

1 Well, in myocardial infarction, there was  
2 the COOL-MI study. And this is all from data  
3 presented at TCT last year, and it can be found on the  
4 Web under the Web address listed here. This was a  
5 prospective randomized trial, reasonable-sized, and it  
6 was cooling with one of the endovascular IVC  
7 catheters, versus normothermia during percutaneous  
8 coronary intervention. They had to have a myocardial  
9 infarction less than six hours prior to it. It was  
10 normothermia versus 33 degrees for I believe it was 24  
11 hours, not three hours. That's a mistake. Or no,  
12 excuse me, it was for three hours, sorry. And it had  
13 a relatively quantitative endpoint, a surrogate, which  
14 was infarct size at 30 days by spec. Next slide.

15 And what this showed was that there was  
16 really no difference in the endpoint between these two  
17 studies. Notice that the N for hypothermia in blue on  
18 all these slides, and normothermia in red. The N was  
19 177, which is a reasonably sized device trial. But  
20 again, no statistical difference. Next slide.

21 What is very interesting to us is that  
22 this study was not powered to detect individual safety

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1 events. But when you looked at the main serious  
2 adverse events, there was a trend towards a higher  
3 death rate, vascular bleeding, DVT, shock, pulmonary  
4 edema in this, although none of these were  
5 significant. But in a reasonably sized trial, this  
6 was sort of an interesting trend. Next slide.

7 Well, what about the brain injury studies?

8 And Guy Clifton at UT did a reasonably large study on  
9 acute brain injury. This was again prospective  
10 randomized trial, normothermia versus hypothermia, 33  
11 degrees for 48 hours, injury less than six hours old.

12 They used surface cooling and GI cooling. Endpoint  
13 was Glasgow Outcome Score at six months. And then  
14 they had a series of secondary endpoints. Next slide.

15 Which were many of the tests that Dr. Lazar spoke  
16 about this morning. Next slide.

17 And the results of the trial, absolutely  
18 no difference. And again, an N of 199 on the  
19 hypothermia group, a fairly large trial. And non-  
20 significant for all secondary endpoints and the  
21 primary endpoint. Of course, there's a lot of Monday-  
22 morning quarterbacking, or today it would be Tuesday

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1 morning for Minnesota, but whatever. Yes you can  
2 design a trial that's different, and maybe these two  
3 trials, the COOL-MI and brain injury could be used to  
4 set up a hypothesis for subgroup testing in another  
5 randomized control trial to see if in some subgroups  
6 it might be advantageous. But again, the two largest  
7 trials in these two organ systems find no difference.  
8 Next slide.

9                   Again, in Clifton's trial, it wasn't  
10 powered for individual adverse events, but they had a  
11 statistically significant difference in critical  
12 hypotension, more in the hypothermia group, as well as  
13 bradycardia with hypotension. And the percent of  
14 hospital days with complications were all higher in  
15 the hypothermia group. So it brings to some of the  
16 safety questions. All three of these trials bring to  
17 some safety questions that we may well have in the  
18 future. Next slide.

19                   Well, what about post-event hypothermia  
20 and cardiac arrest? And as Dr. Collins said, there's  
21 two randomized control trials that were published in  
22 New England Journal two and a half years ago. One

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1 I'll call the Australian trial, and the other which  
2 was a multi-centered trial in Europe primarily from  
3 five countries. Next slide. Based on these two  
4 studies ILCOR had the following recommendations about  
5 unconscious adult patients, spontaneous circulation  
6 after out-of-hospital cardiac arrest, cooled to 32-34,  
7 12 to 24 hours when the initial rhythm was VF. And  
8 then a level 4 recommendation based really totally on  
9 anecdotes such cooling may also be beneficial for  
10 other rhythms or in-hospital cardiac arrest.

11 And what I'd like to do now is look at the  
12 data upon which these recommendations are based. Next  
13 slide. Well, let's compare these two studies. The  
14 location, Australia and Europe. And as Dr. Zuckerman  
15 said this morning, we've had multiple instances where  
16 European or out-of-U.S. data is really not consistent  
17 with in-U.S. data. You have to look are these the  
18 same kind of patients, are the EMS systems the same?  
19 In one of these studies, I believe it was an average  
20 of two minutes from the 911 or 911-equivalent call to  
21 the EMS service getting on scene. I can tell you in  
22 San Diego you can add a zero to that very often

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1 because it's a different health care system than in  
2 other places.

3 Inclusion criteria in these two studies.  
4 If you're going to use two studies as essentially a  
5 meta analysis to support a recommendation, well, you  
6 can look at the inclusion criteria, and they're very  
7 different in these two studies, especially in the  
8 Australian study. Women greater than 50 years old  
9 were the only ones included, the only females included  
10 in the study. And much more strict criteria in the  
11 European study. It's interesting in the European  
12 study that 91 percent of the patients screened with  
13 out-of-hospital cardiac arrest were not eligible by  
14 these inclusion criteria. Next slide.

