through the process of inclusions and exclusions.

But one patient population that I do think merits a bit of thought is the hospitalized patient in a CC or critical care environment. I have the privilege of sitting in oversight of a large registry in heart failure, and I can tell you that, of over 100,000 patient episodes, there's a 1.5 percent incidence of CPR being administered. That's 1,500 patients. That's decidedly more than any of the studies we've seen.

Now, that incidence may be higher or lower for other cardiovascular illnesses, but my point is that, in an ICU setting, you can overcome the informed consent issues, because, as a matter of fact, upon admission to the ICU, these issues can be discussed. So you have that opportunity.

You may be doing a lot of prep work for low incidence, but at least you'd get around that, because in my judgment the informed consent is the most difficult part of this whole problem.

Secondly, you have the chance to learn more. I don't think that this area is as well defined

as it should be. So you get to understand what the pre-existing clinical circumstances are and what the precipitating factors might be. You understand the latency quite well because you can chronicle almost everything that happens.

So I would think that that would be a patient population which you could start your investigation, and then move from the ICU setting to the broader hospitalized patient population and then to the outpatient setting. Usually the focus of these kinds of efforts is to start in the out-of-hospital scenario. It's very dramatic. It's very immediate. But it's so heterogenous that the efficacy is hard to demonstrate.

I think that -- and I don't disagree with the notion of a broad net, but for this paradigm maybe you start with a narrow funnel and then widen it as you identify in whom it works best and how so.

ACTING CHAIRPERSON MAISEL: Dr. Ornato.

DR. ORNATO: Dr. Yancy, I have to agree with you on your comments with respect to the population that you've just described. But I have to

also I think take issue from a slightly different perspective, because when one looks at the literature on heart failure patients who arrest in an ICU, coronary patients with ischemic disease who arrest in a CCU, floor patients in a hospital, both on telemetry and in non-telemetry as well as other general areas of the hospital, as we see in the National Registry of CPR, which has over 25,000 in-hospital cardiac arrests now from 400 different hospitals in the U.S., and we contrast each of those venues and the patients and their presentations and outcomes with out of hospital, they're totally different animals. Totally different animals.

The pathophysiology is different. The initial substrate in the myocardium in terms of high-energy phosphates, for example, are wildly different. The outcomes are quite a bit different, and that's one of the problems that I think faces us in trying to figure out what the right model is.

And that's perhaps the reason I took the initial stab at answering the question, by saying there are so many of these other confounders, often we

find it's just easier to throw the broad net. Then, as we get more information, subset it and do our secondary analyses on the subsets.

Second -- and I need to let other panelists get in, but I want to reiterate the heterogeneous etiology of cardiac arrest. The V-fib going to -- to fine V-fib to asystole, Dr. Somberg I think very properly and correctly pointed out, we've all lived with, we all understand it, and it's a correct model.

It doesn't necessarily apply, as we all know, to other etiologies of cardiac arrest. For example, pulmonary embolus. It's now estimated that 5 to 10 percent of out-of-hospital cardiac arrests occur due to sudden, unexpected massive pulmonary embolus. It may even be higher in certain hospitalized patient groups.

Those patients tend to present, as documented in the literature, by decision rules that have been prospectively obtained and then validated in secondary data sets. A high percent of those patients present with shortness of breath followed rapidly by

cardiac arrest with pulseless electrical activity as their initial presentation. That's a special presentation.

There's a trial underway in Europe called TROICA. I sit on -- I chair the DSMB. It's looking at thrombolytic therapy for out-of-hospital cardiac arrest.

If we were to restrict trials to the VF model, it would be hugely problematic, because we would a priori be excluding innocently, and not realizing it, perhaps one of the most attractive groups that might have at least a theoretical opportunity to respond to that form of therapy.

So I guess my final point, in summary, is that the more you get into this can of worms, the more you realize that unless it's a very specific device for a specific scenario, like VF, you're often better off throwing the broad net and then leading up to your design and secondary analyses, trying to filter out, and using criteria for whom you exclude from analysis as the way of filtering down to get a homogeneous group.

ACTING CHAIRPERSON MAISEL: So at this point, why don't I ask Geretta to start reading the questions, so we can make sure we cover all the topics that are of interest.

MS. WOOD: "The following are considerations when defining the cardiac arrest trial patient population. The defined trial population can support a reasonable enrollment rate. The population defined has the potential for providing scientifically valid data. The population defined, and, thus, the results obtained from these patients may be able to support a wider population of cardiac arrest patients.

"Please discuss the following regarding the inclusion/exclusion criteria. The first question: should the study exclude non-witnessed arrest, or should the study include both witnessed as well as non-witnessed arrest?"

ACTING CHAIRPERSON MAISEL: Well, if I could just summarize our thoughts regarding general inclusion/exclusion criteria, I think the consensus is that we certainly don't want to exclude important patient populations from being studied. It seems that

both witnessed and non-witnessed arrests could be and should be studied. However, it may not be appropriate to study them in the same trial.

And identifying more uniform or well-defined patient populations for individual studies may be helpful. And that probably -- that may apply to the documented ventricular fibrillation in the next question, although we may argue over the ability to diagnose the rhythm accurately.

DR. SOMBERG: Bill?

ACTING CHAIRPERSON MAISEL: Yes. Dr. Somberg.

DR. SOMBERG: I think that was well put, and I just want to say I think we're trying to develop a general process here. And, you know, there are very specific -- it's like two things. You know, a suit that fits all size 40s, or one that only does something for a unique population.

So, you know, it is not to exclude anybody or any groups, but I think this -- that the only way you can have this meeting is to have some sort of general idea if you had a general treatment for a

general cardiac arrest.

ACTING CHAIRPERSON MAISEL: Al, did you have something you wanted to add?

DR. HALLSTROM: Well, I would just like to strongly support both Joe's and Henry's comments. I think in out-of-hospital situation, it's going to be very difficult to -- to put in place very complicated inclusion and exclusion criteria, even the simple issue of witness versus non-witness.

But I think that data should be collected, and I think one should be able to define your primary comparison group based on data that is collected prior to the intervention. So I would strongly encourage that trial design allow more patients to be enrolled than are actually defined for the primary comparison.

ACTING CHAIRPERSON MAISEL: Okay. Next? Judah.

DR. WEINBERGER: I have a comment I'd like to really direct more at the biostatisticians, and that is if we throw the net wider, don't we have the possibility of decreasing the power, or increasing the number of patients we'll have to enroll to see an

effect by confounding it with lots of other patients who have either underlying problems that are not going to be treatable, or other diseases that are not going to be allowed in principle to receive a primary positive endpoint?

And by opening up the trial, we're going to vastly increase the cost to the sponsor of coming to a positive endpoint.

ACTING CHAIRPERSON MAISEL: Okay. I think, in general, I think what we're --

DR. NORMAND: Should I say "perhaps" like --

(Laughter.)

-- other people? No. But yes. I mean, and I think I also heard a statement that the efficaciousness is very different. And so, obviously, you could have some -- so, yes, you will, and you don't want to be -- have such a large population that you could have a big effect and no effect and a negative effect. So --

ACTING CHAIRPERSON MAISEL: I think we all recognize the difficulties with these populations. I

1 think answering the question of: should we exclude
2 non-witnessed arrests, or exclude certain patient
3 populations, I think we're saying, no, we should not
4 necessary exclude patient populations. Is that
5 accurate?
6 DR. MARLER: It's been my observation that
7 exclusion criteria don't generally make the trial that
8 -- as much easier to do as you might think. You still
9 have to be there. You still have to do the --
10 actually see the patient and determine the criteria.
11 And by that time you've done a lot of the work.
12 By excluding a significant number of
13 patients, you discourage people participating in the
14 trial. So I don't think there's that much to be
15 gained in terms of either power or in terms of ease of
16 execution or cost as you might think in excluding a
17 lot of patients.
18 ACTING CHAIRPERSON MAISEL: Dr. Zuckerman,
19 did you want to comment?
20 DR. ZUCKERMAN: Yes, if I could ask Dr.
21 Hallstrom to elaborate a little bit. What I took from
22 Dr. Halperin's comment is that he's looking to do a

trial with a wide net. And then, at the end of the day, instead of doing classic intent-to-treat analysis, he wants to do some filtering such that the comparison may not preserve the randomized component of the trial fully.

You know, there are problems in this area, but do you have any practical considerations that you can provide us with? You know, classically, we do like to use intent to treat and not focus on subanalyses.

DR. HALLSTROM: Yes. I think -- what's the reason for intent to treat? It's to be sure you don't have bias. So I think the intent to treat is kind of -- has gotten kind of carried away. If you have data that is collected before you actually put in place the intervention, and that data is collected -- therefore, is not affected by the intervention, you can use that data to select a subset of the patients who were treated by other intervention. And you will have an unbiased comparison group.

And I think it addresses the issue that was raised over here. For example, if you mix

ventricular fibrillation on asystole patients with a common treatment, and you dilute the power because perhaps in the asystole patients you have expectation of very little increase in survival -- or none -- yet the complications of trying to separate the two at the time of the intervention may make it very difficult.

You can still restrict your analysis to the VF patients, provided that data was collected before the intervention.

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. HALLSTROM: If it would be unbiased.

DR. MARLER: And the subset was prespecified, you said?

DR. HALLSTROM: Well, I think you always have to pre-specify. Otherwise, you're playing around with your alpha and beta a lot.

DR. SOMBERG: I would just make the point that that's great for hypothesis-generating, but it wouldn't be for a definitive trial for approval. If you had a device that only worked in a subset, say the people with the VF, and they were 20 percent, and 80 percent had asystole in the study, but you had a

fantastic signal if you did that, and I was sitting on the Panel two years from now or five years from now, I would recommend that they do another study to take people with VF and prove that point.

Because so often -- and I can give you -- you know, examples right now where we see subsets that work. They do the study, and the study comes out negative. So it's -- it's not clear-cut that the one variable that you've picked out is the one that's operant in the determination. So I think that's a very slippery slope to make a decision on.

