidence intervals of the individual studies are very, very wide which I think is what Mike was talking about which is different from what equivalence study is.

So, I guess until I hear the argument for equivalence I don't see failure of being better as synonymous with equivalence.

DR. DOMANSKI: One other comment I would make about that is I think that studies that are not randomized are really in this particular case not very useful. I think you are left with three studies, and Paris isn't one of them.

MR. PILOT: May I be recognized? I am Larry Pilot, counsel for the firm and appreciate that Dr. Callahan attempted to clarify what the criteria in the statute are and particularly Dr. Brinker raised the question that he did because the responsibility that you have as advisory committee members, and there is a distinction between advisory committee members and consultants who are given temporary voting status is to apply the criteria in the statute, that is the federal Food, Drug and Cosmetic Act which provides that you evaluate, in giving your recommendations to the agency in the context of reasonable assurance of safety and effectiveness, and I believe that the discussion that Dr. Ornato provided earlier was a good reflection of what you need to consider in balance with respect to whether or not this device is equivalent to standard CPR.

Clearly on the safety issue I believe you have spoken quite clearly on that subject, and there is no dispute as to safety.

With respect to the effectiveness is there reasonable assurance of effectiveness for the claim? Now the claim, of course, can be modified. The indication that the company provided to the agency is their perception of an appropriate claim, but clearly that is something that can be modified as part of your discussion, and finally in the

context of what the company is attempting to do here, it is make this device available to practitioners in this country, first responders who can decide for themselves whether or not this is an adjunct to CPR that they would like to use as there are many adjuncts to CPR that are available in the marketplace today none of which, not a single one of which has gone through the premarket approval process and that concern also, applies to AEDs. We have heard discussions about AEDs. There isn't a single AED for any device that I am aware of in the chain of survival that has gone through the premarket approval process.

So, your mission today, of course, is to consider the information, and it is not just the combined analysis. Those papers and the additional documents that were submitted in support of the claim by the company. So, I appreciate your listening to me.

Would you like to recognize Dr. Alpert?

DR. CURTIS: I would not dream of doing anything else.

DR. ALPERT: I am Susan Alpert. I direct the Office of Device Evaluation here at the center, and I would like to do some clarifying. First of all, Mr. Pilot's comments about devices not coming through the premarket approval process are absolutely right. Ninety-some odd percent of devices going to market in this country go

through a premarket notification process which still is FDA clearance. It is FDA oversight, and it is a premarket authorization.

The rationale for a product of this sort coming to a PMA, a premarket approval application has to do with the fact that there is no predicate for this device, and the device therefore has to establish independently that it is reasonably safe and effective for its intended use as labeled.

That was getting to Dr. Stuhlmuller's comment. It is as labeled. The issue is does the evidence in front of you, we are asking for your advice, your opinion as to whether the evidence presented in this premarket approval application provides reasonable evidence that the device will be safe and effective as it is labeled for its intended use.

The fact that the control in the study is standard CPR has to do with the ability to control a study in a first-response situation, but we are asking does the data, does the evidence support a reasonable level of safety and effectiveness, reasonable assurance of safety and effectiveness as labeled.

The concern about whether or not the device is equivalent to or better than CPR is a postulation that we will have to determine based on your advice as to whether

there is evidence here that it is safe and effective as labeled.

The question then if depending on your recommendations would be how we regulate, what the labeling needs to look like. As Mr. Pilot said, "Labeling can change," and that is the kind of advice that we are looking for from you, and the questions that will be raised for your discussion, but as was pointed out it is reasonable assurance of safety and effectiveness, and it is as labeled, and we are going to get an opportunity now I believe to talk about those questions.

DR. CURTIS: Thank you.

Dr. Becker, any other comments?

DR. BECKER: No.

DR. CURTIS: Okay, at this point what I would like to do is start us going through the questions. Now we are going to get through these and then before we get to the point of the actual Panel recommendation there will be an opportunity for the company to make a few comments if they would like, and, also, the open public hearing will be done at that time.

So, what I would like to do is start with the questions and see what kind of a consensus we can get with them.

The first one that we have has to do with primary

outcome issues. In the evaluation of the Ambu CardioPump CPR assist device there are several important outcome measures including return of spontaneous circulation, 1-hour survival, 24-hour survival, discharged from the hospital alive and discharged from the hospital neurologically intact. The question is what is the right level from the above list to establish clinical benefit? For example, suppose an adjunct intervention substantially improved ROSC rates but had the same or lower survival to 1 hour or to discharge.

I will open that to any member of the Panel who would like to make comments or start the discussion.

Dr. Domanski?

DR. DOMANSKI: I am not sure that I know the right answer to that, but I think it should be set higher on that list rather than lower, that is 1 hour or perhaps 24 hours because in the business of dying suddenly and being resuscitated you know you do that for a lot of reasons that no device that supports circulation initially can help so that I think to be a strong link in the chain a device for instance like this one, if it could show early return of spontaneous circulation and 1-hour survival I think it would be pretty compelling.

Now whether it should be 1 hour or return of circulation or 24 hours I am not sure but I think it

certainly should be that rather than discharged alive.

DR. CURTIS: Personally I would have to say that I believe the 1-hour survival is something that would be important because as we have been mentioning before you have all these parts of the chain of survival and all that, and I would expect the devices being used in CPR to be helpful in getting a patient alive to the hospital. To say that that, you know, you would like that to mean that they, also, get discharged from the hospital alive, but there are so many other variables that are included in that that I think that would be nice, but in my own mind I don't believe it would be necessary to prove that in order to say the device was effective.

Return of spontaneous circulation though I think is a little bit, that is one I personally wouldn't favor because there are plenty of times during a resuscitation attempt that everybody feels a weak pulse transiently. Sometimes that can even be a little bit subjective I think, and I don't know that I, myself, would want to hang my hat on that one as if we got any return of spontaneous circulation that that would be good enough for an intervention.

The way I look at it, I would be in favor of the 1-hour survival idea, but I think we need to hear from other people.

DR. TRACY: Anne, it strikes me that the other types of interventions that we do for patients with sudden death we are looking at long-term survival. We want to improve long-term survival. I think you are right that there are parameters and factors involved after the initial resuscitation that are going to determine that may be putting too great of a burden on the initial resuscitative attempt.

However, if you promptly did resuscitate somebody you would expect to see a better long-term survival I would think. If it was really terribly effect at an initial resuscitation I think it would translate or you would like it to translate into better long-term survival.

I agree completely that the return of spontaneous circulation is too subjective, and it is asking too much of a compression device to somehow return spontaneous circulation, but I would think that at least 1 hour, and I think we should look at discharge from hospital alive.

Just parenthetically discharge from hospital neurologically intact certainly if some of these parameters of improved hemodynamics and cerebral flow were translated into actual benefit for the patient you would expect a greater degree of them being neurologically intact that are not, but I don't know that I would hold it to that.

DR. CURTIS: One other thing you might think about

as an analogy might be something like epinephrine. We use epinephrine during cardiac arrest. We are looking for a short-term goal. I don't think anybody would look to see whether or not the patient got out of the hospital to decide whether or not we would use that drug during a cardiac arrest situation. We are looking at more short-term outcomes. Did we get a blood pressure? Did we get a pulse? Did we get him into the hospital?

DR. BRINKER: I would like to turn this around a little bit. I think that we may be asking an awful lot of the technology for the kind of group that we are looking at. I think for these outcomes I would like to be reasonably sure that in a hierarchical status that there is no disadvantage of a device over standard CPR in terms of discharge of a neurologically intact patient because you could for some reason like give a whole lot of epinephrine, get a heart rate back that lasts for a few minutes and that could stroke out the patient or something else and turn out having a better spontaneous circulation incidence but a worse incidence of getting out of the hospital in worst case.

I think in something like this if I were to have designed a study perhaps I would looked at how good this device was at supporting the circulation because that is what it does, and I would want to know that it did that and

document that, and then I would want to know that it was no worse at least than the standard care and all these other things.

DR. CURTIS: What would be your outcome measure then?

DR. BRINKER: I might look just as Tom Ferguson was suggesting at some of these measurements of either blood flow, blood pressure, cerebral flow maybe, cerebral doppler, or something during the actual CPR, and I know that that is not easily done when you are going out in the field but it is rather easily done in a relatively small number of patients for in-hospital arrest, and my feeling would be that if you got that kind of data and showed no detrimental effect in these larger studies then one could justify some sort of labeling.

On the other hand, I think I personally think that if this did no better than CPR that labeling obviously cannot reflect any of that and it becomes a question whether a transducer to one's hand should be, would even be a viable product.

So, if I were the company I would urge them to seek in a small well-defined study using well-defined easily obtainable end points some benefit.

DR. TRACY: Jeff, in Section 5 combined analysis on clinical studies, Page 15, there is a pretty remarkable

study of evaluation of standard and active compression CPR in acute human model of ventricular fibrillation done during defibrillator implants.

Amazingly enough the ACD versus CPR was evaluated and what they did find was the mean coronary perfusion during the compression phase was higher with the ACD than with the standard CPR. So, to make a long story short in this model where patients underwent multiple inductions of EF with each subject acting as his own control ACD-CPR significantly increased arterial blood pressure. coronary perfusion pressure, minute(?) ventilation and negative inspiratory pressure compared to standard CPR.

Now, I don't know why -- there are some interesting human data in this section that we haven't talked about, I think because we have been concentrating on the studies, but this is sort of an isolated --

DR. BRINKER: That is the kind of data I would want, but I would want it in a different milieu than elective ventricular fibrillation. I would want it in a spontaneous situation to show that over some period of time that this is effective in maintaining these parameters, and I think that could be done relatively straightforwardly and easily, and all I want from the large studies because I think it is so difficult to show a difference in what you really want which is discharge from the hospital, I just

want some reliable reassurance that this isn't detrimental.

DR. CURTIS: Let me ask you if you could take that study on the defibrillator patients and do it in a small group of patients who had a cardiac arrest, same thing and you show the improvement in coronary flow and the other factors that are there is that good enough, even if 1-hour survival is no different to prove efficacy?