15 Well, what about the actual act of  
16 cooling? Well, in Australia it started in the field  
17 with cool packs. In Europe, it started on hospital  
18 admission. Cooling method was cool packs, then ice  
19 packs in Australia; air-cooled mattress and ice packs  
20 in Europe. Target duration: 12 hours in one study, 24  
21 for the other study. Temperature: 33 for one, 32 to  
22 34 for the other. Re-warming: active in one study,

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1 passive in the other. And you can look at some of the  
2 standard deviations and some of the curves in one of  
3 the studies, and you can see that the standard  
4 deviation goes above 38 degrees, which indicates to me  
5 that there was hyperthermia present in some of the  
6 patients. And this is in the control group. And I  
7 think we all know for sure the effect of hyperthermia  
8 on neurological function. There's a great deal of  
9 cardiac surgery literature relating to that. Next  
10 slide.

11 Primary endpoint. Australia, it was  
12 survival to hospital discharge with essentially this  
13 CPC-type score. And I don't know what the  
14 requirements are to go home or to rehabilitation in  
15 Australia versus what happens in the United States.  
16 It's so variable among communities in the United  
17 States. In Europe, it was the CPC score good or  
18 moderate, as Dr. Lazar spoke about this morning. Next  
19 slide.

20 Well, what about the results? And you can  
21 see the success endpoint of either on the left side  
22 Australia discharge home, or at six months on the

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1 right side. And when you look at the difference in  
2 control groups, which looks like different populations  
3 being studied, or different processes of care. And a  
4 p-value of 0.046 on the Australian study, which was an  
5 N of 43 I believe for the number in the hypothermia  
6 group. And if you look at the confidence limits on  
7 the bottom for the Europe study, you know, identity  
8 1.0 is fairly close there. Next slide.

9 Well, you also look at mortality. And not  
10 a statistically different numbers in the Australian  
11 group. And again, when you look at the confidence  
12 limits of the European group, you know, up to 0.95.  
13 So perhaps there's a trend here, but there's also a  
14 couple of questions on how these studies were  
15 performed. Next slide.

16 In the Australian study, originally it was  
17 designed to be a sample of 31 patients in each group.

18 After the study was completed, the primary endpoint  
19 was not significant. Therefore, they enrolled more  
20 patients. I can say that for the agency, the FDA,  
21 that's probably not a study design that we would think  
22 is rigorous enough. The final p of 0.046 is just

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1 that, 0.046. There was no alpha spending penalty  
2 assigned even though -- you could say there was an  
3 interim analysis, but actually it was a final analysis  
4 and then add more patients. So the question is is  
5 this really a study that shows a difference between  
6 the two groups with any rigorous statistical design.  
7 Also, seven of the patients, about 10 percent, were  
8 randomized and treated, and then dropped from the  
9 study. And you worry about selection bias in the  
10 patients dropped. Next slide.

11 European study also. We don't know how  
12 many patients were designed to be in that study, but  
13 they stated that they stopped the study early because  
14 of low enrollment and end of funding. We don't know  
15 if data analysis was performed and then the study was  
16 stopped, or what the status of that was. And we don't  
17 know the planned number of patients in the study. And  
18 we don't know if interim analyses were performed.  
19 Next slide.

20 Well, what about the adverse events? The  
21 Australian study simply says that there were no  
22 clinically significant infections in either group,

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1 which would be far different from any other post-event  
2 hypothermia study done or published. There was really  
3 no mention of any other adverse events. European  
4 study, three patients had hypothermia stop because of  
5 arrhythmia or hemodynamic instability. And we don't  
6 know the complications during hospitalization. All  
7 they reported -- next slide -- were the complications  
8 during the first seven days after resuscitation from  
9 cardiac arrest. And you can see that in every  
10 complication studied that I've listed on the top,  
11 bleeding, pneumonia, sepsis, pulmonary edema,  
12 arrhythmias, there were more, but not statistically  
13 significantly more, in the hypothermia group. And on  
14 the bottom are listed several complications that were  
15 either equal or less than one percent difference in  
16 those. Next slide.

17 And as Richard Felten just said, there are  
18 multiple cooling methods that the agency is looking at  
19 to develop hypothermia, from head cooling, neck  
20 cooling devices, all kinds of surface cooling devices,  
21 GI lavage, which as Dr. Witten told me is really not  
22 regulated by the FDA. There's no devices specifically

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1 for that. And endovascular, meaning extracorporeal  
2 circulation, and IVC catheters. As cardiac surgeons,  
3 we have a long 50-year history of surface hypothermia  
4 and then endovascular hypothermia, and feel that there  
5 are a great number of differences between initiation  
6 of hypothermia in those groups. And the question is  
7 would the efficacy be the same if you have a study of  
8 a surface method that shows improved liver function or  
9 something, and an endovascular catheter. Because you  
10 want to assume that the results are the same for both  
11 safety and efficacy. Final slide, please. Second to  
12 the last slide.

13 Well, the ILCOR made the recommendations  
14 that I showed you at the beginning based on these two  
15 studies. And you really need to judge whether you  
16 think that one would base blanket recommendations on  
17 those two studies. But finally they stated that  
18 future research is needed to determine optimal  
19 duration, and target temperature, and rates of cooling  
20 and re-warming. As you can see from the two studies  
21 that were looked at that they used different durations  
22 of hypothermia, methods of getting there, and all

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1 kinds of things. And so the question is do those two  
2 studies really give you something of which you can  
3 base objective performance criteria, things like that.