ACTING CHAIRPERSON MAISEL: Dr. Weisfeldt.

DR. WEISFELDT: In a sense, we're starting this discussion with entrance criteria when we haven't really decided what the outcome is that we're going to accept. And if we look at this issue from the point of view of other major cardiovascular diseases, as to what has really influenced devices and drugs, it's survival to some reasonable quality.

And if we say that that is the ultimate endpoint variable that we're going to go toward, and our purview is devices in CPR in a large group of

1 people with substantial mortality, then the notion of
2 having entrance criteria that optimize the possibility
3 that that device is going to save lives, and that
4 group is a substantial group of folks among the many
5 who die, that to me seems to be the optimal approach
6 to the entrance criteria.
7 It does go a little bit to Lance Becker,
8 who is really a co-conspirator of mine, and the phases
9 of resuscitation. But, clearly, if you're studying a
10 better defibrillator, you have to have ventricular
11 fibrillation as the entrance criteria. If it's a
12 pacemaker, you have to have asystole.
13 If it's somebody -- and, arguably, there
14 are some data to suggest that there's a phase in which
15 defibrillation has not worked or other measures have
16 not worked, where very clearly there is lots of data
17 to suggest that better circulation is going to work.
18 But it's a subgroup that's identified somehow related
19 to downtime, and arguably response to initial
20 defibrillation.
21 So you could see a device for circulation
22 if we were going to demand an outcome of improved

survival in which there would be a certain set of entrance criteria that reflected the group that needs circulation.

And then, if you go toward, if you will, a metabolic intervention -- hypothermia -- it's unlikely that hypothermia in somebody who, because of defibrillation or CPR is alive and alert and heart is functioning fine, and has no problems at five minutes after ROSC, that probably is a patient you would want to exclude from a study of a metabolic intervention hypothermia, because they -- it's not likely that you're going to improve survival in that group.

So my answer is the entrance criteria should reflect the place in the resuscitation population where that device may have some survival value, and the endpoint that we're seeking is improved survival.

ACTING CHAIRPERSON MAISEL: Why don't we move on to Part C. I think we've addressed A and B.

MS. WOOD: Okay. "Based on the literature regarding early intervention and survival outcomes, should there be a limit on the time that has elapsed

between arrest and initiation of CPR?" If so, can you suggest how best to obtain accurate, unbiased time estimates?"

ACTING CHAIRPERSON MAISEL: Dr. Ornato.

DR. ORNATO: Once again, I'm going to start it. Yes, there should be, but that's Nobel Prize material for someone to figure out a way to do it. All joking aside, it's a wonderful question, and there is quite a bit of interesting science in the last decade and a half or so, since Chuck Brown and others looked at such things as median frequency for the VF patients.

And now there are a whole family of different measures for VF patients looking at the relationship between time and markers such as the characteristics of the electrical rhythm. The problem is that, unless we have a device on the patient as in Dr. Yancy's population, which I think is a wonderful example, where they are in an intensive care unit, where you've got them on a monitor, where many of our monitors, hopefully all of them, most of them, have a time stamp, you know, where you know where the event

begins, then for such patients, absolutely, we ought to be paying attention to that.

But for the majority of our studies, particularly for the in-hospital but non-telemetry-monitored patients, and certainly for the out-of-hospital patients, they are usually not on any device that's giving us an atomic clock synchronized time stamp.

And so we just technologically, at the moment, simply don't have the means to really start the time at the beginning. And short of that, even such things as when they collapsed or when they passed out, aren't always particularly active, because -- or accurate, rather, because usually it's a layperson who is the witness, and they may not realize that the person may be underperfusing but may not be totally without perfusion, at least for a brief period, a la they go into V-tach but have some perfusion. Then, when we see them they're in V-fib.

Final comment is that, remember, there's a practical side of this. A lot of these trials are being done in the field, where the major of arrests

occur. Often the people "enrolling them," are firefighters, EMTs, paramedics, especially if we're talking about first responder interventions, some of the airway devices or CPR devices.

These are not research nurses. These aren't people who are going to be able to methodically go through a hospital chart for 30 minutes before going in to see the patient to decide whether they've got exclusion or inclusion criteria. These are people whose focus is on trying to get that patient to survive.

That's I think why you're hearing the sentiment expressed from some of us who have worked in this area and stepped on all the landmines and realized that it's scientifically great to be able to get the pure group. It certainly makes your power much simpler and much smaller. But the practical perspective on this makes it impossible to do that in many cases.

ACTING CHAIRPERSON MAISEL: Anyone with -- sure. Dr. Brott.

DR. BROTT: Well, we have the experience

of trying to treat patients with stroke within 90 minutes, and we actually treated somebody off a Delta airliner. But the nice thing was is that you had electronic verification with that patient. You know, the pilot knew what had happened, and so forth, and we -- and so I would say I agree. I mean, I know how difficult it is to get the time.

But I think somebody made the comment operational, and I think that in this electronic age that trials need to be designed so that if they're in the ICU that time is definitely part of the protocol. I haven't really seen that.

In publications that I read as a neurologist, you know, I'm interested and I'm looking. I really haven't noticed this. And I'm a hospitalist, and I see the cardiac arrest charts, and I really don't see too often in the note monitor documents V-fib started at 11:21 a.m. In fact, I can't think of a progress note that stated that in the last few months, and I've seen, you know, a number of in-hospital cardiac arrests.

So my suggestion would be that any trial

have operational times such as, when did the call come into the life squad? When was the first rhythm recorded? Some of these papers have that, but most of them don't. And I think that five years from now, in 2010, we should have a lot of electronic time markers that we can apply, so that we don't have to speculate about four to six minutes with as much uncertainty as we have today.

DR. ORNATO: Could I respond to that, Bill, briefly?

ACTING CHAIRPERSON MAISEL: Yes.

DR. ORNATO: You're exactly right. The problem is there are three, four, or maybe five papers in literature on timing in resuscitation, both out of hospital and in hospital. I'm co-author on two of them.

They've all shown the same thing and that is that people don't synchronize their watches to the atomic clock. And there's so much heterogeneity, for example, in the National Registry of CPR, the largest repository of in-hospital cardiac arrest data in the world, something like I think it's 5 or 10 percent of

our data have interventions like defibrillation or CPR or drugs being charted five or 10 minutes before the cardiac arrest supposedly begin, because there are different people and different machines using different timepieces.

And the result is that it -- you know, if you average it all out, it looks great. But if you look at an individual event, and you try to figure out what happened, it just doesn't work.

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. SOMBERG: Another consideration is the duration of the cardiac arrest treatment, and that's been ongoing, and when you put the intervention in. And while this question asks, how long should you be down before the treatment was initiated, many studies don't look into this, and it is a major factor.

If someone is receiving first responder CPR, then more advanced ACLS, and then you finally get an investigator in his office, you know, an hour later, that's totally different than if it's applied within five minutes or something.

So while I don't have a magic number, I

1 think it has to be specified, and the earlier that the
2 intervention is applied the more likely it relates to
3 the outcome.
4 ACTING CHAIRPERSON MAISEL: So I think
5 just to summarize, I think we're saying documenting
6 time as accurately as possible, using medical records
7 if possible, and first responders and call times and
8 things like that, to provide the best estimate.
9 So let's move on to D.
10 MS. WOOD: "Should the study patients be
11 limited to patients who have arrested in the field, or
12 should the study also include in-hospital cardiac
13 arrest patients?"
14 ACTING CHAIRPERSON MAISEL: I think we
15 already addressed this. We said both can and should
16 be included, although probably not mixed in the same
17 study, and that they are -- there are important
18 differences in these populations and should probably
19 be studied separately.
20 E?
21 MS. WOOD: "If field patients are to be
22 included, should CPR be initiated by professionals

only, or can patients be enrolled if timing is recorded by and CPR is initiated by bystanders?"

ACTING CHAIRPERSON MAISEL: Again, just on the general theme of inclusion, I would think we would want to include both these patient populations, recognizing that there may be important differences in outcome, and that these data should be carefully collected and perhaps pre-specified subgroup analysis.

MS. WOOD: "Do you have any other suggestions regarding the inclusion/exclusion criteria?"

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. SOMBERG: Well, I think certain conditions impact on outcome later. Let's say someone falls on their head, and that initiates the cardiac arrest. Obviously, that will impact on neurologic outcome. Someone who is exsanguinating due to a large laceration of the femoral artery, or something of that nature, hemodynamic support. So there are certain logical things that have to be taken into account.

ACTING CHAIRPERSON MAISEL: Any other comments on the inclusion/exclusion criteria before we

move on?

DR. YANCY: Just one observation, if I might. If you think about what we've just talked about, we've basically said we would include all etiologies. We said that we would include in hospital, out of hospital. We would include CPR by professionals and lay individuals. And it's relatively time-insensitive because it's so hard to quantify.

I really think that that is a very, very heterogenous grouping, and that represents a huge challenge.

ACTING CHAIRPERSON MAISEL: I agree with your statement. We also, I think, commented that we would like to aim for more uniform, well-defined studies, so that individual studies would study more well-defined populations, but that we didn't want to exclude any of these patients from future study.

So why don't we move on to the study endpoints, and why don't we open by just having a general discussion.

Jeff.

DR. BRINKER: I think that one of the problems with past clinical studies in resuscitation has been the issue about what is an acceptable endpoint. If the FDA, for instance, takes the position that survival is the ultimate and only acceptable endpoint, then this reflects dramatically, actually, on both the inclusion criteria and the study design.

I think that there should be some surrogates that can be used when you're looking at specific issues. So that if you wanted a -- if you designed a device, for instance, that could maintain profusion of vital organs without effective cardiac contractility, you might be able to use a surrogate endpoint, such as blood flow, and maybe cerebral blood flow, which I think would be important because it's a conveyor to other therapies.

And except for the patient who has sudden ventricular fibrillation, is immediately defibrillated, it seems to me that the ultimate save of patients, both physically and physically with a neurologically intact system, is to use a variety of

devices, or intervene in a variety of different areas -- maintain cardiovascular function, improve the utilization of vital nutrients by the brain by downgrading metabolism, things -- a whole bunch of things.