DR. BRINKER: To me it would be as long as there is no detrimental effect of the device compared to normal.

DR. CURTIS: Dr. Ferguson?

DR. FERGUSON: I would like to agree with you about the 1-hour survival time. I think from a practical standpoint the idea is that any device whether it is a hand or this device the goal is to move them along in the chain, and if we can get patients to a situation where we can get hopefully all the patients but at least many of the patients to the hospital setting then we have got a better chance to move them along.

As regard to the comments that were made just now I couldn't agree more. I think physiologic studies combined with this could be a condition of approval in the way we have done with some other devices that have come through here and ask for the company to set up a study which would be a postmarket approval.

DR. BECKER: I guess I might disagree with some of

the comments on the Panel just in that I think you have got to show discharge from the hospital as a primary end point and the reason I say that is we learned a lot from the epinephrine studies that we did where I can just show you gew(?) gobs of studies. That is a statistical term.

(Laughter.)

DR. BECKER: That show increased ROSC, increased 1-hour survival and even increased 24-hour survival. What happens those patients end up dying of postcardiac arrest myocardial dysfunction, and it happened in the peds patients and it was completely mystifying to all of us who were involved in those studies as to how on earth could it be that after this deluge of animal data on high-dose epinephrine how could the clinical trials that took place be coming out like this, and actually one of the investigators who has been referred to here was very involved in it and just had to seriously eat crow with major criticism of looking at that as an end point, and so, I guess I am going to make a strong pitch that discharge from the hospital alive is something that I think needs to be demonstrated before one can really feel reasonably comfortable at making kind of large policy type decisions, and certainly I can tell you that the thinking among my colleagues at the AHA in terms of levels of evidence would involve probably that outcome.

Now, I don't think you have to take it all the way to neurologically intact, and the reason that I don't -- I think that is optimal if you have that data. It adds a lot of cost, but most of our studies show very similar neurological scoring.

I mean there is like between 60 and 80 percent neurologically intact survivors in virtually every study that has ever been published, and so, the thing is as we look over a huge amount of data that number doesn't seem to change very much as you go through.

So, I am not sure you have to go that far, but I want to make a pitch that as an outcome variable that is what you need.

I see these other ones and certainly the physiologic data as being important process variables that I would like to see, but I think in the final analysis before devices are let loose into the public you have to show the discharge from hospital.

DR. FERGUSON: I couldn't disagree more with that because that is asking the company to control areas of the patient care that they cannot control, and if we read the labeling for the device this is for its use in emergency situations out of hospital.

DR. GILLIAM: While I will disagree, I think the gold standard to all of our efforts to resuscitation is to

get the patient out of the hospital neurologically intact. I think that may be the ultimate goal. I think these other end points, obviously if you don't survive the 1 hour you won't be discharged from the hospital.

So, I think the 1-hour survival is an important mark along the way, but ultimately the discharge from the hospital neurologically intact if we look at studies like this I think those data are pretty important for us to make these decisions.

I think those two end points I am happy with. I think the 24 hours doesn't necessarily add anything to me nor do I think the return of spontaneous circulation is that particularly important, but I think if we are going to look at someone discharged from the hospital, quote, alive, that you may as well do that one complete and look at the neurologically intact patient and see whether you are really making a difference long term.

I don't know exactly how you would go about looking at blood flow in humans. I am pretty surprised that they were able to repeatedly do CPR on patients during implant of the defibrillator. I would hate to have been the IRB person to try to pitch that to my IRB board.

They never in 100,000 years would allow you to do such a thing. So, I think you might be putting the bar a little high if we ask them to say, "Let us electively put

people in VF and measure outputs."

DR. BECKER: Just to clarify that, they only did that when the defibrillator failed, and they had to do CPR anyhow, and all they did was use the two different techniques. They didn't do exactly what you are saying.

MR. JARVIS: I can clarify part of that. The study that is being referred to, the Minnesota study actually these are ICD patients that are in the OR having the ICD implanted. So, they fibrillate them anyway to make sure the ICD is working correctly, and in that area, in that time frame the patient is defibrillated or in VF. The IRB allowed a 60-second time frame to either do standard CPR or ACD. Then they went ahead and started the defibrillator.

DR. DOMANSKI: That remains a little scary though because that is not how you usually do it. You usually buzz them a little before you have to pump.

DR. GILLIAM: You shock them more than a couple of times before you pump, if necessary, but other than that I think those are the two end points that I think are going to be very important no matter what cardiac resuscitation device or devices.

I think the 1 hour and discharge from the hospital neurologically intact would be kind of hard to argue.

DR. CURTIS: Okay, any other comments on that first question?

DR. SIMMONS: I guess I would like to comment. I guess I have to disagree with Rosie. I don't usually do that but I do this time. I think it is putting a burden on the device that we are not even saying that the device wants to claim. I mean the idea is we want to get them to the hospital alive, and so you want to resuscitate them from an acute event.

A lot of these patients maybe shouldn't have been resuscitated in the first place. A lot of them may have had a myocardial infarction. They may not have enough muscle to live anymore, and you are going to have to do a huge study to ever show any improvement I think in discharge out of the hospital.

So, I think you have to go back and look at what you are claiming the device is going to do, and if the device is supposed to produce CPR, resuscitate the patient and get him into the acute care facility I don't know whether I really care about discharge from the hospital. If you are going to claim that the device improves cerebral perfusion by 180 percent during CPR, then I think you have got to prove that the patient gets some benefit from that claim, but if you are just going to claim the device gets the patient to the hospital with intact heart rate, blood pressure and can be admitted to some sort of CCU I don't think 24 hours, that would be good. One hour would be

better.

Return of circulation, I actually kind of like that one and discharge from the hospital I don't know that I would necessarily make them prove.

While I have still got the microphone, let me comment on that. Sitting here thinking about this issue of equivalence and what to compare it to and you cannot compare it to nothing. I mean what are we saying, "It is better than watching the patient die or what?" I mean you have got to compare it to something, and so if it has got to be at least as good as what I have now which is manual CPR, it has to be at least as good as that and then maybe at least have some other potential benefit that can be proven one way or another, 24-hour survival, something like that.

DR. GILLIAM: I don't think we disagree on that. I think though what I meant as far as discharge from the hospital neurologically intact, I think that is a piece of data that in the future, not necessarily to hold the company to showing that for a device like this, but that is important information because it may show that if we can get survival for 1 hour that it may have late-term benefits that if we just allowed them not to even look at it we may never know.

DR. CURTIS: I think the way I have been looking at it is that your primary outcome measure would be 1-hour

survival but I think you definitely ought to collect information on whether or not they are discharged from the hospital alive just not have that be the primary outcome that you are looking for statistics on.

DR. GILLIAM: I agree with that.

DR. CURTIS: Good.

Let us go to No. 2. What is the most appropriate measure of neurological function? Any volunteers on that one?

There is a scale used and I don't know --

DR. BECKER: OPC and Glascow(?) and Comma(?) scale are probably the primary ones that have been used. There is an overall performance category.

DR. CURTIS: Any other comments on that issue?

All right, we are going to move on.

DR. SETHI: I think it would be nice to have a neurologist's input on this particular issue. I don't feel comfortable in telling you about neurological function. I am not expert in that, but it is worthwhile getting someone. Maybe Dr. Becker is an expert in that and if that is what it is, that is okay with me.

DR. BECKER: What I really should have said to this one is it depends on what the question is, and so I don't want to say that this is a poorly worded question, but this is a poorly worded question, and the reason is it

depends what you are trying to show, and so, you know, the most sensitive neurologic indicator is actually very subtle stuff that can only be picked up on neuropsychiatric testing, but you are not going to do that in a study of 10,000 victims of cardiac arrest where you are going to do neuropsychiatric testing on every single survivor. This is not going to be feasible, but the question is you know what really is your question.

If you were giving a neuroprotective agent during cardiac arrest and asking what the effect of that is I think you would be held to a much higher standard in terms of neurological functioning. I think if you are looking at some of these other things it is different. So, I really think it just depends on your question.

DR. CURTIS: All right, No. 3.

The combined analysis evaluated the results from seven separate clinical studies. Only the Paris study showed a statistically significant survival difference for ACD-CPR. This study has major methodological differences from the other six studies and the results of the Paris study strongly influenced the survival difference in the combined analysis. Is it appropriate to include the Paris study in the combined analysis?

DR. WITTES: It seems to me again this is a what is the question kind of question. If the question is here

is a device used in this country with the patterns of care and the patterns of when people come, how people are resuscitated and how the ambulances get there and so forth then it seems to me this is not, should not be included.

If on the other hand this were a, well, yes, maybe that is the period. If that is the question then I think it should not be included.

DR. BRINKER: I think it is most important to include it for safety data but for efficacy data I agree.

DR. CURTIS: So, for efficacy data you would not want to see it included. All right.

Other comments?

DR. FERGUSON: Yes, I hate to be the maverick here but I don't understand how we can sit here and pass judgment on an outlier when we don't have any specific exact reason why. I have heard the statisticians talk back and forth about this at a level that is over my head, admittedly, and maybe I am missing the point and I would be happy to be instructed about it but I think they went to some care to be sure to include all the studies they thought were appropriate for their analysis, and perhaps we could move from that point to throwing out all of them but the three. You know, I don't know if that is what our job is to do. That is my question I guess.

PARTICIPANT: I certainly would suggest that.

DR. BRINKER: Maybe I can cut to the chase because some of these questions are designed to answer from an approach a matter that maybe can be shortcut here. One issue is approval of this device with the claims that the company wants associated with that device, and that is why this discussion is taking place because those claims are based on the suggesting that the combined analysis is, and this is that there is some meaningful clinical benefit in terms of the survival, the use of this device.