4 Next slide, which is the final slide I think.

5 So, we have a series of questions for you  
6 that Dr. Ogden will read for you. And essentially  
7 there are two kinds of questions. Do you think that  
8 post-event hypothermia is the standard for treating  
9 out-of-hospital cardiac arrest patients in the United  
10 States? I did a little survey in the San Diego area,  
11 and it's not the standard in any of the hospitals that  
12 I surveyed there. And I believe we've done a survey  
13 here in the Washington area and found one hospital  
14 that routinely does that. So do you think that the  
15 data, essentially these two randomized studies, lead  
16 you to believe that one accepts the principle of post-  
17 event hypothermia in cardiac arrest patients. And  
18 then second, if you do accept post-event hypothermia,  
19 would surface induced hypothermia be equivalent to --  
20 in safety and efficacy -- to endovascular induced  
21 hypothermia. So these are the questions that we would  
22 like you to discuss this afternoon. Thank you.

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1                   ACTING CHAIRPERSON MAISEL:    So before we  
2 get to the questions for the panel, first I'd like to  
3 ask Dr. Witten to introduce herself since she has  
4 joined this afternoon's panel.

5                   DR. WITTEN:    Yes, thank you.    I'm Dr.  
6 Celia Witten.    I'm the division director of the  
7 Division of General Restorative and Neurological  
8 Devices in the Office of Device Evaluation at FDA,  
9 which would be the reviewing division for cooling  
10 devices with labeled indication for post-arrest  
11 hypothermia.

12                   ACTING CHAIRPERSON MAISEL:   And at this  
13 point I'd like to ask the panel members if they have  
14 any questions for the FDA.

15                   DR. SOMBERG:    Is it appropriate to ask  
16 have there been any -- are there any trials currently  
17 under way for these devices that have resulted from  
18 discussions with FDA?

19                   DR. WITTEN:    Unfortunately because of  
20 confidentiality we wouldn't be able to answer any  
21 questions about ongoing studies.

22                   ACTING CHAIRPERSON MAISEL:   Dr. Becker.

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1 DR. BECKER: Yes. Again, I appreciate the  
2 really thoughtful analysis on these studies. Could I  
3 just ask a little clarification in terms of the  
4 timing. Because it seems to me that one of the things  
5 that has not really been addressed is the very  
6 important consideration on timing, and the induction  
7 of hypothermia which may explain a lot of the kinds of  
8 things that you've been describing.

9 DR. SWAIN: I agree with that. I've sort  
10 of spent my career studying hypothermia, and  
11 especially cardiac surgery and brain protection. And  
12 you're right, I have no doubt whatsoever that the  
13 minute you take a ligation band off a coronary artery  
14 or carotid on rats, or whatever we're studying in the  
15 laboratory, and induce hypothermia right after that it  
16 does work. To some degree. Whether it's persistent  
17 is also a question. And when we look at the Monday-  
18 morning quarterbacking of all these studies, when you  
19 get a negative study, which is essentially that  
20 Australia study is a negative study, is what could  
21 have been done better. And oh, it must be because it  
22 was too long, in the head bump patients, Clifton's

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1 patients and all that. Well, then one would need to  
2 design a study where it's less long. And that's the  
3 challenge in any clinical medicine is developing a  
4 treatment that is based in reality of when you  
5 actually see these patients. These patients, cardiac  
6 arrest patients, you end up seeing a lot sooner than  
7 you'll see the myocardial infarction. I've got chest  
8 pain after lunch, and it must be the burrito I ate.  
9 Whereas cardiac arrest, you pretty much know, even  
10 though you're off by a few minutes, but you pretty  
11 much know when that occurred. So I think that is a  
12 problem, and it demands a good trial design.

13 ACTING CHAIRPERSON MAISEL: Dr. Yancy.

14 DR. YANCY: Judith, as you reviewed the  
15 COOL-MI trial, what was in our brochures suggested  
16 that for the subgroup with the anterior injury pattern  
17 that there may have been by a retrospective subgroup  
18 analysis a signal, a hypothesis that can be generated.

19 I have a sense you might want to clarify that or  
20 refute that.

21 And secondly, looking at the adverse event  
22 table, it's certainly was a powerful statement you

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1 made looking at the direction of the numbers, but  
2 looking at the p-values it was only one variable that  
3 really got close to what we might traditionally  
4 describe as a trend. So I thought you might just  
5 develop both of those again.

6 DR. SWAIN: Yes. And as I said, there are  
7 no statistical difference in those, the COOL-MI  
8 adverse events. And the study was not powered to  
9 detect that. So no problem, we're looking at the  
10 trend.

11 As far as the Monday-morning  
12 quarterbacking, which is post hoc retrospective data  
13 mining analysis, then I think one can do that in COOL-  
14 MI, in Clifton's study. And Clifton's also done it,  
15 saying is there a subgroup that might benefit, and  
16 then let's design a study to test that subgroup. And  
17 I think that's very real. But you know, the problem  
18 you have on subgroup analysis is you don't know how  
19 many analyses were performed to find the one group  
20 that benefited. And Sharon-Lise will be able to  
21 comment on that I think a great deal. We very often  
22 see, and forget about cardiovascular neuro devices,

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1 let's talk about orthopedic devices or something. We  
2 very often see a failed study, and then go for  
3 subgroup analysis and find something that might be  
4 beneficial. And what we need to do is test the  
5 hypothesis then that anterior MIs will benefit from  
6 post-event hypothermia.