So that I would -- and it would be very difficult to attack all of these things in one study. So I would -- I would like to think that one could piecemeal the specific device using surrogate endpoints rather than necessitating an ultimate survival benefit to show efficacy.

ACTING CHAIRPERSON MAISEL: That seemed to get the Panel riled up.

(Laughter.)

Why don't we start with Dr. Halperin.

DR. HALPERIN: You know, I think that to really get a good answer to what is the correct endpoint, if there is a correct answer, we really have to understand what are we doing during CPR. Because I think it becomes much clearer, if you really understand what your particular device or approach is doing.

For instance, if you have a device, since that's my area of expertise, that it augments blood flow during CPR, there is many, many studies that have shown that if you have viable animals or viable patients, if you augment blood flow during CPR you'll improve survival, even long-term survival.

However, if, in fact, you augment blood flow in somebody who is not viable, you might get improved short-term survival, but then they are brain dead, even though the heart may still be viable, and you may get only short-term survival.

So I think that, then, the -- what the -- the physiology of the device, as well as the inclusion/exclusion criteria actually interact very strongly here, because if we had only viable patients that were enrolled in a study we might get improved survival at discharge if we had augmented blood flow. But, in fact, if we had a lot of non-viable patients enrolled in the study, we might get improved short-term survival, but not improved long-term survival.

So I think, then, we have to take into account the inclusion/exclusion criteria, as well as

the physiology of what's happening in deciding what is the appropriate endpoint.

ACTING CHAIRPERSON MAISEL: Dr. Kato.

DR. KATO: Well, initially, when I first read over the packet, I was very concerned about device -- specifically about devices and their ability to try to look at only one part of the chain of survival, or chain of survival concept, much like the recently-approved over-the-counter AEDs.

I was actually fearful that, you know, the over-the-counter -- using the over-the-counter AEDs as an example, while we have considered it to be effective and safe for the treatment of ventricular fibrillation, there are a number of assumptions that go along with it.

For example, you have to speak -- you have to be able to understand English. You have to have another person there. In the absence of a secondary person to apply the paddles to you, and if they are unable to understand English, then you're basically out of luck even though the device will work.

And I then thought about what we have done

in the cardiovascular surgery field. And much like looking at CPR and the CPR success, it's really -- you're really looking at a system approach or -- and a system outcome. However, devices per se are going to be helping at every step of the way.

And so while one of the problems is that, in the cardiovascular area, for example, particularly in cardiovascular surgery, we use devices such as aortic cannula, cardiopulmonary bypass machines, but -- but all of this technology and all of these devices, including monitoring in the Intensive Care Unit, you know, required technology which occurred at different steps or at different time intervals during the past 20 or 30 years, and only recently has all of that technology come together to create a system of care which has been highly effective.

And so, therefore, I've had to change my -- in the past 30 minutes of this discussion, change my idea about that -- that I think that these devices, for better or for worse, are going to have to be evaluated on their own intervention in the area of the chain that they are going to work.

And that the -- that looking at CPR -- cannot be looked at CPR per se but as a step in that entire system of care, which then is really a different issue that the FDA doesn't necessarily address, because the FDA doesn't regulate, you know, a process of care. And that's where the device, again, has to be looked at very specifically at one point in that chain.

ACTING CHAIRPERSON MAISEL: Dr. Becker.

DR. BECKER: Yes. I'd like to sort of echo some of those sentiments, and to suggest something perhaps radical. That what we really need to be concerned with is the labeling, and I think that is what we're supposed to be taking care of, as a matter of fact.

And so what I'd like to really highlight is that it would seem to me that we need to have a system in which -- where we have truth in advertising, where devices can be labeled for what they do, even if what they do is a small part within the chain of survival.

So an example might be a device that

simply allows you to call 911 faster some way. One would hope that it would be labeled as a device that allows you to call 911 faster. I don't think it would be appropriate that it should be held to a standard that one would have to do a trial to show that there's better survival based on the whole system that Dr. Kato has just described so well -- a very complex system as to whether or not there's really survival at the end of the day.

And that, to me, I think the important thing is really the labeling. That a device, for example, that claims that it produces superior survival at the end of the day I think really needs to demonstrate that in an unequivocal way. But I think there has to be the opportunity that a device that clearly labels exactly what it does, that physicians are allowed, if you will, to do what physicians do, which is to utilize some judgment and to have access to those kinds of devices.

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. SOMBERG: This is a very complex area, and, you know, you can sort of think about things

carefully one day, come to one conclusion, think about things the next day and maybe even come and -- well, you did it in 30 minutes; it takes me 24 hours.

(Laughter.)

But I think these devices are a little bit like obscenity. You know, it's hard to define it. But when you see it, you know what it is. That was paraphrasing of Justice Black, I believe, who stated that.

But if it was a device to call 911, I have no problem. But let's say it's a device to change the cardiac rhythm in a way that could be beneficial or harmful. It gives you pacing support. It cools the body. It warms the body. It thumps twice as fast as any man could do. I mean, you -- and it costs an awful lot of money.

I think you have to deliver more than a transient benefit, and, therefore, I think there's always going to be a need for a Device Division in the FDA, to go through each application and see how it applies.

So I think my personal feeling is that

it's not going to be feasible to come up with an endpoint. But if I had one of the major devices before me, such as a defibrillator, a cooler, a supporter, you would want to see some definitive benefit.

If I have something that gives me a better grip on the chest wall, I would have a different criteria. And maybe that's a simplistic approach, but I don't see how -- thinking about this for multiple 24 hours while this meeting was planned, I don't see another approach to the problem.

ACTING CHAIRPERSON MAISEL: Dr. Zuckerman.

DR. ZUCKERMAN: Okay. You know, the Advisory Panel is trying to get to the heart of the matter, which is understanding the choice of the primary endpoint and what might be acceptable for FDA approval. And while I agree with Dr. Becker that appropriate labeling and indications for use is part of the equation, I do think that it might be more instructive to go back to Dr. Weisfeldt's original paradigm and challenge.

The first thing is the agency, for more

complex CPR devices, is interested in the assessment of a reasonable assurance of safety and effectiveness and defining clinical utility for that device. In clinical language, that usually translates into a reasonable risk-benefit profile for the device.

As Dr. Weisfeldt indicated, I would agree with his choice of the ultimate primary clinical endpoint of interest. And, certainly, if a trial was designed that way, it might have a very easy path through FDA. But is that the only path to show reasonable assurance of safety and effectiveness in clinical utility?

The answer may be no, with the following caveats. You know, people talk about the chain of survival. They talk about surrogates. But from our perspective, we're interested in this Advisory Panel perhaps giving us some more information about, one, why these surrogates might be appropriate. It's important to recognize that we're just now looking for endpoints that correlate with the primary endpoint that Dr. Weisfeldt has suggested.

It's more correlation and capture of the

ultimate treatment effect, and how you define that is essential, because certainly we've seen many examples in the cardiovascular literature where so-called surrogates turn out to be very problematic, and we don't find clinical utility, etcetera.

So, you know, one trial plus use of external data for an intermediate endpoint may be inappropriate, but I think the Panel needs to flesh out what are some of those endpoints and how you can get to the goal line that way, rather than just saying that there is something out there right now.

ACTING CHAIRPERSON MAISEL: Dr. Yancy.

DR. YANCY: Bill, I would tend to strongly support that Bram just said. I think there's already evidence in our packet that there is an approach that increases the return of circulatory stability, but with no downstream effect on the number of lives that are discharged in a meaningful, productive way.

So the inclination towards surrogates, even though it makes the clinical trial design at the outset seem to be a little bit easier, I think at the end of the day for this circumstance it doesn't affect

the outcome we're looking for. And so I would adhere to what I think Dr. Brinker said earlier, that being discharged alive and functional is topmost.

And obviously there are some iterations of technology that do have very specific approaches or very specific purposes, and that would be intuitively clear that that's all that they do. But for a device that is ostensibly designed to improve the outcome, then we should insist that a meaningful outcome is demonstrated.

ACTING CHAIRPERSON MAISEL: Dr. Ornato.

DR. ORNATO: Okay. Here's the problem. You've got time-dependent physiology. The first three to four minutes, as Drs. Weisfeldt and Becker have pointed out, are totally different, roughly, than the next three or four, and roughly from that point forward, as best we know today, physiologically.

When you've got a very powerful intervention, like early defibrillation, and you can apply it very early, as we did in the PAD trial, it makes total sense -- in fact, in my opinion, it makes absolutely no sense to look at anything other than the

longest reasonable interval that you can power a trial for. At least in PAD we powered it to survival to discharge, looking at neurologic outcome as a secondary outcome.

The problem is for many of the other interventions you're beyond that first three minutes in terms of where they're kicking in. And so you've got the problem from the get-go that the cardiac surgeon had back in the '50s and early '60s.

And, Norman, I think you're absolutely right on the money. You've had a revelation that in the CPR world of research has been talked about for years, which is that if we were all back in the '50s and talking about how to design trials that relate to the performance of open heart surgery, either to correct congenital heart problems, VSDs, tetralogy, or to fix valvular heart disease or coronary disease, it would take multiple advances -- anesthesia monitoring, in some cases pressor management, management of fluids, shock, blood, blood products, grafting materials, valves, etcetera, etcetera, sutures, not to mention all the technological things that relate to us

humans.

It would take multiple of those to be able to get your first person through that procedure alive, neurologically intact. And so once we get beyond that first easy three minutes of the VF patient where defibrillation is the therapy, we're now into the demand where we have to, we believe, correct at least a minimal number of things in order to have anything likely result in neurologically intact outcome.

If we fail to correct those things, we may be overlooking very powerful interventions that we will never be able to determine have value, because they are being studied in the traditional way one intervention at a time.