Now, if the company or if we were to suggest that for instance that there isn't a, because of the methodologic differences and everything else, all the doubts that we have about the nature of the studies and the statistical analysis that went into them, if we were to suggest that for the short run at least that we don't have evidence that this is a superior efficacy than CPR but that it was as safe as CPR and the data would suggest at least to me it would suggest that it is not worse than CPR in terms of efficacy, then I might be able to want to discuss an approval as an alternative without any claims of superiority and it would enable me to suggest that, and then I would suggest to the company that they go and do the right study to show some clear-cut benefit to this device over CPR if such exists, and that is why I where do a specific subgroup and a well-defined end point that they should be able to obtain, and

that is the way -- that would be my rationale.

DR. CURTIS: To me the way this question is worded it sounds like a very bottom line thing where you either say, "Well, we either put the Paris study in and therefore it is positive and it helps, and that is the answer," or we take the Paris study out and then it is a negative outcome or no difference and then that is the bottom line, and that kind of negates the entire discussion we have had all day long here about the differences in the studies and whether they were randomized or not randomized, and I think the consensus here is that I am not so sure you have to come down to am I going to include the Paris study or not.

We recognize problems there in the analysis of the data, and I don't think we ever did get that covariable thing really answered and it is not going to happen today, so we are not going to go through that anymore, but I think what it comes down to is that it is not so simplistic, and it doesn't require that we keep the Paris data in or we take the Paris data out.

The truly randomized studies didn't show a difference and this one here that we thought there were some problems with was different enough from all the other studies that we had some concerns with it, and I think there is going to be a general consensus that there has not been proven beyond, to a reasonable degree that there is

superiority to this device over standard CPR.

DR. TRACY: I guess the question would be if we just look at the randomized study, and we see that there is not a difference I think we will probably accept that, but does that prove, can we prove equivalence on the basis of that?

DR. WITTES: I think it depends on the estimated confidence interval of the pooled data and that we don't know the answer to.

I mean if that confidence interval were very narrow, then it seems to me that is equivalent, but if it were very broad and actually included a high probability of harm, then I think even those three together don't show equivalence, and that was really what I was meaning that I haven't seen the data put together to answer the equivalence question.

DR. CURTIS: So, that data could be available, might be something we could look at, but we don't see it here now is what you are saying.

DR. WITTES: Yes, but intrinsically it is here.

DR. CURTIS: Okay, other comments?

I think No. 4 is going to be easy. It says that the Paris study included use of an automatic mechanical ventilator in the breathing circuit, and I think that has been dispelled that that was not true. Did I hear that?

DR. BRINKER: No, that was dispelled that there was an impedance but we never dealt with --

DR. CURTIS: All right, let us go through it.

DR. BRINKER: It is a mechanical ventilation that might help.

DR. CURTIS: All right. So then can we reach conclusions about the safety and effectiveness of the ACD-CPR without the mechanical ventilator from these data?

DR. SETHI: I don't think so because part of the study was that they used a mechanical ventilator. It goes hand in hand or at least I cannot reach a conclusion that the Paris study shows, I mean I cannot say that without the mechanical ventilator ACD-CPR is any better than standard.

DR. CURTIS: Okay, other comments?

All right. Let us move on.

Now, we get to methodological issues. What other statistical or methodological approaches can be used to analyze these studies in a combined fashion, taking into account that the studies differ in study populations, protocols, investigators and countries?

Maybe, Dr. Wittes you could summarize what your thoughts have been about this?

DR. WITTES: Okay, I guess I am not actually as rigorous as Mike. I mean I think that ideally it would be the three randomized studies on their own. I think though

that one could take these non-randomized studies with their biases or their perhaps biases and try to do some exploratory modeling, some sensitivity analysis, something to build in what do you think the amount of bias, what is a reasonable amount of bias that one would feel, and I would do really a lot of analysis, not just a few and look at the sensitivity of the estimated odds ratio as a function of the various models and the various kinds of playing around with the data. To me this is a playing-around-with-the-data kind of analysis.

DR. CURTIS: A little bit of a problem I see here is that Questions 6, 7 and 8 are kind of the same.

DR. WITTES: Yes, actually, you know, some of the meta analysis people recommend putting in some sort of weighting factor, and that is related to No. 6. You weight various studies by their validity, and there is a huge literature on how to put together studies of various quality and various sizes and so forth and again I think in a situation like this where you are really doing, yes, you identified, I mean the investigators identified the studies prospectively and then identified a method prospectively, and that should be I believe the primary analysis, but then because of all the problems you do the best you can to see how robust that primary analysis is to reasonable assumptions that are different.

DR. CURTIS: How do you do that?

DR. WITTES: Oh, I think you do lots of analyses, lots of models, lots of graphs, lots of numbers and you look to see in a very qualitative way, you assess in a qualitative way the quantitative results. That is the best I know, but I think it is really important not to come up with just one answer because there isn't here.

I mean you want to look at, you are not going to summarize by one number. You are not going to summarize by one P value. You are going to look at the effects of various covariates, how important are they individually; how important are they collectively; how do they influence the estimate of treatment effect, and none of this can ever be as satisfactory as either a large randomized study or a meta analysis of only randomized studies, but I guess I believe there is a place for getting what you can out of data that you have as long as you build in some sort of sensitivity.

DR. CURTIS: If you look at No. 7, they are talking about the strengths and weaknesses of the various options. You said that you would look at it in various ways and look at graphs, look at tables, look at data that come out.

Is there any guidance you would want to give the FDA about strengths and weaknesses of various options or is there a preferred initial approach; is there any way to

start that you would favor?

DR. WITTES: I certainly would have started with the three randomized studies, and I would have done that and looked at okay, the three randomized studies, what did they show, and then take on the other studies perhaps in decreasing order of what seems like the likely effect of the bias.

I mean that to me is the most important thing. I would not exclude California. I mean that is the second-largest study. I would have that. Any analysis that I could put California in, it would be there, and I find I am very uncomfortable without seeing the California data.

I mean I guess to me you want to get as much data and you want to look at the analyses in as many different reasonable ways as possible and if the results come out very different then you don't have an answer. I think that is part of it. If reasonable approaches give you different answers then it is hard to interpret the data.

DR. CURTIS: So, at least for No. 6, I mean I think with other things we have said that we favor the randomized studies, and even if it is qualitatively in our own minds we are giving them more weight than the others ones, and then you add the other ones in the way you mentioned.

Any other comments on these? They seem to be more

statistical and study design issues.

Okay. No. 8 says, "Based on your discussions of these methodology issues have you been provided an adequate analysis of these data?

I think the general consensus would be no in that there are things that you have mentioned all day that would have been nice to have seen here. I don't think we have to go back over that again.

All right, let us go on to No. 9. Do the following indications for usage adequately define the patient population for which ACD-CPR would be appropriate?

Now, I have been told that there was different wording in the Panel pack than in what our questions are, and so this is what we are being asked to discuss is what is being displayed right now, that the Ambu CardioPump is intended to be used as an adjunct to cardiopulmonary resuscitation, CPR.

It is indicated for use in the treatment of adult patients with out-of-hospital cardiac arrest, absence of effective pulse and respiration and then in parentheses there is the addendum, to improve overall efficiency of CPR. That is a suggestion from the sponsor. So, that could be put in or taken out depending on our discussion or our recommendations.

Rosie, why don't you start?

DR. GILLIAM: I was looking at what is there but, also, on Page 3, I guess, under Section 2, the labeling. I don't think they have improved efficiency of CPR. I don't think they have documented improvement in that at all. So, I don't think that is fair to do that type of labeling because I don't think we have demonstrated the proof there and even in Page 3 when they introduce their indications for use they start off by saying, "To improve the overall efficiency of cardiopulmonary resuscitation." I think we have to be very careful when we go to labeling that we don't allow a device to really make a hit that it is somehow better.

I mean if someone wants to use this device I don't have a qualm at this point with saying that it is not safe. I don't know that it is unsafe, but I don't know that it is in any way better than using your hands, and so I think to imply that it improves the efficiency when it is a 25 to 30 percent drain on your physical stamina; so, if you want to talk about improving efficiency we already know there is 25 to 30 percent more effort than without it.

So, I think that claim not only cannot be made, it is wrong.

DR. CURTIS: So, you would like to see that last phrase left out?

DR. GILLIAM: I don't think that last phrase should be in at all.

DR. CURTIS: Okay. Otherwise it sounds --

DR. DOMANSKI: What is an adjunct?

DR. GILLIAM: I think adjunct just means it is a help.

DR. DOMANSKI: They haven't shown that it helps.

DR. BRINKER: Adjunct is an addition and I think it is an alternative. It may be used as an alternative, and I would take out out-of-hospital even though that is the only group it used, but the cardiac arrest is a cardiac arrest.

DR. CURTIS: Otherwise the implication could be that it is not intended for use in the hospital.

DR. BRINKER: Or any other place except out in the field somewhere which I don't think is probably correct and may be hurtful for a doctor who does want to use it in the hospital.

At any rate if there is any suggestion as to -- something to consider might be, also, that clinical trials have not, wouldn't likely agree with, while animal studies suggest an improved hemodynamic response, clinical fail to demonstrate any benefit.

DR. GILLIAM: I wouldn't put that in because that implies that it is possibly a benefit.

DR. BRINKER: Clinical trials do not demonstrate any benefit over standard CPR.

DR. DOMANSKI: But I still don't know what an adjunct is.

DR. BRINKER: Take out the word so you won't have to worry about it.

DR. DOMANSKI: Maybe that would be a good start. I guess the question is whether it is indicated for anything. That is a concern I have.

DR. BRINKER: My feeling would be that if this was used in a large number of patients as an alternative to traditional CPR and these patients had in my eyes, my interpretation no worse an outcome, and if we were given a reasonable charge which included the statement that if this is effective as a CPR device, not more effective than standard CPR but basically as effective --

DR. DOMANSKI: We have just had our statistician tell us that they haven't demonstrated equivalency.

DR. BRINKER: Statistical equivalence is very rarely demonstrated in any of the trials that we have passed on in the past.

DR. DOMANSKI: But if they don't demonstrate superiority and they don't demonstrate equivalence I guess I wonder what they have demonstrated.