7 ACTING CHAIRPERSON MAISEL: Any other  
8 questions for the FDA? I'd like to move on to the  
9 afternoon portion of the open public hearing and ask  
10 if there's anyone in the audience who would like to  
11 address the panel on this topic today? Seeing none,  
12 we will close the open public hearing. It seems a  
13 little premature to take a break, so why don't we move  
14 on to the FDA questions.

15 MR. OGDEN: My name is Neil Ogden. I'm  
16 the branch chief for the General Surgery Devices  
17 Branch. And we have three questions. The first one  
18 has three parts.

19 There have been two randomized controlled  
20 studies reported in the literature describing the  
21 beneficial effects of mild hypothermia in a select  
22 group of patients who are comatose after cardiac

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1 arrest and have spontaneous returned circulation. In  
2 these studies hypothermia was achieved by various  
3 methods of surface cooling.

4 Part (a). Do you believe that the  
5 existing data in the literature are adequate to  
6 support the safety and effectiveness of surface  
7 cooling for achieving mild hypothermia in unconscious  
8 adult patients with spontaneous circulation after out-  
9 of-hospital cardiac arrest.

10 Would you like me to read all parts?

11 ACTING CHAIRPERSON MAISEL: Why don't you  
12 read (a) and (b), because they go together.

13 MR. OGDEN: Part (b). If you believe the  
14 existing data are adequate to support such a labeling  
15 indication for blankets and other surface cooling  
16 devices, please discuss any recommendations for the  
17 instructions for use. For example, temperature,  
18 length of treatment, et cetera.

19 ACTING CHAIRPERSON MAISEL: Discussion  
20 from the panel. Dr. Somberg?

21 DR. SOMBERG: I'll be glad to see if I can  
22 get someone excited. It's always more difficult to be

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1 an evaluator on the basis of some data, as opposed to  
2 having two sides make an argument and then try to  
3 judge that. But from what I saw, I thought there was  
4 interesting data. And it certainly wouldn't be an  
5 area I would tell someone interested in becoming  
6 involved in investigative studies to avoid because  
7 there's nothing that looks positive here. But at the  
8 same time, I do not think it rises to the level of  
9 enough information to support an application for a  
10 particular device or therapeutic approach. I was  
11 struck by the small number of patients involved given  
12 the size of the problem, and the difficulty of  
13 demonstrating success. And we've heard this morning  
14 about the different neurologic scales, et cetera, and  
15 the difficulties there.

16 So I think you have to have a larger  
17 study. You have to look at composite endpoints. You  
18 have to have a good validated means of assessing  
19 benefit, and probably you have to look at patients who  
20 are more likely to do better than to take all comers,  
21 especially with a small sample. But I think if this  
22 was a 1,500-patient study, or a 500-patient study, and

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1 it was appropriately designed, some of the data  
2 supports that cooling might be a benefit. But I don't  
3 think that paper has been published or that  
4 presentation's been made.

5 ACTING CHAIRPERSON MAISEL: Joe.

6 DR. ORNATO: You know, John, you raise a  
7 great point, and I can't disagree with you. You're  
8 absolutely right from a scientific standpoint. It'd  
9 be great if we could have a 500, 400, 1,000 patient  
10 study. And it would certainly be great if we had more  
11 than just VF out-of-hospital patients in the larger of  
12 the two. But I think the challenge that we all have  
13 as we've I think shared with one another this morning  
14 is how difficult an area it is for clinical research  
15 to be done in this area. And frankly, from I guess my  
16 own perspective, when I saw both of these studies come  
17 out I was almost as amazed that they were able to get  
18 the number of cases that they were able to get.  
19 Because remember, you're only talking about people who  
20 survive that initial resuscitation event. And so  
21 we've already filtered out a very large percent. And  
22 that's why, Dr. Brockman, you're absolutely right.

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1 We're winding up with a very small percent of the  
2 total number of patients. But that's almost in part  
3 inescapable because of the poor initial ROSC. And you  
4 add on top of that the fact that in both of these  
5 studies I think to some degree they made an attempt to  
6 not take all comers.

7           The challenge for most of us trying to  
8 apply this information clinically is not whether to do  
9 it but to whom. The problem is even more complex in  
10 that someone, I think several of you pointed out that  
11 one of the open questions is is it now the standard of  
12 care. If you look at it from the perspective of the  
13 standard of care being defined in the normal legal  
14 sense, it's not, because very clearly most communities  
15 are not broadly applying this. So in a court of law,  
16 the usual legal definition would not apply. In  
17 National Registry of CPR, of the 400-plus hospitals,  
18 as of not this last quarter but the quarter before,  
19 which are the last data that we've looked at, we have  
20 only 10 or 11 hospitals who have admitted to doing one  
21 or more hypothermia cases post-resuscitation. Now,  
22 that sounds dreadful, and it arguably might be if you

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1 take the perspective that we should be applying the  
2 ILCOR guidelines. But I want to caution everyone that  
3 these are in-hospital cardiac arrest patients in  
4 NRCPR. It excludes those patients who have arrested  
5 out of hospital. And of course, the two studies are  
6 primarily pre-hospital cardiac arrest. So in essence,  
7 it's an extrapolation of the existing data for  
8 hospitals to be reporting in NRCPR that they're  
9 applying it on in-hospital arrest patients. So that's  
10 the reality of what little data we have. But I think  
11 the bottom line is it's a very small number of  
12 hospitals, and a very small number of patients who yet  
13 are getting this form of therapy, rightly or wrongly.