I think that's really the sentiment that I think Dr. Lurie got us started on, and why we're beginning to give you what seems to be schizophrenic answer to your question, because I think we all agree that what really matters unquestionably in the end is survival to at least discharge and probably beyond, clearly with better neurologic measures. I don't think any one of us disagrees with that ethically,

morally, economically, and all the other ways.

The problem is: how do we get there?

ACTING CHAIRPERSON MAISEL: Since it seems there may be a little division among the Panel on this aspect, maybe for some people who feel that surrogate markers are acceptable, could you talk about the specific endpoints or markers that you think would be useful?

Dr. Halperin.

DR. HALPERIN: Sure. That's a great distinction there, and I think that when we've grappled with this problem in the past the issue is -- is, again, what is the purpose of this CPR intervention that you're actually studying?

And for at least blood flow devices, the purpose of the blood flow devices, you know, is to restore oxygenated blood flow to the brain and the heart mainly, to keep the brain viable and to restore viability of the heart, so it will beat again.

Certainly, if the brain is -- you know, too much time has elapsed, so that there actually has been brain damage, but the heart is still viable, the

device will actually -- could do its specified and desired effect and actually bring the heart back by generating increased blood flow.

If there is not brain damage, though, then the patient would be viable. So in that situation, then, to test how good that particular device is working, short-term survival might be more than adequate, because then it would show that, in fact, the device is efficacious or not, if there was no improved short-term survival, and then that -- then, trials or some ways of screening out patients who are non-viable could be studied, or the device could be used on them in the future, in fact, with the great prospect that, in fact, the device would be useful for improving survival to discharge, and, you know, long-term survival.

So in that situation, then, some measure of short-term survival would probably be more than adequate. So, then, the endpoints that are used, then, are improved hemodynamics, return to spontaneous circulation, say 24-hour survival, and then survival to discharge. These are the main endpoints that are

used.

And I would, then, propose that useful surrogates could be some number of hour survival to show the hemodynamic efficacy of a device. That's what was being proposed by the sponsor, and then, depending on the particular inclusion/exclusion criteria, longer-term survival could be appropriate.

ACTING CHAIRPERSON MAISEL: Dr. Weisfeldt.

DR. WEISFELDT: I don't often disagree with Dr. Halperin, but I'm going to try.

(Laughter.)

And I'm going to try to defend the notion that you can't get away from reasonable-term mortality. And that is to say that -- that if it's hemodynamics that we're talking about, there are interventions that improve brain blood flow and decrease myocardial blood flow.

The heart may well be viable, get ROSC as a result of the device and its use, but, in fact, myocardial damage may have occurred that is greater as a result of using the device that, let's say, improved brain flow but diminished myocardial blood flow by

increasing right atrial pressure.

There is certainly some hemodynamics that one can think about that would likely increase brain blood flow but reduce myocardial blood flow. And maybe the other way around as well.

So you get -- to some degree, you get back to the issue of: how confident are we of the intervening variable? We have no MACE. There is no summated endpoint that predicts survival like there is in acute/subacute ACS. There is no real variable except survival.

And if the issue is the need for multiplicity of interventions in order to improve survival, then somebody has got to step up to the batter's box and say, "Okay. These are the three. Here's a drug, a device, a methodology in this group of patients, where we need to intervene with a whole cocktail in order to improve survival."

So you look at the shock study, look at the study of patients with cardiogenic shock and acute myocardial infarction. Very close to the group of CPR.

All kinds of speculation about what might be beneficial, what might not, like intra-aortic balloon pumps, bypass surgery, angioplasty. So you do a randomized study in which you use reperfusion, basically, as the endpoint.

You randomize patients. You do everything in the intervention arm to have successful revascularization. You improve survival, and that changes the standard of care, and that justifies, obviously, the huge expense and approach to survival.

So I -- I think it's the challenge to put together what is the right cocktail to test it, but I still think the endpoint is survival.

ACTING CHAIRPERSON MAISEL: Dr. Weinberger.

DR. WEINBERGER: I agree with the sentiment expressed by Dr. Weisfeldt, but I think that we -- the bar is being set very, very high. I think that the best CPR intervention generically could possibly do, the very best it could do, would be to return the patient to the pre-CPR state. That's the best you could possibly expect from a CPR

intervention.

So that if the pre-CPR state made it unlikely for the patient to leave the hospital, the post-CPR state, with the best possible intervention in the world, is not going to make it any more likely for the patient to leave the hospital.

I think that asking for a device to return you to the pre-CPR state is too high a bar as well. So, obviously, some of these patients are going to come out with renal failure. Some of these patients are going to come out with some cognitive impairment, and the question is, is what do we find as an acceptable endpoint for that -- for pre-CPR state, plus or minus a certain amount.

And the question for us to deal with as clinicians is: at what point do we expect return to the pre-CPR state to be defined? And not continue monitoring the patients for the natural history of the rest of their underlying illnesses. So that we are dealing with a broad slice of medicine here, on top of which an event comes along and drops the patient down.

And I think that what we have to decide on

clinically, as clinicians, is at what point do we assess return to pre-CPR state and decide that we've gotten close enough to make that a useful therapy?

ACTING CHAIRPERSON MAISEL: Dr. Marler.

DR. MARLER: I just wanted to comment that we've been talking about a chain of physiological events. Also, there's a chain of development, and, I mean, the usual way to proceed with your so-called surrogates is to see -- you may be interested initially to find out if a device actually does increase blood flow. But the reality of it is, if I understand what has been said, is that sometime or other, if it's going to -- you're going to improve patient outcome, you're going to have to get there in the first few minutes.

And so that if you first establish that the device can increase blood flow, then it seems to me that it's going to have to be able to be used early on anyway, if there is ever going to be anything -- any treatment. Regardless of how many different interventions there are, it's going to have to be used early on.

Now, if the device doesn't have any potential effect on brain function, that might be one thing. But increasing blood flow -- most of the devices we've talked about would seem to have an immediate effect on outcome, both neurologically and cardiologically. So the development can also be put in a chain or in stages.

ACTING CHAIRPERSON MAISEL: Why don't we go to the questions to make sure that we answer everything that is asked of us, and we'll have another chance to talk about the surrogate endpoints.

Geretta.

DR. BROTT: May I just make a -- just a very quick comment?

ACTING CHAIRPERSON MAISEL: Sure.

DR. BROTT: Being a neurologist, every endpoint I've heard is the same ones that I read about 30 years ago. And so I guess when we come back to it, between now and then it would be nice to hear from people who know about this more than I do. Is there anything new? I was very intrigued on this BNP and heart failure and, you know, as a brain doctor I

1 thought this was pretty neat.

2 But are there new non-neurologic

3 endpoints? And my comment was for neurology there are

4 no endpoints. With MRI, there are now series looking

5 at post-cardiac arrest MRI changes. And for those of

6 you who take care of patients with stroke, I mean, you

7 look at an MRI scan, and basically you can tell from

8 10 feet whether or not the patient has had a stroke,

9 as small as a pea you can tell from 10 feet.

10 And it seems to me that, again, looking

11 forward to 2010, we need neurologic measures of brain

12 injury, ideally that could be expressed as a number,

13 ideally that could be added and subtracted, ideally

14 that wouldn't be dependent too much on differences in

15 culture, language, pre-arrest neurological function.

16 And so I have my concerns about the cognitive

17 measures.

18 We've been working on this for a while,

19 and it's tough because of those problems. But I think

20 tissue-based measures of brain injury have real

21 promise, and could be incorporated into the studies

22 that are being done now as secondary outcome measures,

and perhaps be ready for primetime in five or 10 years.

ACTING CHAIRPERSON MAISEL: Thank you.

Geretta.

MS. WOOD: "What would appropriate clinical endpoints be for efficacy in a cardiac arrest study? Survival. If so, how would survival be defined? Would functioning in a vegetative state be considered surviving?"

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. SOMBERG: Well, I knew at some point I'd bring this in. I was -- I'm involved in a number of drug studies, and there are certain benefits that are certainly not as powerful as defibrillators, we heard. And I've thought about this long and hard, and I think survival, immediate survival, termination of -- you know, was one endpoint, the arrythmia.

Survival at one hour, survival to hospital, survival in 24 hours, were all along the chain, but it's useful because each one of these points gives you access to the next part moving along. If you don't survive approximately 24 hours, you're

not going to get revascularized. You're not going to have these things. If you don't survive one hour, you're not going to have a balloon inserted, and you're not going to be -- you know, to these other points.

So I think there is merit to those endpoints as opposed to an endpoint of hemodynamic -- you know, I feel a pulse, the FIO2 is better, the end-tidal CO2 is better. We may have prognostic indications, but I don't think those are substantial enough to warrant the prolongation of the person's terminal event to -- for such at the time.

So I think certain indicators -- you know, for certain devices that's indicated. But we have to say what we're studying, and if we're studying a device, and to -- to cool someone to save neurologic function, then I think survival at one hour and 24 hours has no meaning.

So just saying survival at one hour and 24 hours has to take into account -- or making your choice of endpoint has to take into account what you hope to accomplish and what sort of prolonged

intervention you apply.

ACTING CHAIRPERSON MAISEL: I'm not sure we can tackle the "would functioning in a vegetative state be considered survival." It sounds -- religious is one comment.

(Laughter.)

Bigger than all of us. But certainly survival alone may not be adequate. Obviously, if everyone survived but they're all in a vegetative state, that may not be a worthwhile device. So that kind of brings us to Part B, which is the neurologic issues.

MS. WOOD: "What are meaningful neurological endpoints? And how should they be evaluated? Is a composite endpoint acceptable?"

ACTING CHAIRPERSON MAISEL: So we heard mention of the MRI. Dr. Brott or Dr. Marler, do you want to try to tackle this one?

DR. MARLER: MRI or composite endpoints?

ACTING CHAIRPERSON MAISEL: The entire question.

(Laughter.)

DR. MARLER: Maybe I could begin by just a comment. I think that whether you analyze it statistically as a composite endpoint or not, any endpoint in neurology is usually a composite of several separate measures. And the problem with the fine points of cognition is you need finer and finer -- more and more components in your assessment as you look for smaller changes in brain function.