DR. BRINKER: Look at all the places we have looked at. You can count on the fingers of one hand those that demonstrated superiority in clinical trials. They

almost all --

DR. DOMANSKI: I am not sure that is true.

DR. BRINKER: It is true.

DR. GILLIAM: Remember the Medtronic(?) pacemaker was a consensus. We felt that the device was safe in both senses of the word but we just simply said that they couldn't make any claims that two sensors were better than one, but here I think the thing that I tend to agree with Mike I don't think we have demonstrated that this is a replacement or a substitute for CPR. I think it is used in performing CPR.

DR. FERGUSON: That is the point I wanted to make, Madame Chairman. I think the word "adjunct" is not bad here because if you put alternative, I mean CPR is cardiopulmonary resuscitation, and this is an adjunct for the cardiac aspect of it to be specific.

DR. CURTIS: I think if you were going to use the word "alternative," it would have to be alternative to standard cardiopulmonary.

DR. BRINKER: Alternative to manual cardiac chest compression.

DR. CURTIS: I think I would like to hear more comments from the other members since this is an important part of what we are doing here.

DR. SIMMONS: I am not sure that you might take

out "it is" and might even put in "may be indicated." The other thing I might throw in there would be something to do with training, you know something like may be indicated for the use in the treatment of adult patients without cardiac arrest given sufficient proper training prior to utilizing the device of some nature, some phrasing like that.

DR. BRINKER: That can go in the warning.

DR. SIMMONS: I guess that is true.

DR. TRACY: One of the big problems I am having in worrying about the whole thing of this label thing here is I am struggling with the idea that I don't know if this thing is even equivalent to standard CPR, and I guess I am worrying that there may be some hidden detriment to it. So, to worry about whether it is an adjunct or alternative it seems sort of moot to me at this point. I cannot worry too much about the wording until I think we know what the reality of this thing is.

DR. SPYKER: One of the struggles we have as we prepare these questions is to avoid the appearance that by working on the labeling you are assuming approval or that you are assuming that this device will be approved and sold, but as you understand as Susan and Larry have explained we only can decide whether it is okay as labeled.

So, it is kind of a chicken and egg problem. We don't know how to do it any better, but we need to sort of

struggle through if it were to be approved. So, make that hypothetical. Work through the best labeling you can and then we can sort of ask the final question.

DR. TRACY: Then if you work with what we know about it, then it is going to become an incredibly wishy washy indication for use with all kinds of may, could possibly, possible alternative, may or may not harm the patient, may or may not provide benefit. I would defer on giving any definitive answer about that.

DR. WITTES: But if we assume for an argument that you could take the three randomized studies and estimate, and we know when we take the three randomized studies there is essentially no effect; I mean that is what they are going to average out, but if they are large enough, and I tried to do some calculations, and I cannot do them fast enough, if they are large enough so that the confidence interval around that "no effect" is very narrow so that it excludes the possibility of large harm, then maybe there are data here. Maybe there are sufficient data to say, "Yes, it is equivalent."

I just don't know because I haven't seen the calculations, but it may very well be that one could do that in a rigorous way.

So, in that case, would it be reasonable to assume that that could be done?

DR. CURTIS: I think that is one possibility that, you know, one of these suggestions or things we could ask for today would be to say that we think that it is important to go back and analyze the data to find out if there is equivalence.

Now, if the answer to that came back positive the way you are saying. You look at those three randomized trials, and you get an answer that says, "Yes, it is equivalent," then I think if you had that piece of information what would the labeling say? I think there definitely is a consensus to leave out that last phrase if nothing else.

DR. GILLIAM: I don't have a problem with the use of the wording almost as it is with the out of hospital taken out because it doesn't make a claim, and it just says essentially what the device is. It is a help or something that will assist CPR.

That is all it is. It doesn't make a claim that it is effective. It doesn't, I mean assuming that it is not harmful, at this point I am willing to leave that to the statisticians, but I think we have to be very careful about the indications for usage and further in the introduction statement of the labeling package where they make several claims of enhanced which you know as far as the chest impressions leaving enhanced, active expansion of the chest,

those are data we just have not been given in any way, and I don't think we can allow any of that to be in the label at this time.

DR. CURTIS: We have the dictionary definition of adjunct here. Something joined or added to another thing but not essentially a part of it.

So, is adjunct or alternative the correct word?

DR. BRINKER: It may be an adjunct according to resuscitation but an alternative to manual chest compression.

DR. CURTIS: That is true. So, either one would probably --

DR. BRINKER: I like the term "alternative" rather than adjunct because adjunct implies that it is something additionally beneficial.

DR. CURTIS: I agree with you.

DR. FERGUSON: I vote for alternative to chest compression.

DR. GILLIAM: So, you would say that the Ambu CardioPump is intended to be used as an alternative to manual chest compression --

DR. FERGUSON: In the performance of --

DR. GILLIAM: In the performance of cardiopulmonary resuscitation.

DR. CURTIS: Okay.

DR. GILLIAM: And the next sentence with out-of-hospital taken out?

DR. CURTIS: Correct.

DR. GILLIAM: And a period.

DR. CURTIS: Right.

DR. BRINKER: And somewhere in the labeling I would put that I would agree that there are data that suggest that there might be some hemodynamic benefit associated with this, but no clinical benefit has been documented in clinical trials over standard CPR.

DR. CURTIS: Okay.

DR. BRINKER: And no other claims of benefit anywhere.

DR. CURTIS: Okay, No. 10, is the proposed contraindication section appropriate? What patient size should be used? Are there any other contraindications to the use of this device? The way it is worded now it says that the Ambu CardioPump is contraindicated for use patients under 88 pounds or 40 kilograms.

DR. BRINKER: I think, No. 1, this hasn't been tested in the pediatric age group so that there is no clinical experience or there should be no clinical experience in patients under 18 or 16, and secondly, they give some anecdotal data about patients with small thoracic configurations, and I would let them, with the FDA work out

what that definition is. I don't think we have to do it.

DR. CURTIS: Something that hasn't come up and I am just wondering about, what about the patient with a flail chest or some trauma? Are there reasons why somebody wouldn't use it in certain patients?

DR. GILLIAM: We do CPR and the compression is the same. So, I don't know whether there is any difference.

DR. CURTIS: Is there any potential detriment to the decompression?

DR. SIMMONS: I think that patients with flail chests and fractured ribs you actually compress less forcefully though, and if you actually had this gauge on there, and you were trying to generate 80 pounds of pressure on somebody with a -- because I think the whole hemodynamics gets screwed up when they have flail chests and they are not getting the increase in intrathoracic pressure, and you might actually, I don't know. I do different CPR in somebody with multiple fractures and flail chest than I do in somebody with an intact chest.

So, I don't know. I wondered about that, too, but I don't know how you would prove it.

DR. CURTIS: And we don't have any information right now that says that you shouldn't do it I guess is the answer.

DR. BRINKER: There is no experience.

DR. SETHI: I am still concerned about the patients who are anticoagulated, and I wonder if the sponsor would have some time to take the data out on how many patients were on anticoagulation and what happened to those patients.

It doesn't appear to at this point cause significant bleeding problems but it is possible that patients who are on anticoagulants they may develop a significant bleeding problem.

DR. CURTIS: Okay, any other comments?

DR. BRINKER: I think that under the side effects, whatever, there should be basically a chart of the clinical experience comparing manual CPR with this which should include the ecchymosis.

DR. CURTIS: Okay.

DR. GILLIAM: They, also, mention under contraindication or maybe a relative contraindication those patients where I think there has been mention of women with large breasts and people with hairy chests and as far as the device I think there may be a mention that that may be considered a relative contraindication to using it if you cannot get the suction.

You don't get an adequate suction, but then that implies that there is some benefit to the decompression.

DR. CURTIS: There are warnings or precautions, I

forget. They are not separating warnings, only warnings or only precautions, but it might be something like that that you saw.

DR. GILLIAM: Not necessarily contraindications.

DR. CURTIS: Right. Any other comments?

DR. SIMMONS: Where are you going to put the training issue? It does seem like the Paris thing was the only one that really showed any benefit was the one that had a lot of sufficient training before they used it. So, I am just wondering where you are going to put that. Are you going to put it in contraindications or are you going to put it in the warnings? I don't know where you are going to do that.

DR. FERGUSON: It is already in No. 1, under indications for use. This is on Page 3.

DR. SPYKER: When we determine similar situations we put high up in the warnings a simple specific note about that and then some detail on that back in the separate section, usually Section 11. So, we have some alternatives that are usually readily accepted by the sponsors.

DR. CURTIS: Okay, before we get to the Panel recommendation, we are going to go to the open public hearing, and one of our scheduled speakers from this morning was late and is now here, Sam Kazman from the Competitive Enterprise Institute.

MR. KAZMAN: Thank you very much. My name is Sam Kazman. I am general counsel of Competitive Enterprise Institute or CEI which is a non-profit organization that attempts to study the unrecognized costs of government overregulation.

My apologies for not having been here when scheduled this morning. Coming from Falls Church, Virginia, I had assumed that the Parklawn Building was the northern-most reach of FDA and when I arrived there with no transportation here, I realized how mistaken I was.

Neither I nor CEI have any financial ties with Ambu International nor have they picked up our transportation expenses, let alone the hefty cab fare from Parklawn to this building.

CEI addressed the issue of the CardioPump in the spring of 1995, and at that time the medical assessments of this device ranged from neutral to positive. It was clear, however, that the device would not pose any added risk.

Dr. Michael Callaham, professor of emergency medicine at the University of California, San Francisco and an author of one of the less favorable CardioPump studies at the time wrote the following in an unpublished letter to Time magazine: Quote, we do not yet know why it appeared to work in one study and not another. We do know that the device has shown no adverse, no significant adverse effects.

Three years have now passed, and I think that that is still clear on the lack of evidence of any real risk from the CardioPump. What the new data do indicate are, however, what seems to be some continuing question as to beneficial effects.

Once again, there are studies ranging from slightly negative to significantly positive. I think two points ought to bear attention here. One is that there is no study that shows any strong negative effects. As to those studies that show strong positive effects, there are several possibilities.