14 Which now brings the flip side of it,  
15 which is that from a medical-legal, and a medical and  
16 perhaps an ethical standpoint it pushes us into a very  
17 interesting discussion of not the legal definition of  
18 the standard of care but to some degree what  
19 obligation we clinicians have to apply evidence-based  
20 expert recommendations that are made in this case not  
21 just on a national or an international basis. We are  
22 all well aware of the fact that translation of

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1 evidence-based guidelines into clinical practice has  
2 been a problem across the board with the 200 or 300  
3 major papers that have been written on that topic in  
4 the last 10 years. I just recently reviewed the  
5 literature. It's a very large body of information,  
6 and with very little exception there's been a huge  
7 translational problem. Everything from as simple as  
8 giving people with ST elevation MIs aspirin to  
9 initially use of therapy and beta blockers and  
10 cholesterol-lowering agents and the like.

11 Take the flip side of the issue of what is  
12 the standard to which we are being expected to comply  
13 even in the legal sense. Lots of folks get into  
14 trouble when there's been a bad outcome in courts of  
15 law when there are national consensus guidelines that  
16 urge a certain therapy when they're evidence-based and  
17 meet the kinds of criteria that ILCOR's document now  
18 provides. So I know I'm going around in a circle  
19 here, but what I'm trying to do is to as best I can  
20 provide somewhat of a balanced perspective that I  
21 think there are two different ways of looking at this.  
22 They both have merit. I think, John, you've

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1 articulated properly one of the sides, and I think  
2 there is another side. I'm a bit hard-pressed to  
3 know, because there are only two trials, because they  
4 have some problems, you know, where the FDA really  
5 ultimately ought to come down at this moment where we  
6 know we'd love to have more data. I can tell you that  
7 many of us clinicians and researchers who work in this  
8 area feel compelled to apply hypothermia, at least as  
9 narrowly defined as it is in the two studies that were  
10 the basis of ILCOR. And I think the reason we're  
11 somewhat persuaded, even though we'd love to see more  
12 evidence, is that it does have reasonable science  
13 behind it from animal models. It wasn't a great  
14 surprise that this outcome occurred. Peter Safar, the  
15 late Dr. Safar, I think led us in this direction for a  
16 couple of decades now. And so it's somewhat  
17 consistent, I think, with what the animal models  
18 suggest. I'll stop there.

19 ACTING CHAIRPERSON MAISEL: Dr. Normand.

20 DR. NORMAND: I have two questions which  
21 may be very naïve. So the first question is if you  
22 have an out-of-hospital arrest, and this procedure is

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1 applied, and then presumably you're brought to a  
2 hospital, is that part -- no. Lots of people are  
3 shaking their head no.

4 UNIDENTIFIED PARTICIPANT: This is mostly  
5 applied after you got to the hospital.

6 DR. NORMAND: After, that was my question.  
7 So in theory, that's in hospital billing data. I'm  
8 just trying to think of another data source is what  
9 I'm going at. And in terms of --

10 UNIDENTIFIED PARTICIPANT: No, because  
11 they can't bill it.

12 DR. NORMAND: They can't bill it. So  
13 that's the question. I don't know if that's ethical  
14 or unethical to ask, but I was wondering whether or  
15 not if you're billing for the data, the hospital's  
16 going to be reimbursed for it. In any event, my  
17 question was is that going to -- is there another data  
18 source that may be potentially available to look at  
19 either via hospital discharge claims or via Medicare  
20 or something like that. But people are shaking their  
21 head no.

22 DR. ORNATO: Right now there is no billing

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1 code for it.

2 DR. NORMAND: There's no code.

3 DR. ORNATO: We've actually reviewed that.

4 There is no billing code for induced hypothermia.

5 DR. NORMAND: So it's free.

6 DR. ORNATO: It's free care.

7 DR. SOMBERG: The ice is free. Not all  
8 hotels, but some.

9 DR. KATO: Well, I don't think you bill  
10 for the hypothermia per se, but you bill for the  
11 cooling blanket. If that's what you're going to do.  
12 And that would definitely have a code within the  
13 hospital. If you use the blanket, right.

14 ACTING CHAIRPERSON MAISEL: Dr. Brott.

15 DR. BROTT: I think these two studies are  
16 kind of an example of studies that were very simple,  
17 and could be done very easily, which many people  
18 probably in the audience and on the panel would love  
19 to be able to do. But here we are, because the  
20 results were not a slam dunk we're looking for other  
21 clues, and I think that for instance from the  
22 neurologic side if we had some other neurologic

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1 endpoints, they weren't primary, but they were looked  
2 at, and they were all consistent with these primary  
3 endpoints, I think we'd be feeling much more  
4 comfortable. So these two trials may be examples  
5 where simplicity actually has ended up to be a  
6 disadvantage.