My understanding in limited contact with patients who suffered from cardiac arrest is that there is some small component of change, but what we're really concerned about is a pretty obvious, serious, and major loss of neurological function.

ACTING CHAIRPERSON MAISEL: Dr. Brott.

DR. BROTT: I would, again, stress the importance for kind of a look at cognition as a continuous variable. I note -- and the discussion was made, you know, are we all there, or are we not? And, of course, the people around this table, we value our cognition so much that we might be attracted to this dichotomous view. But once the brain is injured, of course, the brain is different. It's not like being

quadriplegic where your brain is the same, and you're quadriplegic.

In this case, your brain is injured, and so your standards of what you consider to be meaningful, everyday activity may be different. Your standards in terms of what's acceptable movement may be different. Your taste in food, your taste in companions, can all be affected by that brain injury.

And so it's very unique in terms of injury to the brain, and what classifies as acceptable everyday life. And that's why I think you need a -- if the ideal, we don't have it, and we heard that we don't have it, is something that tries to assess, in a numeric fashion, cognitive function, so we can at least get some ordering of patients and their outcome, not are they bad, are they good, but to be able to sort them along some kind of scale from a cognitive point of view.

The NIH stroke scale was mentioned. That's nice. It gives a number from zero to 42. It correlates with the size of the infarc. It tells you, with pretty good sensitivity, whether or not your

middle cerebral artery is occluded. And it also correlates with functional outcome.

Something like that would be very nice. And, of course, that's for, in a way, functions we share with our pets. You know, can we move, can we see, and so forth. So the challenge is much greater for cognition, but I really think that we have to do that.

And then for the future, MRI -- I was mentioning, for those of you who have had a crick in the neck or a crick in the back, and you get your MRI scan and it's negative, because you've got changes on both sides, as so many of us do, and is it causing a problem or not, well, now there's T2 fat saturation, which can show inflammation of the issue around an inflamed facet and how the synovia. And this is within the last six months.

DWI with stroke, look what it's been able to do. And so I -- I think that MRI is an area which might provide that continuum of brain injury that we could express numerically to use as a meaningful surrogate marker in future studies, again, thinking

ahead to 2010.

DR. MARLER: I think in the meantime, kind of the consequences of what I was saying, is that if there is a neuropsychological outcome, it might begin as a more or less -- something like a six-point scale. And then, at the upper end of functioning, it might have to break up into many smaller points, depending upon the outcome that you're looking at.

But I still think that you'd get a lot of information from a relatively simple, straightforward brain function scale. I don't know, I'm thinking of a Rankin scale or any similar scale that assesses a person's ability to function.

And I think what's more important for clinical trials is the reliability of those scales. The ability of different people evaluating the same patient at the same time to get the same scale value is incredibly important as to how well -- how much power you get out of that particular outcome.

ACTING CHAIRPERSON MAISEL: So it seems we've discussed a number of different scales, all of which have shortcomings, many of which may be

acceptable under the right circumstances, such as with the goal being that they be accurate and reliable in the patient population that's being studied, if that's possible, although it sounds like that may not exist right now.

DR. MARLER: Dr. Brott and I are both familiar with the statistical methodology of global outcome measure that combines several different measures. You could combine, you know, the presence of lesions on an MRI scan with a Rankin scale with a Trail Making B Test. And it gives you the ability to kind of increase your power rather remarkably.

ACTING CHAIRPERSON MAISEL: Dr. Normand?

DR. NORMAND: I did bring up the statistics first, so I'm going to interject right now in terms of the analysis of using the scale measures. And yes, indeed, there are novel methods, statistical methods, to include multiple measures, either serial measurements combined with survival as well as combined with more biological measures.

I think, you know, this is all important. However, I do think it poses a challenge to the

sponsor of such a trial to do the power calculation for that analysis. And while it could potentially provide a more powerful study, I do think that the FDA needs to be open-minded about looking at such calculations in order to: a) identify a clinically meaningful improvement when you have a multivariate type outcome.

And it's not that it's not doable; it's doable, but I don't -- I've not seen such calculations done where people around the Panel will say, "Well, I understand that," because actually it's enormously complex. It's right, but yet it's complex.

The other thing that I'd like to mention -- and Dr. Lazar mentioned this when he was speaking earlier -- and that has to do with the fact that when we have -- a question was raised by one of the panelists about the missing data. We do have an issue with Items A and B, and that is survival and the outcomes. They are related. Obviously, if you're dead, you can't be measured on a particular outcome. And so we have to worry about informative censoring.

So there are other statistical issues that

are raised when you consider both A and B. I actually vote for having both A and B. I think you should consider items in addition to survival when you're doing such a trial. I'm just recommending that we need to be more open-minded about the type of analyses that are done when you have such data available.

And, moreover, I think there needs to be a little more broad-mindedness regarding the power and sample size calculations that are provided in such a trial.

ACTING CHAIRPERSON MAISEL: Dr. Somberg.

DR. SOMBERG: Often these trials are small, and, in fact, until recently I think one of the problems in resuscitation work was that the small numbers of patients in many of the critical trials -- I think it is to be encouraged that you have larger n's in this area of study.

With that said, I think that emphasizes the need to have the secondary endpoint evaluation simple. So, you know, it's nice to do some of this work, but I think it may be up to the NIH to do multiple MRIs, etcetera, in a circumstance, while to

develop certain devices one has to come up with simpler measures of neurologic function. Otherwise, these studies may end up with 20, and then you'll be faulted for the number, and you really have to have -- the number is what I think is most critical.

DR. BROTT: I would agree with that. And I was actually thinking just before you spoke that -- can you justify MRI after an arrest today as standard of care? And I think we're getting close to that. And in terms of the companies needing to pay for it, for example, but I think we're getting close. And I certainly predict by 2010 MRI would be standard of care, and so would not be -- necessarily be part of the research budget.

It might be tricky, but I think that it's a technology we could still use, like a lot of the standard of care things that you're getting already.

ACTING CHAIRPERSON MAISEL: Why don't we move on to Part C.

MS. WOOD: "Are there clinically acceptable surrogate endpoints that can be used? For example, return of spontaneous circulation, 24-hour

survival, hemodynamic improvement, quality of life, work status, functional status, etcetera. Should these surrogates be primary or secondary endpoints?"

ACTING CHAIRPERSON MAISEL: While much of our discussion focused on this issue, it seems like we're a little bit divided. Certainly, at the one extreme, Dr. Becker's example of a device that calls 911, I think we could all agree would be acceptable, although I doubt there would be a PMA for that device.

I sense that we're split over the things such as hemodynamic surrogate endpoints and, Bram, I wonder if you have what you need, or do you need more specific comments?

DR. ZUCKERMAN: No. The agency can always consider surrogate endpoints, but the real question is, at the end of the day, for a particular device with labeled indication: have you shown in your package reasonable assurance of safety and effectiveness and clinical utility?

So let's go back to the Weisfeldt example, the last example that Dr. Weisfeldt gave, where he utilized a mid-level surrogate, but then the real

outcome of interest went in the reverse direction.

So that's a problem for the FDA at the end of the day. And certainly if a sponsor were to proposal some type of surrogate endpoint, due to the argument that some have posed that we're trying to treat one portion of the chain of survival, I think still the agency would need to see how the chain finishes up at discharge from hospital, hospitalization discharge rates, what's happening, what power we have for some of those secondary endpoints to look at negative trends, etcetera.

So it's not a simple question that you're asking us.

DR. ORNATO: I have a question.

DR. ZUCKERMAN: Yes.

DR. ORNATO: I have a question for you, Bram. What I think Mike elegantly put forth as a hypothesis is this whole issue of a strategy trial versus a single-drug or a single-device trial. And that's a hot topic, and resuscitation, as most of you know, these days.

And we look at AIDS as an example, where

multi-drug cocktails are used or Hodgkins' Disease or childhood leukemia or even some of the carcinomas -- breast -- where strategies that use in some cases surgical intervention followed by X-ray therapy and/or chemo in some combination are now in many cases appropriate therapies that are advances.

Here's my question. Non-FDA -- already non-FDA approved interventions, like a new CPR device, in combination with a drug, or perhaps two drugs, may be required for a sensible strategy going after the physiology. Is that something that could be handled by the existing regulatory process?

In other words, suppose a trial is done, and in the end a cocktail with three totally unapproved things -- a) would it be allowed to go forward? Is there a way? And b) in the end, could you give each of those three things labeling? Obviously, it would have to be in concert with the other two. But do you see the problem?

DR. ZUCKERMAN: Yes.

DR. ORNATO: Is it solvable?

DR. ZUCKERMAN: Fortunately, we have an

office of combination products, and we're already starting down that road with the drug-eluting stent approvals. And certainly we'd be interested in talking with any potential sponsor that wants a device and drug approved simultaneously, and all of the, you know, labeling quandaries.

But I think -- let's perhaps keep it a little bit simpler and get back to the way you started your response to my comments. I'm glad you mentioned the AIDS example. It's a great example where an appropriate surrogate was developed for trying to improve the efficiency of treatments.

However, I think one needs to recognize that there was a lot of work developed by NIH and others of putting data sets together to really validate the surrogates, etcetera. One problem perhaps I still see is in our discussion here of the literature, the quality of these surrogates, is still questionable. And that becomes a question, then, for FDA at the end of the day, and it goes back to Dr. Weisfeldt's points.

DR. HALPERIN: Let me just make one --

ACTING CHAIRPERSON MAISEL: Dr. Halperin, and then Dr. Becker.

DR. HALPERIN: One quick point on that, because although I know cost is not supposed to be an issue with the FDA, but, in fact, cardiology trials have been all over the map, anywhere from a few patients to many, many tens of thousands of patients.

And cardiac arrest trials can be very difficult to do, and, in fact, a number of trials that have shown improved return to spontaneous circulation and 24-hour survival probably would have shown improved long-term survival if the studies were much, much larger, because, in fact, some of the differences in the survival to discharge group have been much larger, in fact, in differences that have been shown in other areas like in survival using thrombolytics.