One is that there is something peculiar about those studies, but once again one can ask which way that would tend to push their results. The second possibility is that the people involved in those studies have found some way to take the fuller advantage of the CardioPump's potential.

Dr. Ornato, who had to leave early pointed out that in this field progress consists of tiny steps. If that is in fact the case then we would submit that there is a danger to insisting that every step in technology in this area has to be unequivocally clearly a step forward. We think it ought to suffice if the step seems to be promising, especially if there is no evidence of significant adverse effects.

Remember, approving the CardioPump will not force its use by anyone. Non-approval of the CardioPump, however, will prevent its use by everyone.

In a sense this is a judgment call, but we would ask you to make this judgment in the context of one other judgment that I want to describe in closing.

In 1996, CEI commissioned a professional poll of cardiologists regarding their views of FDA, and I will leave the results of that poll for you. In that poll 65 percent viewed FDA as being too slow in approving new drugs and devices and 71 percent believed that the agency's approval process had hurt their ability to give patients the best possible care on one or more occasions.

Lest you think that somehow cardiologists were unique in their views, a poll that we had taken the preceding year of oncologists showed very similar results in views of FDA.

In closing, we would ask that you do your best to assure that FDA's review of the CardioPump does not become yet another such occasion.

Thank you.

DR. CURTIS: Are there any other members of the public, and that right now doesn't include the company who would like to make a comment?

Go ahead?

MR. DUNNS(?): I am Donald Dunns. I am a private citizen.

DR. CURTIS: And no financial interests?

MR. DUNNS: No financial interest whatsoever.

I have been listening to these comments, and I used to be an FDA reviewer, but it seems to me that this device wasn't studied to its best advantage as I hear from the Panel which I think is true.

It wasn't to its best advantage, but the physiological benefits as demonstrated in animals and human studies that were referred to do make you think maybe something good might happen if you use this device.

Now, when you say that it is equivalent or not to CPR, if you say that it is equivalent, then you are automatically admitting that it is safe and effective, and therefore it is approvable.

There is a difference, however, that it is probably a more vigorous way of applying CPR but fortunately FDA doesn't regulate hands or the weight of the EM technicians. So, who knows how vigorous they might be? I do think that I think training is a very important factor and I, also, think that the point about harm coming which I am not sure was demonstrated or not; I don't have the data, you could maybe suggest a postmarket study to see if there is harm.

Thank you.

DR. CURTIS: Anyone else?

Would anyone from the FDA want to make any comments at this point?

DR. CALLAHAN: I am just sitting here wondering what is the basis of the effectiveness of the device. I heard that the CPR was effective.

DR. BRINKER: In terms of all the parameters that were measured, that is the return of spontaneous circulation, 1-hour survival, survival to discharge and I guess 24-hour survival one assumes that if there were no CPR or no device there would be nobody reaching any of those end points.

That may not be a correct assumption, but ethically it would be impossible not to perform some sort of CPR on non-respiring patients.

DR. CALLAHAN: I guess my question is what is the difference between this and CPR? Is this not CPR?

DR. BRINKER: That is the question that I tried to put to you in the beginning. This is cardiac compression with a, if you want in its simplest term a transducer between the hands and the chest and the question was if that is the same as just the hands alone, is that equal in efficacy, and the response I got from FDA or I thought I got was, yes, it is.

Therefore, it is as effective as CPR and

DR. CALLAHAN: I am not sure you heard that from FDA. I certainly didn't hear that from FDA. I am just asking the question if, for example, we have seen for example in these studies that the way when you cannot utilize for whatever reason, hairy chest and so forth you can still perform CPR with the device, and I guess my question to the Panel is are we looking at CPR with this device, standard CPR?

What additional are we gaining? Are we looking at a device or is just in fact, CPR? Your question before was asking the efficacy question of a transducer if the transducer, if this is a transducer that purportedly is going to add something to CPR. Otherwise you are comparing it to CPR, and my question is is it CPR; it is plain and simple CPR?

DR. GILLIAM: I don't think we, at least my understanding was we are not making a claim that it is adding anything to effectiveness. I don't think we can make that claim. I don't think we have any evidence that it does anything that you cannot get with regular CPR, and we cannot comment.

There is based on I guess I could say anecdotal data or perhaps animal data that it might do something beneficial, but we don't think that has been demonstrated to

be. The decompression phase is something you cannot do with regular CPR, but we don't have any evidence that that is effective.

So, I think at this point in labeling we have been addressing not necessarily what it does but making sure that we make it very clear that we don't state something that it does not or has not at least at this point in time been shown to do.

DR. TRACY: I would like to add to that in terms of my thinking about what I will ultimately say, I am concerned that we don't really know anything, and I just am curious how close we are to knowing something that is something about this thing in terms of its equivalence and its potential for harm, and that I think is a question I have to ask you because at this point I look at the information and to me it looks like they are equivalent but I realize that there are other factors in there that might affect a determination of equivalence, and I don't want to approve something that potentially has harm when the potential for harm has not been explored. So, how close are we?

DR. BRINKER: Tom, may I ask one question? Let us say that this device had no claim to decompression, that all this was was a thing that went between your hand and the chest and happened to have a little spring gauge on it to tell you pretty much how much pressure you are putting down.

Then it would be a predicate 510K device, right?

DR. CALLAHAN: Could be.

DR. BRINKER: Probably would be and there is probably no reason assuming that there is no down side to it, no claims, no decompression, no nothing except that it is another way of putting the pressure between your hands and the chest and, also, had a little spring gauge to maybe serve as a guide to CPR, it would never have gone through this process.

DR. GILLIAM: That is the point I would like to make though, in answering Tom's question, the device does have, and we have largely ignored it, the device has an adjunct if we can use that word which I think could be very important in the field, and that is the strain gauge because there is, if there is anything that kills people that are undergoing CPR it is inadequate compression, and inadequate compression is difficult to gauge when you are out there pumping on the chest yourself.

I mean who came up with this 2-1/2 inches anyway? How do you know that that is going to do it for you, and so I think the addition of a strain gauge on the intermediate letting the decompression aspect go along, I think that is an adjunct that would be helpful to all persons who are doing cardiopulmonary resuscitation.

DR. WITTES: But why didn't it show up except in

Paris? Why didn't it show up in 24-hour or 1-hour resuscitation?

DR. FERGUSON: I cannot, of course, answer that, Janet. I mean I cannot answer a lot of questions that are coming along here, but I was trying to answer Tom's specifically when he said, "What is the difference between this?"

This is one additional thing that has been added. If you want to discount that, you can do that, but if you go out and do chest compression then that would be nice to have. I mean that is all I am saying.

DR. CURTIS: I think what we have got here is a method for performing CPR. That is what this thing is. I is a way of doing it, and I think in terms of safety and effectiveness issues we want to know that it is as safe as doing standard manual CPR and that it is as effective, and the whole issue about as effective comes from the -- we are not going to be able to answer it because of the fact that we don't have that information, but it is there to be analyzed and could be answered.

DR. BECKER: I want to try to answer Tom's question which is that I thought what I heard you say before was that the as effective part went to whatever the labeling was, that that was what we were supposed to render our judgment on. So, if the labeling that we have now kind of

amended up here in a way basically says that it is equivalent to, an adjunct to standard CPR, and it doesn't make a statement that it is superior to then I am assuming that is the answer to your question, that that is the effectiveness.

DR. CURTIS: I think you have to know though that it is not less effective than standard manual CPR because if it were less effective we wouldn't want it.

If it didn't work as well as standard CPR --

DR. BECKER: I agree. It is sort of predicated.

DR. CURTIS: That is right, but if it worked worse --

DR. BECKER: We are sort of predicating that on some statistical information that we don't really have right now.

DR. CURTIS: But it is obtainable.

DR. BECKER: But it is obtainable. So, I think what I am kind of hearing the group suggest is that given the appropriate statistical information that would actually show a reasonably narrow confidence interval so that the group could be clear that it seemed that it was unlikely, relatively unlikely that it would be less effective than standard CPR, that given that that it could be labeled and approved as has been sort of amended up here.

Now, I have just tried to summarize that to answer

your question. I would like maybe people to react to that.

DR. BRINKER: I think Tom is getting back to something I had mentioned before. This could be an invisible device, and if I did a trial and half the people got standard CPR and half the people got standard CPR with an invisible device and they both came out the same, and we could approve the invisible device on the same basis that we are approving this, I think that was the core of the question, and I tried to get at that before.

The impression that I got was that if this device used as it is used was as good as regular CPR regardless of the fact that it might only be a simple mechanical transducer that it is approvable, and that is the basis for my comments.

DR. CALLAHAN: I am just trying to clarify what I heard, and so that is like what Dr. Domanski said before about the towel, only it has a gauge on the top.

DR. GILLIAM: Also, I don't know that there is any indication that the gauge does help. I mean I am not sure that that is tacit that knowing that number means anything or may even not be detrimental. I don't know that you have any evidence that that is the case.

PARTICIPANT: The gauge is the one thing that I frankly think may actually be detrimental. It gives one a false sense of I am pressing on the chest at the same level

20 minutes later.

It doesn't mean that that same level would be appropriate. I don't think we have any -- I think the gauge is the last thing I feel comfortable with. I don't think there has been anything that demonstrates that this does harm. To my way of thinking right now I think the statistics, the data can be obtained from the randomized studies, and maybe we can live to see that happen, but as far as is effectiveness, I don't think we have demonstrated that.

I sort of personally think that there is probably some benefit to the lifting of the chest. How much it is, and it may be that it is going to be so minuscule that we would have to have 100,000 patients to see even a fraction increase.

I think one comment I do want to make concerns a public speaker who had a concern about 71 percent of the physicians would say that we move things through the FDA too slowly. I think that more than likely that number might even be higher than that, and if I were to add that it would probably be an even higher number if we were to say how many physicians have the first clue as to what the FDA actually does, the number would be very, very high.