7 ACTING CHAIRPERSON MAISEL: Dr. Becker.

8 DR. BECKER: I think it's important to  
9 sort of keep in mind if you will the relative strength  
10 of this compared to many other things that we have  
11 accepted in practice. And so while it may seem  
12 perhaps odd to the panel that based on these two  
13 studies there's an international recommendation, I  
14 think it's important to keep in mind that if one went  
15 through the ACLS algorithm and looked at drugs like  
16 epinephrine, you couldn't find two randomized trials  
17 for epinephrine right now. You could not find two  
18 randomized trials for lidocaine right now. And those  
19 are absolutely, absolutely accepted types of  
20 intervention so that when the international groups  
21 that have looked at this have really done what I think  
22 is a very thorough and admirable evidence-based

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1 evaluation that would involve an evaluation of all the  
2 animal literature that seemed relevant, the human  
3 literature that seemed relevant, the associated types  
4 of studies. And when they then lay that out on a grid  
5 which is actually done and is available to anyone  
6 who's interested in it, I think you do begin to see a  
7 picture that is compatible with the kind of  
8 conclusions that they've drawn.

9           And I just do want to highlight, because  
10 maybe it wasn't clear from Dr. Swain's comments, that  
11 the international recommendation was really for a very  
12 limited group of patients. It was sort of represented  
13 as a blanket statement. That's not really true. The  
14 indication was for comatose survivors of out-of-  
15 hospital ventricular fibrillation, witnesses  
16 ventricular fibrillation. I mean, it's a very narrow  
17 indication. And so I think as a clinician, my take on  
18 it is to have two randomized clinical trials in the  
19 New England Journal of Medicine is way better than  
20 just about any other aspect of the ACLS algorithm that  
21 I'm familiar with. So, I think the thoughtful  
22 approach is that whether, you know, they're definitely

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1 not perfect. They're not perfect studies. But they  
2 certainly in terms of guidance for clinicians, they  
3 have to be very powerful kinds of evidence that we  
4 take into account in trying to both come up with  
5 international guidelines, and in terms of guiding our  
6 own therapies. And I just think it's important to  
7 sort of keep that in mind as we judge these studies.

8 ACTING CHAIRPERSON MAISEL: Dr. Halperin.

9 DR. HALPERIN: It's been mentioned that  
10 hypothermia is clearly not the standard of care today  
11 because it's not practiced in many hospitals. And  
12 that kind of was put in the context of ILCOR  
13 guidelines being published. But I think that most  
14 U.S. facilities actually use the American Heart  
15 Association's guidelines to at least guide them, if  
16 you will, as to what advanced life support therapies  
17 will be used. And in fact, there is no AHA guideline  
18 on hypothermia that's been published to date. It's  
19 being considered, because the hypothermia studies were  
20 actually done after the year 2000 when the last  
21 guidelines were published. And the next guidelines  
22 are not going to be published until probably late 2005

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1 or 2006. They're actually being worked on now. And  
2 certainly the ACLS subcommittee is pondering that with  
3 ILCOR, and there will be some guidelines that will  
4 come out. And I suspect that given what Dr. Becker  
5 said about the two randomized clinical trials, plus  
6 all the other data, and the fact that the hypothermia  
7 data far exceeds the quality and the quantity of the  
8 data that exists for most ACLS recommendations, that  
9 in fact it will get a fairly strong recommendation  
10 from the American Heart Association, which will be  
11 consistent with the ILCOR guidelines. So then that'll  
12 be published I guess in 2006.

13 So then the issue is, you know, then will  
14 it be adopted and become a standard of care at that  
15 time. I don't know, but I suspect it'll be used a lot  
16 more than it is now. So it'll be an interesting  
17 situation where in fact the clinical guidelines  
18 recommend that hypothermia be used in that situation,  
19 and then it'll be up to the regulatory boards to  
20 decide what is appropriate to do for the devices that  
21 would actually allow that to occur.

22 ACTING CHAIRPERSON MAISEL: Dr. Ornato.

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1 DR. ORNATO: Henry, that's a really good  
2 point. AEDs came on the market in the late '70s, I  
3 guess, early '80s, if I recall correctly. And the  
4 number of sales as somewhat of an index of clinical  
5 use was, I don't know what the numbers are because I'm  
6 not obviously in that industry, but as an end user, it  
7 was pretty small. And this was called to our  
8 attention back in '87 or '88 as I recall when I was I  
9 believe on the AHA ACLS subcommittee. And we issued  
10 an -- after reviewing the data that then existed, we  
11 issued an interim ACLS guideline on the use of AEDs,  
12 and we actually added a module to the ACLS text. And  
13 if you look at the proliferation of the use of AEDs,  
14 it suddenly shot up after that. So Henry, I think  
15 your point is exactly right, that an AHA guideline,  
16 although it doesn't legally meet the definition in a  
17 courtroom of the standard of care, it certainly drives  
18 this whole topic.