So I guess part of this issue is that, is it the agency's mission to really make megatrials happen in cardiac arrest research where nobody is actually going to do them? And then, are we going to then potentially be in the situation of denying potentially very useful advices simply because there's

not enough money to actually do a trial that's big enough?

DR. BECKER: I'm wondering if I can just ask a question. And it follows up on something that Dr. Yancy raised, which is just, have we used the post-market data to sort of our full ability to use? And I'm just wondering how the agency feels in terms of our current use of post-market.

In other words, we're very, very concerned that sort of this -- this whole demonstration of effectiveness and, you know, as we move into sort of the next decade with more and more devices and possibly combinations, and very complex types of potential physiology, you know, is the post-market, you know, an opportunity to provide additional input to the agency on a device?

DR. ZUCKERMAN: The agency is always concerned with finding the right pre-/post-market balance. And certainly in response to Dr. Halperin's concerns the agency is also -- Center for Devices and Radiological Health is also obligated to find a least burdensome way for device manufacturers, etcetera.

1 But by the same token, let's take the
2 example that you've posed, Dr. Becker, of, can post-
3 market be a substitute? No, it can't be a substitute
4 if up front we haven't met our specified goals of
5 reasonable assurance of safety and effectiveness and
6 clinical utility.
7 But certainly that benchmark may not be
8 perhaps, you know, an improvement in the rate of
9 neurologically intact patients who are in the
10 hospital. And, yes, I think there definitely is a
11 role for better development of post-market study of
12 these devices to appreciate the iterative way that
13 these devices need to be developed.
14 Certainly, our experience in the past has
15 been that once a product is approved, generally the
16 manufacturers may lose interest quickly in doing post-
17 market studies. But that's why we're here today about
18 trying to change the paradigm.
19 ACTING CHAIRPERSON MAISEL: Why don't we
20 move on to question 3, please, Geretta.
21 MS. WOOD: "Based on the clinical
22 endpoints discussed above, what length of followup

should be considered for the efficacy endpoints? If a device was associated with a 24-hour survival advantage, but did not improve hospital mortality, would this device be considered efficacious?"

ACTING CHAIRPERSON MAISEL: It seems we already touched on this topic quite a bit. There can be numerous endpoints along the way -- resuscitation, and with return of spontaneous circulation, hospital admission, hospital discharge, etcetera. It sounds like from the FDA perspective, and perhaps from the Panel perspective, hospital discharge alive is an important endpoint.

Do people feel that's something preceding hospital discharge as an acceptable endpoint? Hospital discharge alive?

Dr. Somberg.

DR. SOMBERG: Well, what I said before, I think under certain circumstances for certain types of devices we might ask less. You know, survival one hour and 24 hours might be a consideration when other things are to be followed. But you wouldn't want to base it on just some sort of a priori surrogate, which

sounds physiologic.

But I think to ask for, you know, what happens 30 days later, and it's often 30 days to get out of -- 10 days to get out of the hospital is -- there's a tremendous chain of events that's occurring. And I don't know if you want to have cardiac surgery and all other considerations confound that.

But that said, it's important to find that data out, because if it doesn't do any difference, or markedly negative, that may impact on the use of the device.

ACTING CHAIRPERSON MAISEL: So how do you feel about the statement here, "If a device was associated with a 24-hour survival advantage, but did not improve hospital mortality, would this device be considered efficacious?"

DR. SOMBERG: I would say with certain panels with certain devices with a PMA, it may be efficacious. But not if it's aimed towards an intervention once you get to the hospital for long-term outcomes.

Let's say you had something to improve

neurologic function, whichever way you would do it, and you gave it the -- it made no difference on how people: a) got out of the hospital, and b) how they neurologically functioned, the small subset that got out had no difference in neurologic -- it would be a negative study, even though they may show some changes like MRI or brain scan, reduced infarc, reduced -- whatever.

So it's very hard. You know, you're asking to be pinned down in advance, and to write sort of like a check without filling in the amount.

(Laughter.)

ACTING CHAIRPERSON MAISEL: Dr. Brinker.

DR. BRINKER: One might get the impression that what we really are looking for is a magic bullet that we can utilize in any scenario where a patient has an arrest in a hospital, out of hospital, untimed or anything else.

And that magic bullet would bring about a prolonged survival or at least post-hospitalization survival, in a neurologically intact person. And, theoretically, anything short of that would be not

acceptable.

And I think what we do when we think in those terms is to exclude the building blocks, the iterations that usually go into eventually the development of something close to a magic bullet or combination bullet, that can achieve this. And I would hate to think that we're frustrating progress or evolution by insisting on too high a threshold for acceptance, even though that threshold would not seem to be ideal or even satisfactory.

Again, this brings up the issue of efficacious versus clinical utility. Something that keeps you alive while you're doing it may be efficacious, but it's not clinically useful unless it keeps you alive way after you stop doing it. And if that's going to be a significant obstacle, we may be delaying the evolution of the ultimate magic bullet, if such exists.

ACTING CHAIRPERSON MAISEL: I think it also leads nicely into our next question, which is the balance of effectiveness with safety, which may also have an impact on what are acceptable endpoints and

time endpoints.

MS. WOOD: "What should the primary composite safety endpoint include?"

ACTING CHAIRPERSON MAISEL: Jeff.

DR. BRINKER: I'd like to just make a shot at some things. I mean, clearly, it shouldn't cause -- a study drug or device shouldn't cause increased damage in a system over the control. I think that would be the primary safety endpoint.

Assuming that there is no other -- assuming that there is either equal efficacy -- that there is equal efficacy, the two modalities, or superior efficacy in the study arm, the safety part of it would be an issue that the study arm shouldn't cause more damage than the accepted or standard arm.

ACTING CHAIRPERSON MAISEL: Dr. Weisfeldt.

DR. WEISFELDT: I'd also argue that from a safety point of view the -- having data on safety through the period of hospitalization as a reasonable standard. Thinking about the possibility that there may be a device, may be a drug -- epinephrine -- where ROSCs may be improved because you improve myocardial

1 blood flow, but you diminish gut blood flow, it's well
2 documented that Gram-negative sepsis is a common
3 accompaniment in the first week or so after
4 resuscitation with GI organisms.
5 So it could be that the effect of a drug
6 or device may be to improve 24-hour survival, but yet
7 from a safety point of view or a complication point of
8 view, serious complications may occur in that period
9 between 24 hours and discharge from the hospital that
10 would be undetected if we weren't looking for or
11 insisting on safety in that period of time. So I --
12 it just goes back to the same theme that safety issues
13 are more than 24 hours.
14 ACTING CHAIRPERSON MAISEL: Joe.
15 DR. ORNATO: I think that Dr. Lazar has
16 enlightened all of us, and I'm personally very
17 appreciative because I've learned a lot from his
18 comments and summary this morning. Many of us
19 previously -- and I'll speak for myself -- thought
20 OPC/CPCs were perhaps a little better than they really
21 are.
22 But I think the concept of neurologic

outcome as a safety measure is clearly at the top of what I would think my list would indicate. I think the idea of having some measure -- obviously, we need a better one -- of neurologic outcome, as well as overall performance measure return to some kind of functional status has in the CPC/OPC -- is still probably valid, although I think I've been convinced this morning that we clearly need better tools.

The final piece of this, though, is that in this really unusual area of clinical medicine and emergency critical care, I think one could make an argument that death is not the worst outcome. In fact, I would like to make that argument.

I think a severely neurologically impaired person who survives for a significant period of time, but without what I think most of us would consider even to the naked eye meaningful existence to themselves or those around them, is arguably far worse than a merciful, rapid death.

And so I think as the agency looks at this complex question, one of the paradigm shifts that explicitly I think is obvious to me is that perhaps

some kind of a scoring system, as the question is begging might be worth researchers considering and worth the agency considering looking at. And that it may very well have a rank that's very different from most other clinical trials.

ACTING CHAIRPERSON MAISEL: Dr. Yancy.

DR. YANCY: The safety issues are largely device-specific, whether it's a resuscitative device, a defibrillatory device, a chest compression device, etcetera. But I think along the same lines of the safety referable to the device is the safety of the application. That is to say, there is a learning curve. There is a teaching phenomenon that has to occur.

The greatest example would be the minimally-invasive open chest massage. I mean, the technique might be perfectly appropriate and may do a great job getting your surrogates met. But if the learning curve is so steep, then it becomes a problem, because any device or platform that is developed will be widely distributed to people with widely disparate skill levels and aptitude levels.

1 So I think any safety equation is not only
2 the safety of the device per se but the safety of the
3 application.
4 ACTING CHAIRPERSON MAISEL: I think that's
5 an excellent point. So, in general, it sounds like
6 our primary safety endpoints are also our
7 effectiveness endpoints and mortality neurologic
8 outcome. There are some device-specific endpoints
9 such as bleeding or infection for hypothermia devices,
10 which we'll discuss later, etcetera.
11 So we discussed -- well, you can read
12 question 5, if you want.
13 MS. WOOD: Okay. "What length of followup
14 should be considered for the safety endpoint?"
15 ACTING CHAIRPERSON MAISEL: And we've
16 discussed this as well. It sounds like at least
17 through the hospitalization would be a reasonable
18 endpoint for that. So now why don't we try to wrap
19 things up pre-lunch and go quickly through the study
20 design. And I think I'll just have Geretta read the
21 questions, and we'll go right into them.
22 MS. WOOD: "Can a scientific study be

performed using a single-arm study with historical controls, U.S. and/or OUS? If so, should the historical controls meet the same inclusion/ exclusion criteria? Do you have any suggestions on how to reduce bias if historical controls and/or OUS data are used?"

ACTING CHAIRPERSON MAISEL: John.

DR. SOMBERG: I don't think historical controls could be used in this area very effectively, and it would be nice to say so, but I think things are changing. There are differences especially with different data sets from Europe versus the United States who were, we heard, who participates.