So, I think that those types of numbers indicate to those of us who are physicians who are in practice that

we need to know more about this process, and I would probably challenge all of us in this room including industry that 90 percent of our problem may be solved if we correctly inform the public as well fellow physicians and industry people exactly what the responsibility at FDA has been because I have gotten quite a lesson over the last 5 years.

DR. SPYKER: Madame Chairwoman, I have three brief comments on equivalence. First of all, equivalence, an equivalence study is different from the superiority or hypothesis study. Neither the sponsor nor the agency has suggested this in the design and execution of the study. It is quite appropriate, perhaps, for the second device that we approve in this fashion, but it is certainly not at all what was done in this particular case.

DR. SETHI: I have one comment. I think I take the view that this device can be harmful. You take, for example, a fat person with a lot of hair, and you try the device and you are attempting to do the compression. You have wasted a very important period of time before you go to manual compression.

So, I think we should not take for granted that you cannot hurt the patient. You can hurt the patient by not using it properly. In terms of the patient where you cannot use the device in those patients in a certain percent with a little experience you can harm the patient. So we

have to keep that in mind.

DR. CURTIS: I think I would like to go ahead and ask the sponsor now to make their comments. You are limited to 15 minutes maximum.

DR. LANGE: On behalf of the company, Ambu, I would like to say, "Thank you," to you all. It has been a very interesting day from our point of view. All we are asking for, and I would like you to remember that is to make the device available to licensed practitioners to have the opportunity to use it in the system like AEDs, like thumpers(?), like high doses of epinephrine.

It is one of the most studied devices in the chain of survival, and it has been shown for sure to improve hemodynamics which I guess you won't see with an invisible device or a towel, but I don't know.

We will of course, report postmarket surveillance studies. I would like to stress that fact that there are no devices on the marketplace today used in the chain of survival which has been evaluated by PMA process, not thumpers, not even AEDs. We are the pioneers here.

Coming back to the claim, it was not our purpose to claim superiority to anything. It was just to express the purpose of using this device or adjunct or whatever like other links in the chain in general of course, is to improve the chances.

While would you else want to do it? But of course rephrasing the claim can always be discussed. Training, yes, training is extremely important, and we realize that and that is, also, one thing that is mentioned in our directions for use, and we have all the material that people would need in order to do training.

Wished end points for CPR devices in general; yes, you could wish for that, but that is not what we are going to show today. We are going to show reasonable assurance for safety and effectiveness for the proposed claim, and in terms of equivalence none of the studies were designed to show equivalence, and I just heard from the statistician there that making a study that was able to show equivalence would take tons of patients for something like that, but in terms of equivalence, I would like to end up by giving the words to some people who have used this device for very many years and let them tell you what they think about equivalence.

Thank you for your attention.

DR. MAUER: Just one last word as far as harm and harmful is concerned. If you want to take a prospective randomized study you can take ours, and we can prove that there is no harm in our study, and I can tell you that I used that device since more than 5 years in the prehospital and the in-hospital setting, and none of my patients was

harmed with that device.

We improved in these patients which is very difficult to measure in the prehospital setting, we improved hemodynamics and can measure oxygen saturation during CPR. You can see patients waking up during CPR.

I have never seen that before with a need of sedation, and in the intensive care unit you see a real improvement in systolic blood pressure and cardiac output, and I think it is good to give our clinicians the possibility to use that device and to take their own decisions if they should take it or not and to be able to evaluate or to establish their own training program with that device because that device as a side effect improves training and improves quality of CPR because with the help of that device while you are doing CPR you can see how good is your CPR. You cannot do that with standard CPR.

The last words from me, I would like if you would not be able to use it here in the United States if you would come to Germany, I would be glad to invite all of you to do CPR, ACD-CPR with me together and then we can rediscuss that.

Thank you.

DR. BRINKER: You know, if you could have designed your study to effectively demonstrate that your quality of CPR is better and that the training or the ability to train

someone to deliver CPR was really better, much of this discussion could have been shortened, and perhaps you can go back and do that.

It should be quick to do. This is not a very complex kind of thing. It would have certainly helped us.

DR. MAUER: If you are at the end of such a process you always know your mistakes, perhaps, and it is very easy now to tell me the things that should have been done, but it is a good proposal. We are using ACD-CPR in some months together with the valve and perhaps we can prove that. I will think it over, and perhaps we will do that.

Thank you.

DR. PLAISANCE: We just want to suggest about one thing, okay? We discussed a lot about the Paris study, and I am not sure I am proud of that, but long discussions and for me it is important to say that when we have discussed about statistics and things like that which are of importance, we now are using this device every day. We are sure corresponding to our results. Perhaps it is bad. Perhaps it is not.

In several towns in France, not only Paris this device can save lives, but we have to train a lot. We discussed a lot about some important things and once again studies, but we didn't discuss about the training and training a lot, and if you are not training or trained, if

you don's supervise the technique you are practicing standard CPR with the device. That is all, and the only difference is the compression phase. If you don't train, you do not have good technique.

DR. FRASCONE: Dr. Plaisance, I would love to see a circumstance where the St. Paul Fire Department could have 2 years' practice with this device and respond to patients in 3-1/2 minutes versus 19 minutes and see what would happen to the data.

I think we spent a lot of time today, unfortunately, concentrating on the combined study, and I think what the Panel is struggling with is the entire constellation of data that they have seen, not just the black and white scientific data.

You have seen the physiologic data, both human and in animals. You have heard of our anecdotal experiences of people who have used this device. It is difficult for us to believe the device would not be allowed to be on the market after witnessing that, and I know you have to trust me. Trust me, I am a doctor, but one of the things that really bothers me, and I am from an academic institution, and I think I understand the concept of randomization, but we cannot forget that these are human beings, human beings who are in full arrest who are being treated by other human beings who are trying to do the very best possible thing

they can do for them, and it bothers me a little bit that we forget that sometimes when we are looking at it, and I know it is not scientific, but it is something to consider.

Lastly, I think you will come to the right decision if you just ask yourself, again, as I put it in my little talk in the beginning would you allow one of your family members to be resuscitated with this device. If the answer is yes, I think you have to approve this device.

Thank you.

DR. LANGE: You have heard about equivalence from the petitioners who used the product. Six years it has been available in 70 countries. All we ask is that the United States would be No. 71. All we ask for is to let the petitioners get the opportunity to use it in your system, and I thank you all very much.

DR. CURTIS: All right, it is time to move on to the Panel recommendation. The question we are being asked is based on the evidence presented in the submission is there adequate evidence of the safety and effectiveness of the Ambu CardioPump as labeled.

DR. STUHLMULLER: Panel recommendation options for premarket approval applications for medical device amendments from the federal Food, Drug and Cosmetic Act require that that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on

designated medical device premarket approval applications that are filed with the agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under the conditions of use outweigh any probable risk. Effectiveness is defined as reasonable assurance that in a significant proportion of the population the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows: No. 1, approval. There are no conditions attached. No. 2, approvable, with conditions. You may recommend that the PMA be found approvable subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by your or by FDA staff.

Prior to voting all the conditions are discussed by the Panel and elicited by the Panel Chair. You may specify what type of follow-up to the applicant's response or the conditions of your approval of the recommendation you want, for example, FDA or Panel. Panel follow-up is usually

done through homework assignments for the primary reviewers of the application or through other specified members of the Panel.

A formal discussion of the application and a future Panel meeting is not usually held. If you recommend post-approval requirements to be imposed as a condition of approval, then the recommendation should address the following points: A, the purpose of the requirement, the number of subjects to be evaluated and the reports that should be required to be submitted.

Option 3, not approvable. From the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to Panel deliberations: A, the data did not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposal. B, reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling. C, based on a fair evaluation of all the material, facts and your discussions you believe the proposal labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures you think are necessary for the application to be placed in an approvable form.

Option No. 4, tabling. In rare circumstances the Panel may decide to table an application. Tabling an application does not give specific guidance from the Panel to FDA or the applicant, thereby creating ambiguity and delaying the progress of the application. Therefore we discourage tabling of an application.

The Panel should consider a non-approvable or approvable with conditions recommendation that clearly gives described corrective steps.

If the Panel does vote to table the PMA, the Panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the voting the Chair will ask each Panel member to present a brief statement outlining the reasons for his or her vote.

DR. CURTIS: Do you want to make a specific recommendation here?

DR. BECKER: I will try. I think after hearing everything I would have to say that it is not approvable under Sections, I think it would be in C, and I would like to make the recommendations for what the additional information that would have to happen that I think would make it approvable.

I think that the first thing that needs to take place is that there needs to be either a resubmission of

some statistics that would specifically address the questions we have raised, specifically looking at equivalence and safety, and I think that given such statistics then I think I would have a concern over the labeling that it would need to be relabeled along the lines that we kind of did together here with the terminology that we arrived at, and I would think that if those two conditions were met that it could be approved.

DR. BRINKER: I think that that exact same proposal could be viewed as a proposal to approve with those conditions as opposed to disapproved with those conditions, and I wonder if you could tell us what the implications would be?

DR. STUHLMULLER: At this point in terms of parliamentary procedure there is a motion on the floor. It either has to be seconded or if it is not seconded, then you can make another motion. So, at this point the Chair needs to ask whether there is a second on the motion or not.

DR. WITTES: Second.

DR. FERGUSON: That is the not approved but with recommendations.

DR. CURTIS: That would be not approvable and then what the reasons are for the non-approval. So, there was a second over here from Dr. Wittes.

Okay, now we can have a discussion about this.

DR. GILLIAM: I sort of want to put some sentiments with Jeff, and I admit I am way over my head with the statistics, but if we made it approvable with the condition that the statisticians are able to put together the request that you brought about looking at the three randomized studies and did not demonstrate any harmful effects, in other words, demonstrated that there is a reasonable assurance of safety would that --

DR. BECKER: That would. I guess I would like to defer to someone who is good at parliamentary procedure. The reason that I put it in that form is I think based on what we have seen here today, here and now that has been approved for us to see I simply don't see that information yet.

I think it would be relatively straightforward to obtain it, and I would think that it could happen fairly quickly.