19 The other point is a practical one. The  
20 current inexpensive ice, you know, just things that  
21 are readily available that aren't billable in a  
22 hospital environment, techniques for lowering core

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1 body temperature, seem like they're pretty easy to do  
2 and straightforward, but at least at our own  
3 institution and at the other like institutions that we  
4 communicate with on a regular basis on post-  
5 resuscitation care, we've all pretty much seen the  
6 same thing which is that it's very hard to get our  
7 physicians and nurses to really embrace this form of  
8 therapy. Not as much from the philosophic standpoint,  
9 although that's a vital part of our discussion right  
10 now, but from the standpoint of actually doing it.  
11 It's not particularly easy to use the more crude  
12 methods. The patient is wet, they're sedated,  
13 paralyzed, on a ventilator for a period of time. You  
14 have no way of tracking during that period of time  
15 what's happening to them neurologically. It makes for  
16 a great deal of discomfort in terms of the clinicians.  
17 There are questions that we get all the time about  
18 can I do this, can I do that, can I use it post-  
19 fibroembolytic therapy, can I use it with  
20 heparinization, and so on and so forth. There's  
21 concern about giving medication, and what it does to  
22 prolong the half-lives of medication. It's a very,

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1 very challenging series of clinical questions. And I  
2 think as we've been asking our colleagues around the  
3 country what's going on at their institution with this  
4 specific therapy, what we're finding is it isn't as  
5 simple as do people buy into embracing either the  
6 ILCOR guidelines or the two studies, and the animal  
7 studies that are behind them. But there's a  
8 translational, operational, piece of this that is not  
9 trivial. I think it's a huge chunk of this. And that  
10 may or may not be helped by devices, if they are to  
11 become more readily available in this area. I think a  
12 lot of the nurses would love to have a prettier,  
13 easier method to use, but that's perhaps not,  
14 obviously, the gist of what our scientific focus ought  
15 to be.

16 ACTING CHAIRPERSON MAISEL: Clyde.

17 DR. YANCY: Bill, to get back to the  
18 question before us. I respect the opinions from Drs.  
19 Becker and Ornato, and I definitely respect the  
20 process that the ILCOR effort represents because I  
21 know those processes pretty well. So I think that we  
22 would have to acknowledge that there are sufficient

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1 data, albeit a little bit soft, that we can in fact  
2 say yes, that the existing data adequate support the  
3 safety and limited effectiveness of surface cooling  
4 for achieving mild hypothermia in such patients as  
5 have been described.

6 I guess the real dilemma we have here has  
7 to do with taking the next step. That is, what's on  
8 the board, in which patient, and under what  
9 circumstances. And all we can do is steal a page from  
10 the typical cardiovascular trial and say it has to be  
11 in those patients that were studied that meet the  
12 exact same profile, and the therapy has to be given  
13 the same way. And then that becomes the push point.  
14 Because the question is do we take data that are  
15 already different, although I admit they've been  
16 vetted through our highest tier review, and say we can  
17 extrapolate the paradigm to an approach other than  
18 surface cooling, that is endovascular cooling, or do  
19 we require the endovascular cooling to go through the  
20 same sort of process. That is, I think, where the  
21 rest of our conversation needs to reside, because I  
22 have to accept that surface cooling has some benefit.

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1 But where do we go from here?

2 ACTING CHAIRPERSON MAISEL: Before we get  
3 to the endovascular cooling, I think something that  
4 I'd be interested in further discussing is obviously  
5 not all cooling is the same, so if someone brings in a  
6 product to the FDA, whether it's an ice pack or a  
7 cooling blanket, what standard does it need to meet to  
8 get approved, to show safety and effectiveness. Is it  
9 enough to cool as fast and as long as one of these  
10 other trials, or is there some other standard?

11 DR. YANCY: Yes, I couldn't agree with you  
12 more. Remember that the ILCOR also puts a proviso on  
13 its own statement that as soon as it says it's safe  
14 and effective immediately, more research is needed to  
15 address these very issues. So I think we have to be  
16 very careful how this is positioned.

17 ACTING CHAIRPERSON MAISEL: Jeff.

18 DR. BRINKER: Just from a regulatory point  
19 of view, it's not clear to me that these devices that  
20 already exist for cooling need to be labeled for  
21 cardiac resuscitation in any way. What is the  
22 agency's feeling about that?

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1 DR. WITTEN: I'll answer that, and then I  
2 will really be happy if someone will answer Dr.  
3 Maisel's question that he asked. And the answer is  
4 that if a sponsor came in with an application for a  
5 specific clinical indication, even if the device was  
6 already on the market for the general indication, we  
7 would need to evaluate it and make a decision.

8 DR. BRINKER: Well, that's the point. I  
9 think that it's -- with a guideline that suggests  
10 cooling is potentially good and probably should be  
11 used, perhaps in the absence of any other reasonable  
12 alternative. There's a strong likelihood that without  
13 any regulatory prodding, that there would be no  
14 further controlled studies thought to be even  
15 ethically justified. And it seems to me that there  
16 needs to be some thought about this, especially in  
17 view of the fact that there are alternative cooling  
18 methods, and the data upon which this rests for out-  
19 of-hospital cardiac arrest, no matter how significant  
20 and discrete the patient populations were, the  
21 implication is that it's going to be used for all  
22 cardiac arrests. And I don't know whether the data's

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1 there to really support that.