So I really don't think that's the case. I really think you need a randomized group. A company would be risking too much on differences, and I think it's more risky for the company versus cost than it is even for the -- you know, that's -- that would be even worse than the bad scientific data that's collected. So I strongly recommend randomized control trials.

ACTING CHAIRPERSON MAISEL: Dr. Normand.

DR. NORMAND: I heard today that time is a

1 big confounder, that things are changing rapidly. And
2 if that is, indeed, the case, then I don't see how you
3 could use only historical control data. So it seems
4 to rule out the use of historical control data.
5 I would say, though, that Dr. Somberg was
6 using the word "randomized" and "historical control."
7 I think there's a difference. You could have
8 prospective non-randomized studies. It's a difference
9 between historical control and -- they're two
10 different things. So let me just add that correction.
11 DR. SOMBERG: I'm advocating both,
12 prospective and --
13 ACTING CHAIRPERSON MAISEL: Anyone
14 disagree? Okay. 7?
15 MS. WOOD: "If the study is unblinded, do
16 you expect any substantial positive or negative
17 placebo effect, or an effective investigator bias on
18 patient selection or endpoint evaluation? If so, how
19 can these problems be minimized?"
20 ACTING CHAIRPERSON MAISEL: Dr. Brinker.
21 DR. BRINKER: Well, it seems like 90-plus
22 percent of these studies have to be unblinded to the

operator. It's going to be hard to do any kind of CPR study that's double-blinded. So I'm not sure how that exists.

But I do think in non-randomized studies, which gets back to John's comments, as opposed to contemporary non-randomized studies, if you have a randomized study it sort of helps lessen the impact of operator and investigator bias than if you have contemporary non-randomized trials.

ACTING CHAIRPERSON MAISEL: Dr. Normand.

DR. NORMAND: Do you have a comment?

DR. MARLER: I was just going to say one common way to deal with reducing the bias, which can be immense, is to have an observer of the outcome later on who has no way of knowing how the patient was treated as completely independent from the study, and in which someone monitors the -- you know, is sure that the patient isn't -- understands they can't tell -- if the patient happens to know how they were treated, can't discuss that.

So a blinded independent observer in some ways affects this, but the -- you have to worry,

1 though, in that case that there's biased ancillary or
2 secondary or followup treatment introduced in the care
3 of the patient by physicians who know how the original
4 treatment was given.
5 DR. NORMAND: That was the point I was
6 going to make. And an additional point I was going to
7 add is that I think that most trials do this, and even
8 observational studies do this, is to have a good data
9 collection system in hand in order to measure sort of
10 the degree or the intensity of treatment that is
11 indeed applied. So at the very least, you have it
12 measured.
13 ACTING CHAIRPERSON MAISEL: Dr. Somberg.
14 DR. SOMBERG: I think with all this said,
15 attempts should be made to try to intervene in both
16 arms of the study to blind -- for instance, if one had
17 a device for cooling, it may be important to hook up
18 that device and to do everything but to bring the
19 body's temperature down four degrees.
20 It may be important to put something --
21 you know, to take -- to stop whatever you're doing,
22 put something on, and provide some sort of hemodynamic

augmentation, even though it doesn't provide the right augmentation, because all that may certainly confound the study, and the less confounding you have the better off you are.

ACTING CHAIRPERSON MAISEL: Henry.

DR. HALPERIN: Yes. This is an issue where disinterested third parties should probably be the people that are actually doing the CPR. This is one of the disadvantages that have occurred or at least been perceived to have occurred in in-hospital studies where the actual investigators actually doing the CPR.

I think there is inherent propensity for bias in that situation, where people who have really no particular interest in the study -- financially, intellectually, or anything -- would be the appropriate people to then do this. And I think that mitigates some of the bias that could be otherwise potentially there.

ACTING CHAIRPERSON MAISEL: So I think the general message is blind whenever possible, certainly blinding the outcome assessments such as neurologic

evaluation.

Dr. Zuckerman, did you have a comment?

DR. ZUCKERMAN: Yes. I'd like the CPR experts to respond to this point. Certainly, in most areas of device trials, we see negative placebo effect, meaning if you are randomized to the control arm it's a problem for the patient and the doc, even if there is no involvement of the doc in the device company, etcetera.

With CPR trials in the CPR arm, how do you assess the quality of CPR, the control?

DR. SOMBERG: Well, there may be a play of previous data, historical controls. If your control group is so much worse than what everyone else has done to show a signal, some -- there's a problem awry.

ACTING CHAIRPERSON MAISEL: Dr. Halperin.

DR. HALPERIN: Yes. There are some precedents for this, and some trials have actually had an independent third party who is actually observing the CPR, like an ACLS instructor, or what have you. And how good that is is questionable, but there were two really nice studies, fairly large -- one 500, one

about 900 patients -- where ACLS instructors actually observed people doing CPR, and actually the people that did better CPR did better. So it was actually consistent.

But for most trials, there is no way to do it with the current technologies. That may change with newer technologies, but it really is a very difficult question that really is still open today.

ACTING CHAIRPERSON MAISEL: Why don't we move on to question 8, please.

MS. WOOD: "Should the trial design be a non-inferiority (equivalence) or superiority study for safety and efficacy? Under what conditions should an equivalence trial be acceptable? Limited labeling claims.

"If not inferiority, what equivalence deltas would be clinically acceptable for the safety and effectiveness endpoints discussed above? If superiority, such as new technology, would need to demonstrate improvement over current technology, are there new clinical trial designs that can be considered such as superiority for surrogate endpoint

and equivalent hospital discharge rates? Or additional post-market studies on devices technologies to supplement initial pre-market approval safety and effectiveness data?"

ACTING CHAIRPERSON MAISEL: Jeff.

DR. BRINKER: Bram, I just want to get the thrust of this question correctly, because if we're dealing -- let's say a CPR device for hemodynamic benefit, there are no equivalency -- there is no equivalent, right? So it would be impossible to do that study for this category of device.

DR. ZUCKERMAN: Right. But we're talking more generally here. For example, suppose there was a CPR device that was proposed to not improve survival, but just to make CPR easier for the operator, something like that. You know, what do you need in an equivalence trial?

DR. BRINKER: Well, that would be a PMA application, because otherwise it could be cleared through a 510(k), if it was just making it easier for the operator. And the only difference is that it would be a PMA because the labeling would say, "This

makes it easier for you."

I'm trying to put this in the context of, really, what we're trying to settle here. But -- go ahead.

DR. ZUCKERMAN: You know, I think in a general context there could be CPR devices that are so-called equivalent to standard CPR, and the agency would need to consider that application, regardless of whether it's 510(k) or PMA. I think that we would need to see clinical data, and it's important to recognize that, you know, 10 percent of our 510(k) applications, say, need appropriate clinical data.

So let's pose the question, you know, how do you define "equivalence" in a CPR trial?

ACTING CHAIRPERSON MAISEL: Dr. Yancy.

DR. YANCY: Well, I think the only way that we can approach that, Bram, is that we have to look at the limited metrics that are available. And so if we know what the best outcomes are for what return of circulatory stability, or if we know what the global outcomes are for either being discharged, or discharged intact, then as meager as they may be

they become the benchmarks.

And so that would be the reference point for designing a non-inferiority approach, but that's -- I think that's all we can do in that regard. And there may be methodologies for which there is no benchmark, and then you've got to take a totally different approach.

ACTING CHAIRPERSON MAISEL: Dr. Normand.

DR. NORMAND: I have a question about the equivalence and the suggestion that was just made by Dr. Yancy. I guess in terms of if it was going to be equivalence, then I think understanding -- and maybe I'm jumping ahead in terms of how you actually determine equivalence, because I think collecting the data, and having the data available that tells you how much uncertainty is attached to the, let's say, devices already in the market, I think that's a very important problem.

And, hence, I would argue that to define "equivalence," either clinical or even beyond that, I think we need more than just one number. And so I'm worried about equivalence trials in terms of being

able to have the information available to say what the size of the delta would be, because I'm not sure about the line in the sand and where that line is.

So we need information. We need access to information to say sort of what the current state is, and not that it's 20 percent, or whatever it is.

ACTING CHAIRPERSON MAISEL: That gets back a little bit to our discussion earlier about what type of trials would be acceptable. Historical controls I think we decided would not be acceptable. So, for example, a randomized trial might -- would certainly answer that type of question.

DR. NORMAND: Would answer that, yes.

ACTING CHAIRPERSON MAISEL: Why don't we move on to question 9, please.

MS. WOOD: "Discuss the possibility of developing a registry and using the data for future studies. What are some of the necessary data points that should be collected, keeping in mind the use of this data as historical controls for future studies?"

ACTING CHAIRPERSON MAISEL: Sharon.

DR. NORMAND: Okay. I know we all want to

go for lunch, but I actually sat down and thought about this just because we do a lot with -- as I assume everybody here does, with registry data.

So I thought I would take the first crack at it and sort of giving some suggestions in terms of key items that I thought should be in there. But let me throw out the first one. I think it needs to be auditable. You have to be able to audit some of the elements in such a database. And I'm going to say that as the first point.

We could talk about I'm just sort of saying in an ideal world. I think the other thing that would be important to be in there, given that it's been mentioned about confounding over time, is I think that the information that needs to be in such a registry have to be collected in detail that we had information with regard to potential confounders that relate to time of entry, time on the market, when it's done, things of that nature.

And in addition to the -- sort of the usual character -- and people are going to say the usual things in terms of the characteristics of the

patients, the characteristics of the outcomes that are measured.

I do think that in having a registry, in order to tap into some of the information that's going to be needed to supplement either a new design, a new trial, or to understand what's happening currently, I do think a lot of information with regard to the operators of the device and information about the timeframe in which the treatment is undertaken.

And then I think, lastly, I -- I know this is a little bit technical, but I think if we're going -- if one is going to use a registry in order to infer, let's say, effectiveness, then I think one needs to think about including elements that perhaps one wouldn't normally think of including.

And what I mean by that are I think we need to find data that would be related to who got what treatments, but not related to particular outcomes. And for those of you that know what I'm talking about, we need to find an instrument. And so there needs to be the usual cast of information that is typically in a registry, but I guess I'm arguing

for it to include probably much more detail about the operators, about the site where it's being -- where the data are being collected.