DR. DOMANSKI: If, indeed, the data show that.

DR. BECKER: Right, if the data show that.

DR. DOMANSKI: They may not. That is why I would make it kind of conditional that first we need to see the data and then second we need to see the new language.

DR. CURTIS: The other issue is that if it is not approved the company can still return with the answers to that information. Isn't that correct?

DR. STUHLMULLER: Yes, at this point there is a motion on the floor. It has been seconded, and it needs to be voted on, and then the discussion is based on the vote, and then you would --

DR. CURTIS: So, in other words you could vote for or against that motion of non-approval?

DR. GILLIAM: It should be discussed before we vote. I think it is necessary to do that. We have to discuss before we vote.

DR. FERGUSON: I would like to speak against the motion.

DR. STUHLMULLER: But the motion has been made, and it has been seconded.

DR. FERGUSON: Aren't we having a discussion?

DR. CURTIS: There normally would be discussion before you vote.

All right, we can discuss.

DR. FERGUSON: I would like to speak against the motion because I think that if we vote to turn it down we are not taking into account the large body of data that is there which says that the device is safe which is one of our charges and the argument about effective, I think is for each individual to decide. I, personally, think it is as effective as manual CPR.

So, I would go with what Jeff say and hope that it

is approved with post approval conditions in terms of working out not only the statisticians' concerns, but, also, perhaps getting a study started like Jeff and I were talking about earlier which I think would be a great help and easy to do.

DR. CURTIS: Thank you.

DR. BRINKER: I just want to say that the reason I -- I would like to send a message, and the message is that by saying that it is approvable with all the conditions, in reality, semantically, is the same as saying that it is disapproval with those conditions, and I think it is better to say that should the conditions be met it is approvable.

Now, why am I quick to buy that role? One reason is that as was suggested the words that John quoted to us from the regs, as holy as they are are that there should be some reasonable assurance of safety and reasonable assurance of efficacy in our interpretation now of equivalence, because we are considering this not a more effective form of therapy based on the data that were given us but one that is roughly equivalent to standard CPR, and I think that a reasonable assurance is a lot different than wanting to know what the P value is to demonstrate equivalence here.

So, I am comfortable in letting the statisticians and the FDA work it out, but I would like to give the appearance that should it be worked out to their

satisfaction that the other aspects of it would be approvable.

DR. WITTES: The reason I like it where it is is I don't think this is really a statistical issue. I think it is a medical issue, and what makes me nervous about specifying very clearly if you do this, this and the other thing it passes a statistical hurdle, I don't think that is where we are. I think as Mike says, we don't know what the results will be when the analysis comes through. We don't know what the definition of equivalence is and so --

DR. BRINKER: But it is statistical.

DR. WITTES: Oh, I don't think so. To me that is exactly where it is not statistical. There is a lot of clinical judgment that is going to go into the interpretation of the analysis that is going to come through, and so, when I hear you saying, "Let the statisticians and the FDA look at it," I mean I feel my goodness, that is on my shoulders, and I don't think that is, at least the statistician part is on my shoulders. I don't think that is where we are here.

I think we don't know what is going to happen when all these covariates are merged, when the California data come in, and I don't see how we can specify in a narrow enough way to say that if these hoops are done then it is approved.

I mean I agree with you, it is semantic.

DR. BRINKER: But if they are not done then it is disapproved. So, you are putting the onus on the other -- it is a fact with over 2000 patients in some sort of controlled study.

I mean I am reasonably confident that this isn't significantly worse, clinically significantly worse than manual CPR, and I am reasonably confident in terms of safety, and I am reasonably confident that it isn't clinically significantly different than manual CPR in terms of efficacy, and in actuality that fulfills the mandate. If there is a question about putting that into a better perspective in terms of exactly what was the power and the statistics given the three randomized studies, then perhaps you get the California study and looking at everything else, if that dramatically changes something then I think that would have an influence and that should be the rule for it, but I don't see why we should say that we will do the analysis but it is disapproved unless on the basis of the analysis we have some clinical discussion that says, that interprets this statistical aspect of the analysis because I think the clinical -- I don't this is very precise.

DR. DOMANSKI: You know there is an alternative and that is to do a suitably randomized, suitably powered controlled trial with some reasonable end point, whether it

is perhaps 1-hour survival and demonstrate it as opposed to going back to inadequate data and trying to tease it out statistically. The latter is reasonable to try but she is right. I mean there is a lot of judgment that is necessary when you are dealing with data that is really inadequate.

DR. BRINKER: My other point is that is this device didn't have the claims associated with it, the suction aspect to it, if it was just the CPR, whatever, and had a strain gauge on it, we would never be through this process.

DR. DOMANSKI: I don't know, Jeff. I don't know what these things cost, I don't even want to go there because it is going to cost a lot to just do standard CPR instead of doing it with your hands.

DR. GILLIAM: I sort of agree with Jeff. I don't have a real concern that this device is going to be proven to be particularly unsafe. I think that the worst case is that this is going to be a chunk of plastic that is totally worthless except for the cost, and I think that is probably the worst case and that may be particularly aggravating enough that maybe it shouldn't be used, but I don't think sitting here I feel comfortable saying that we should disapprove the device.

If they have done several thousand people and have not gotten the power from the three randomized studies that,

well, it is not several thousand; it is several hundred, but it has totaled a couple of thousand and if we were to look at trying to start another study I think that is particularly, we sort of faced the same problem when we looked at heart valves and to really be perfectly safe for them we would have taken 10, 15 years and I think this is, you know --

DR. DOMANKSI: But, Rosie, this is different than heart valves. The heart valves would take, it is impossible to do the trial because of the numbers and you could never seen an improvement, but the numbers here would be relatively small as a matter of fact, hundreds probably rather than thousands.

DR. GILLIAM: I think we have hundreds, and I would definitely defer to the statisticians. I mean you guys definitely know more than I but it would seem to me that if we are going to see just an incremental, if we are looking for safety and not -- I think we have got to look at a lot of numbers.

You cannot do it from the numbers we have in the three randomized studies. Would there be anything that you would suggest that if you were designing the study right now to start that the randomized studies that we have don't --

DR. TRACY: I think that the issue though is not that we don't have the data from the three randomized

studies. We never looked. They never looked, and I think that the main thing that those of us who have reservations are -- look, look and tell us what the results are, if you look at the randomized. Look and tell us the results. I don't personally feel that we need to embark on another study. I just don't feel that we have analyzed the data to answer the questions that we need to ask to approve this device.

DR. BRINKER: The data are there. I think that the only thing that hasn't been done is to single out those, to look at the amalgamation of those three data sets together as a group, but if you look at it individually they are exactly as you would expect for no difference. One shows a little better one way and one shows a little bit less good in another way, and I don't think you can get a more --

DR. CURTIS: I think we have discussed this pretty well. I think there are differences of opinion, and that is what the point of a vote is, is to stand up and express your opinion.

There is a motion on the table for non-approval, and it was seconded, and I think it is time we go ahead and vote on that motion.

DR. BECKER: A point of information. Are there other implications to not approval versus approval that have

not been drawn out here? Is there any other -- does non-approval compare to approval with the same set of conditions carry any other meaning?

DR. SIMMONS: If it doesn't carry a literal meaning it may carry some implied meaning which I like a lot.

DR. BECKER: I am asking from the standpoint of the agency, is there a difference in what it does to scheduling, to any other types of things to the expedited way in which it gets handled? I don't know any of this.

DR. CALLAHAN: It won't change the process, and we will continue on from the Panel meeting and try to wind up whatever the decision is within the month, and there is always a chance to come back. However, there is always the chance if approved that we will work with them to do other things. That doesn't change the process. It is not a door slamming

DR. CURTIS: All right. Then I call the question. A show of hands in favor of the motion as stated.

DR. CALLAHAN: Voice vote.

DR. CURTIS: Voice vote? Okay.

We need a voice vote apparently.

DR. WITTES: Approve the motion.

DR. TRACY: I agree with non-approval.

DR. SIMMONS: I agree with non-approval.

DR. SETHI: I agree with non-approval.

DR. DOMANSKI: I vote yes, as well.

DR. GILLIAM: I vote against the motion. I vote -- do I have to state how I would vote? I vote against the motion.

DR. FERGUSON: I vote against the motion.

DR. BRINKER: I vote against the motion.

DR. BECKER: I vote to approve the motion.

DR. CURTIS: That looks like six to three to me.

Okay, that is six to three in favor of the motion. So, the motion carries for non-approval of the device, and at this point then we are supposed to list what would have to be done to get the product into approvable state.

Lance, do you want to take a first stab at that?

DR. BECKER: I will try to take a first stab. I would like to see some additional data that would define the confidence intervals for safety and that would attempt to show comparable effectiveness to standard CPR.

Is there a better way? I would look for some help from Dr. Wittes.

DR. CURTIS: I think we definitely should get some other comments on this.

DR. BECKER: Yes, I mean help me out because this is not my thing.

DR. WITTES: I would like to see a separate

analysis of the three randomized studies both for their efficacy and comparison of efficacy to CPR and safety. I would, also, like to see and I don't know whether everybody else agrees with this but an analysis of all the studies including the California study with explicit modeling of the important clinical covariates because that is part I think of the safety issue.

Are there groups of people for whom this may be dangerous or not as effective for one of the reasons that have been discussed around the table, and I think that can only come out of, because of the limited size of the randomized studies, I think that is going to have to come out of the non-randomized, and so I would like to see analysis of those data with reasonable assumptions about the nature of the biases that might have happened. I don't know whether that is definite enough.

DR. TRACY: I would agree with that except that I think that the company made a very good effort at getting the data from California and unless there is some other strong arm of the law that can go after California and force that data out of them I think it is unreasonable to expect them to get the data from California.

DR. BECKER: Except they could use what is just in the published literature.

DR. WITTES: That is all I am asking.

DR. BECKER: I don't want to ask the company to have to go any further with San Francisco.

DR. WITTES: But those data that they have, to include that.

DR. BECKER: And then the second part is I would like to see the revised indication label, contraindication label that would include and reflect the discussion that took place earlier on those items.

DR. SPYKER: I would just like to get briefly on the table the difference between an equivalence trial and a superiority or a null hypothesis trial. We have to come up with a clinically meaningful not worse than delta.

So, I would like at least a few seconds of discussion on what my esteemed colleagues think is an appropriate not worse than delta. Are you willing to look, decide what you mean by primary end point; is it 1 hour, and if that is it then you also need to say that we are willing to be 95 percent certain that the upper confidence limit is not below 1 percent or 2 percent or 3 percent worse. That is the additional thing we have to define as the clinical design change for an equivalency analysis. So, you might comment.

DR. BECKER: I guess I am not really asking for an equivalence study. I am not sure that that is really what we are after here. I think that what I am hearing from the

panel is sort of a reasonable approach to equivalence and what I haven't seen is I haven't seen the company attempt to do that.

DR. DOMANSKI: A reasonable approach to equivalence should be demonstrated in statistically appropriate fashion. I think if they are going to say that it is equivalent, it ought to be equivalent, and I think the question being asked is a reasonable one.

DR. CURTIS: I am not sure I am clear. Can we take the studies that were done already and make that analysis on it and if you think yes, then I think what Dan is asking is then what is equivalent enough or beyond which point is it detrimental and we wouldn't want to consider it?

I mean I think you have to be pretty tight here because if the gold standard is manual CPR that is pretty good and you certainly wouldn't want to accept much worse. The question is what is that number.

DR. SPYKER: In a sense the study as designed and as analyzed used an upper confidence interval of zero. We said that we want to be 95 percent certain that this difference is not less than zero. That is this particular number, and I was a little confused by the discussion but that would certainly be historically and in my opinion an appropriate kind of decision.

DR. WITTES: I think if we do that we know the

answer. I don't think it is going to, the two animal studies aren't going to be -- I think the definition, if we are serious about this being able to go through, the definition for clinical is going to have to be softer than that, I think.

DR. BRINKER: The primary end point is 1-hour survival.

DR. TRACY: It is around 24 versus 20 for the combined study.

DR. BRINKER: I would say then that you need at least 10 percent of that at the minimum. You would have to have at least 10 percent of that, so somewhere in between 2 and 5 percent, I would say difference within 5 percent.

DR. CURTIS: We need to go around and have each member of the Panel mention the reasons for the vote that they made and as you do that if you could it would be very helpful I think to state whether you think that the information that we think is still necessary could be obtained from the studies that have already been done by reanalysis of the data, looking at it or getting more information or whether new studies need to be done and if so what type.

DR. BECKER: Could I start off because I am going to have to leave?

DR. CURTIS: Sure.

DR. BECKER: My reasoning is simply that I have not seen today in the form that I need to see the data to help me make the decision with respect to the statistics, and I do that based on the input from our statistician experts here and that was my reasoning for my vote and in terms of whether they, I would actually suggest that they do attempt to use the seven studies that they have currently combined and I would, also, hope that if possible the California study could be used with the published data within that study if possible.

DR. CURTIS: Thank you.

Jeff?

DR. BRINKER: My vote obviously was based on the fact that while I wasn't enamored with the statistical results, I am fairly confident in my own mind that clinically this is not worse than manual CPR and it is not less efficacious than manual CPR.

My own intrinsic intuitive belief is that in some subgroups of patients it is probably better, and it may be an excellent way of teaching people the right way of doing CPR, and since my motion was defeated for the company while it is doing its other statistical analysis should go and design two studies, and they can both be done very quickly and probably as quickly as the reanalysis of the data.

One is to design a study to demonstrate that CPR can be done more effectively on the basis of flows, blood pressure, etc., and that could be done in hospital on a randomized basis or even a randomized crossover between two forms of CPR and that should be a slam dunk not requiring many patients and show that there is a hemodynamic benefit if there is one and the second thing I would suggest is that there be some way, again, very low numbers of patients to show that the addition of the strain gauge is a helpful means for physicians to deliver CPR in terms of monitoring their effort, and that could, also, be done in a number of ways.

One might be to blind the person, just put a cover over the gauge, let him do what he thinks is right and then uncover it and let him do it to the point of what the gauge indicates.

All these things if shown to be beneficial, and they should be intuitively could be done in a low number of patients very quickly and could be very helpful.

DR. FERGUSON: I agree with everything Jeff has said. I voted the same way because of the same things he said. I will say in addition, however, that it is a little disturbing to me that we hold manual CPR up as a gold standard when it really is a pewter standard if that good, and there are many, many deficiencies about manual CPR that

I don't think we should hold up to say that you should come up to that level because I think what you want ultimately is to have something better.

I think you have approached the physiologic aspect of doing that with the decompression aspects and hopefully with the gauge, but I agree with everything he says. I think those things have to be demonstrated, and I would hope that you could come back for at least some of those.

DR. GILLIAM: I voted the way I did. I feel fairly convinced based on not just the study data but, also, the fact that it is in continuous use in some places that the device is probably not harmful to patients. I think the statistics will probably show that. I would be surprised were the data outcome different.

I am not convinced I have seen anything that suggests that it is efficacious any more so than your hand.

I am less convinced that the strain gauge is at all useful, but I do feel like the decompression probably would serve some benefit. It at least intuitively makes some sense to me, and I don't think we have demonstrated that, but I think that as the company in truth to do any more than they have already done is not unlike the heart valve.

I think it would require a tremendous number of people basically because we are looking at survival in this

group of patients with out-of-hospital arrest and the numbers are very, very small and to see a significant difference I think you would have to do this to get a huge number of patients.

I think it would be very difficult and I think I would be perfectly content if you can demonstrate that the device is not harmful to people, and I think that the statistical data that we already have should be enough to demonstrate that. I don't think it is particularly useful but then again I am not sure that the pump or a number of other devices that have been out there have really been useful other than to protect you against fatigue, I guess.

DR. DOMANSKI: The reason I voted the way I did was I don't think that they have shown even equivalence to the pewter standard of hand, regular hand CPR. I think a way of dealing with the data that would be very compelling would be coming back if they want to show equivalence to standard CPR that appears to be the bar they have to cross over, and I think a suitably powered randomized trial that would do that would be most compelling.

It may be that one could try to tease out the satisfaction of the FDA from non-randomized data, a reasonable level of assurance and that is probably what they will try. I think the other is probably more compelling.

DR. SETHI: I am concerned that the results might

be worse than standard CPR especially in some subgroup of patients, especially in those patients in whom they were not able to use this device. I would like to see the outcome of those 18 or 20 percent of patients separately to see how did those patients do. They are mixed, those patients in the final analysis, and I am just concerned that they might bring down the whole effect.

Second is that though not a large number of patients will be on anticoagulation, a fair amount of patients nowadays are on anticoagulation. This device does cause mechanical compression causing ecchymosis, bleeding, and I would like to see some data on that. How does this affect the patients who are on anticoagulation?

I do think No. 1, I would like to see some data, some results on the patients on whom the device was not able to be used. They were randomized to having the ACD-CPR but for one reason or another they were not able to use and include some data on anticoagulation.

DR. CURTIS: For those who mentioned another study, do you think that it could be done on in-hospital cardiac arrest patients?

I see a lot of nods yes.

PARTICIPANT: I sure do.

DR. CURTIS: Good and how do you factor in the effects of the mechanical ventilation; is that an issue?

DR. BRINKER: Not if it is a randomized trial.

DR. CURTIS: All right, Tony?

DR. SIMMONS: The reason why I voted the way I did was I was not convinced from the few randomized trials that there was any significant benefit over the standard of care that is already existing, and so, that was my definition of effectiveness.

It did not show any effectiveness over nothing, and so that is why I voted the way I did. I do think that I would like to see the stuff come out from the statisticians and the redefinition to be as strong as possible to say that if it does get approved that there is no clinical benefit, and I am not so sure that some of this stuff couldn't be done with postmarketing kinds of surveillance studies to do the in-house studies that have been suggested.

DR. TRACY: I voted the way I did because I am not at all convinced that we have a definition of, that we have shown that this device is safe. Just very, very cursorily looking at the three randomized studies the adverse event rates are somewhere between 13 and 18 percent in those randomized studies, and I don't know what that means, and I haven't seen any data that tell me what that means.

So, I would like to see that this thing is at least safe and at least equivalent in terms of this efficacy because I think there are lots of potential down sides

including fatigue for the operator and the difficulty just in administering this type of CPR.

DR. CURTIS: Do you think that requires a new study?

DR. TRACY: I don't know. I don't think so. I think there are lots of data here that aren't culled out. I think we could look at that carefully and make some clinical judgments as well as statistical judgments on the information but until we would see that I don't think I can comment whether another study is needed. I suspect not but I would need to see it.

DR. WITTES: There is one other thing that came up in the St. Paul study, and that is the patients who were not included because they got the wrong treatment or the ones who were excluded. I just want to make sure that when the analysis of the studies, of the non-randomized studies is done again that those people are included in the group to which they were randomized. I am not sure.

I mean maybe they have been in the combined, but I am confused about what the denominators are. So, it is all those kinds of analyses in addition to what we have talked about that need to be done in a very, very rigorous way.

DR. CURTIS: The hour is getting late. We were asked to give some advice about future development of CPR assist devices.

I would like to turn to that in the last minutes that we have here, and these questions are all separate from the consideration of the CardioPump that we discussed all day.

DR. CALLAHAN: In view of the late hour we can dispense with this, if you would like. I think we have got a good inkling as to what you want anyway.

DR. CURTIS: I don't think you will get any argument from the Panel on that. If you think you have gotten enough out of us from the discussion today I would be happy to hear a motion to adjourn.

DR. SIMMONS: I move we adjourn.

DR. GILLIAM: Second.

DR. CURTIS: Okay, this meeting is adjourned. We will reconvene at 8 o'clock tomorrow.

Thereupon, at 5:20 p.m., a recess was taken until 8 a.m., the following day, Tuesday, June 30, 1998.)