And then, I guess lastly I'll just emphasize that I do think you need to have the opportunity to be able to verify the elements in the registry.

ACTING CHAIRPERSON MAISEL: Dr. Becker.

DR. BECKER: Yes, if I can just maybe add something. It seems to me that one of the potential useful roles for a registry would be to look at adverse events that are not obvious initially, and that there may be a real role for registries in the specific sort of demonstrating or describing adverse sorts of events that are not clear and in early trials.

And the other thing that -- where I think registries may be very useful is for the setting where there's a very -- if you will, a very narrow indication for some type of a device. And the example that comes to mind is sort of like the pediatric defibrillation pads, that -- you know, that was --

that was a device that has been approved, and we knew that there would just be a very small number of patients that would really be appropriate for the use of those types of pads.

And I think it is to the agency's credit that what -- as I understand, was really what came out of that was the notion that there was initial safety data that was presented, and then the idea of an ongoing registry to follow what -- how that data would accumulate, because if we required -- you know, if the bar was a demonstration of survival, you know, we wouldn't have pediatric pads for another 100 years basically. I mean, and that's -- and I mean that in terms of 100 years.

So I think it's very important that we think and we think creatively in terms of how we can sort of optimize this balance of, if you will, pre-market/post-market type of data, so that we can ultimately do the best that we can for all of the citizens.

ACTING CHAIRPERSON MAISEL: Joe.

DR. ORNATO: Thanks, Bill. Firstly -- two

points. One is, of course, registries do exist. NR-CPR is the one that has been mentioned a couple of times today -- in hospital, fairly large. Out of hospital was driven initially by the so-called Goodstein -- first set of Goodstein guidelines. There are now pediatric Goodstein guidelines and a number of other derivatives.

NHTSA developed a DEEDS database, and that, to some degree, has influenced an out-of-hospital project that National Association of EMS Physicians have underway.

But if you look critically at these registries, the problem has not so much been defining the data points. They need to be improved -- everyone knows that -- and they are being improved. But we have a really good starting point.

The problem is they're all biased. They're all inadequately numbered in terms of numbers of cases, and they tend to be a fairly small, fairly biased, select group of sources. For example, NR-CPR has only 400 hospitals in it. The out-of-hospital project that's underway is still really in a pilot

phase.

And particularly for the out-of-hospital registries, we're still struggling with this whole issue of: does HIPAA apply? And if so, when and how? And out-of-hospital registries are struggling trying to figure out if there's a lawful way for them to get -- even simply survive to hospital discharge data. Forget any kind of neurologic outcome.

So the first issue is registries do exist. The methodologic problems do exist, but I think they are solvable. The broader issue is one of society at large really trying to figure out whether we want cardiac arrest to move forward like cancer and trauma have.

They've both been driven greatly by the presence of registries, certainly cancer has, and certainly I think we would all have to accept trauma has as well with the need for trauma registries that are a requirement of our trauma centers nationally. So that's the first point.

The second point is related to it, which is this whole issue of the philosophic, perhaps

1 governmental choice, and that is whether an agency
2 like CDC, which I think is looking at this right now
3 from our conversations with them, should really
4 champion, perhaps with the help of others, this notion
5 that cardiac arrest should, in some form, perhaps
6 certain categories of it, be reportable.
7 That would tear down a lot of the HIPAA
8 problems from the get-go, if a governmental entity
9 required it. It would also deal with a lot of the
10 political and operational issues that hospitals are
11 struggling with whether they want to pay the price tag
12 for the data collection and the filling out of forms,
13 etcetera, etcetera.
14 So that's my two cents. I think it's a
15 very important question you're asking, and I think if
16 it's possible to create a registry by whatever number
17 of years, but certainly by the Healthy People 2010,
18 that would -- that would be a major jumpstart to a lot
19 of things. And it would certainly, I think, help the
20 FDA's effort.
21 ACTING CHAIRPERSON MAISEL: Why don't we
22 move on to the final question.

MS. WOOD: "Can uniform definitions of adverse events be created? If yes, by whom?"

ACTING CHAIRPERSON MAISEL: Should we take that as a no, they cannot be created?

(Laughter.)

Dr. Somberg.

DR. SOMBERG: Take it as a yes. I don't know why I'm -- but take it as a yes, they probably can be created. And it relates to the very interesting discussion the last five minutes. Is there some registry or group -- maybe the CDC or someone else would need to do some standardization, because it's going to be important. If you have a registry, but you don't have definitions, what are you recording?

ACTING CHAIRPERSON MAISEL: Any other comments? Yes, Al.

DR. HALLSTROM: This actually goes back to 8.c. I had a comment here, but I forgot it. The question was whether you could use new trial designs such as a surrogate for the endpoint with equivalent hospital discharge. And I think that sort of thing

should definitely be explored.

I've just looked at some of that recently, and, for example, a number of trials that were showing up here with non-significant hospital survival, but significant hospital admission, had you used a bivariate endpoint so that in -- which is essentially what's being advocated here, those probably would have been significant bivariate endpoints in the right direction.

The problem, of course, when you go to a bivariate endpoint is if you end up somewhere off -- not on that diagonal where you have the same proportional hospital effect, you don't exactly know how to interpret what you're going to do with it. But in terms of sample size, for example --

DR. ZUCKERMAN: If you don't know how to interpret it, perhaps another trial.

DR. HALLSTROM: Right. Maybe another trial. But in terms of sample size, if you're planning for that proportional hospital survival, one of the studies I looked at you had to -- to look at hospital survival per se, you had to have almost a

three-fold increase in sample size over hospital admission.

To look at the bivariate endpoint, you needed about a 20 percent increase in sample size. So I think there are considerable savings, and these kinds of things should be looked at carefully.

ACTING CHAIRPERSON MAISEL: Well, thank you very much.

Why don't we adjourn for lunch, and we'll reconvene in one hour at 2:05.

(Whereupon, at 1:05 p.m., the proceedings in the foregoing matter recessed for lunch.)

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

2:08 p.m.

ACTING CHAIRPERSON MAISEL: Good afternoon. I'd like to begin this afternoon's session in which we'll be discussing CPR and hypothermia. I invite the FDA to begin their presentation.

MR. FELTEN: My name is Richard Felten and I'm a reviewer in the General Surgical Devices Branch, and what I'm going to do is just to do a very brief overview of the devices that are now available for induction of hypothermia. Next slide.

The most common device, obviously, that everybody's really familiar with of course are the cooling blankets. And these devices basically include blankets or even the more complex things like chest vests or leg wraps and so on. And their intended purpose is to simply provide surface cooling using the circulating air or water. And these devices have indications for use that are basically to induce hyper- or hypothermia, or for localized temperature therapy.

Next type of similar product are the

cooling surfaces. These are actually cooling tables on which patients are simply laid. And in this case, the device simply uses circulating cold air to make the table and the surface cool. And these devices are marketed simply for use in treatment of patients who need to be cooled.

Another device that can be used although it is not usually used of course are -- next slide please -- simply cold packs. These of course would be ice bags, or the standard kinds of cold packs that we usually use for localized cooling. And these are actually marketed simply for cold therapy for body services. And these also could be used.

The next device actually is the external heat exchange systems. And in this case you have a series of individual items that are put together to provide the hypothermia. You have the heat exchanger which is intended to cool or warm blood. You have circulating pumps that circulate the blood from the body externally to the external heat exchanger, and then back into the body. And there is a system controller that regulates the whole process which is

1 involved in regulating the blood flow, monitors the
2 temperature, and maintains either the cooling or the
3 warming, which can be done as required.
4 The most recent and the newest product are
5 the endovascular cooling systems. These systems are
6 essentially the same as the heat exchange system in
7 that again you have an external heat exchange system,
8 you have circulating pumps, and you have central
9 controllers. However, in this case, the cooling is
10 actually done internally in the body. In this case,
11 the catheter is used, placed usually in the vena cava.
12 Cold fluid is circulated through these catheters.
13 There is a heat exchange system at the very tip. And
14 the blood is actually cooled within the body itself.
15 When these were introduced or brought to
16 our attention, we were somewhat concerned in this case
17 that there may be some differences in safety profiles
18 between internal cooling of the blood versus the
19 external cooling through the external heat exchangers.
20 And in this case, the agency determined that we did
21 have some questions about safety, and therefore, as
22 you'll notice up here, instead of having just general

plans for hypothermia or maintaining temperature, these devices actually have very specific indications for use. You have a cardiac surgery plan for achieving or maintaining normothermia during surgery, recovery, intensive care. You have an induce, maintain and reverse mild hypothermia in neurosurgical patients during surgery, peri-intensive care. And you have a fever reduction in a specific patient population as adjunct to antipyretic therapy in patients with cerebral infarcts and intracerebral hemorrhages, which require access to central venous circulation.

And all three of these indications were all based on clinical trial data, and which we did look both at the effectiveness of the device to achieve or maintain the production of the hypothermia, or maintaining temperature, and looked at safety. And it's this issue, or this is one of the issues that we're asking the panel to discuss as part of their discussions today on whether or not the endovascular cooling systems do or do not present different questions compared to the external cooling systems,

and is the mechanism of action of producing hypothermia the same or different between these two systems.

And I'd like to now introduce Dr. Julie Swain who will actually give a presentation on some of the clinical information about hypothermia. Thank you.

DR. SWAIN: We're going to switch slides here for a second. Pleasure to talk to the panel today. And I'm going to talk about the topic of post-event hypothermia because some of the devices that we're looking at, perhaps there's been interest in the community of looking at these devices for post cardiac arrest hypothermia.

And I'll introduce the topic by talking about some trials, and myocardial infarction, and acute head trauma, then look at post-event hypothermia and resuscitation. Talk about the ILCOR recommendations that Dr. Collins talked about earlier this morning, the clinical studies upon which those are based, and then kind of an executive summary of the questions for the panel. Next slide.