2 So do we really want to assume that it's  
3 unethical to do any more studies comparing non-cooling  
4 to cooling?

5 ACTING CHAIRPERSON MAISEL: John.

6 DR. SOMBERG: I'm going to be the bete  
7 noire of the group here, because I looked over these  
8 studies before I came, I've looked over them again  
9 after listening, and I think on the basis of less than  
10 200 patients with one study negative on survival,  
11 another study that meets the endpoint of survival but  
12 has we're talking about a 10-patient, 12-patient  
13 difference, they're very small numbers. I thought if  
14 -- knowing that I have sat on this committee before,  
15 if someone came with a device that you hooked up to a  
16 patient and you got these results. Forget about  
17 they're being in the New England Journal. There's all  
18 sorts of politics here. But if you had these results,  
19 I'd be very much surprised if that device had passed.  
20 So I think to set a standard of care based on this --  
21 that's what you're talking about, a standard of care -  
22 - based on this data, and therefore you could just say

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1 you have an equivalent device to cooling packs. Maybe  
2 it does it fast, and maybe it does it with no one gets  
3 wet and electrocuted or what have you, and therefore  
4 we should get approved based on this, and we can't  
5 study it any further, is just going to stifle science  
6 and maybe, just maybe, base everything on a pack of  
7 poorly balanced cards. I just do not believe these  
8 two studies meet any FDA advisory panel standard of  
9 approval.

10 I can't speak for the groups that went  
11 around making -- and I'll just say this. When people  
12 make standards based on practice, it's what best out  
13 there now. You feel pressured to do that. That's  
14 different than evaluating a particular device that's  
15 before you. So I think we should not say because it's  
16 been one body, and another body may do this, so that  
17 it's become the standard, therefore we should say  
18 that's appropriate for the approval of a device or a  
19 drug. And drugs in this area, you say epinephrine,  
20 it's sort of a grandfathered agent. But amniodarone  
21 would have never been supplanted, and lidocaine, if  
22 the results were based on this amount of information.

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1 DR. BECKER: Amniodarone was worse.

2 DR. SOMBERG: No, I disagree with you on  
3 that. I think the data from the arrest trial are more  
4 substantial.

5 ACTING CHAIRPERSON MAISEL: Dr. Hallstrom.  
6 Let's talk about hypothermia devices. Dr. Hallstrom.

7 DR. HALLSTROM: My concern with accepting  
8 these two studies as defining the standard of care is  
9 the difficulty of doing the next study. Because if I  
10 were on an IRB and this was the standard of care, and  
11 now you bring another cooling device which is going to  
12 cool a little faster or some such thing like that,  
13 what does my sample size have to be to do a  
14 comparison? I'm all of a sudden into the 1,000-  
15 patient realm instead of the 100-patient realm. And I  
16 think -- I just have enough questions about this data  
17 that I would like to see a few more 100-patient  
18 trials. And indeed, if the effect is as great as  
19 these two papers suggest, that is all you need is  
20 another 100- or 200-patient trial.

21 ACTING CHAIRPERSON MAISEL: Norm.

22 DR. KATO: I think I have to agree with

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1 John. I'm beginning to feel now that there is I guess  
2 some key words in this question. Because they talk  
3 about various methods of surface cooling, and we're  
4 talking about a labeling indication for a device which  
5 we don't see in front of us. The way this panel works  
6 is that a sponsor comes to us with a device and with  
7 their data in hand, presents it, and then we make a  
8 decision based on the data at hand. I would feel very  
9 uncomfortable trying to prospectively grant anybody  
10 who comes along with a device in the future who can  
11 cool the body using various methods of surface  
12 cooling, sorry for the pun, but a blanket okay to  
13 achieve a labeling indication as such. Cooling  
14 devices are on the market already. They can be used  
15 as off-label devices. They currently have two  
16 articles which they can use to support the use as an  
17 off-label device. But I feel very uncomfortable  
18 trying to make a future statement about what device  
19 could be accepted now, given the fact that there is no  
20 device ahead of us.

21 DR. WITTEN: Thank you for that comment.  
22 And may I ask a follow-on question, which is what type

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1 of information would you want to see. If someone came  
2 in with a surface cooling device application, what  
3 type of information would you want that application to  
4 contain in support of that indication for the device?

5 DR. KATO: I assume that's for the panel.

6 DR. WITTEN: Generally for the panel.

7 DR. KATO: Because that's really Question  
8 (c), right?

9 DR. WITTEN: That is -- yes. Question (c)  
10 isn't quite phrased like that, but yes, that is  
11 Question (c). So we can wait till we get there.

12 ACTING CHAIRPERSON MAISEL: Why don't you  
13 read Question (c) now and we can move on to that.

14 MR. OGDEN: I'd be glad to, thank you. If  
15 you do not believe the literature supports an  
16 indication in the labeling for surface cooling for  
17 achieving mild hypothermia, please discuss an adequate  
18 study design to demonstrate that these are safe and  
19 effective for achieving mild hypothermia in patients  
20 with cardiac arrest. Please discuss possible control  
21 groups, endpoints, and time of measurement of  
22 endpoints, keeping in mind as you refer to your own

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1 experiences whether induction of mild hypothermia is a  
2 commonly accepted practice procedure in your  
3 geographic region such that it would be unethical to  
4 study surface hypothermia versus a control of standard  
5 of care that does not include cooling.

6 DR. WITTEN: And before you start, may I  
7 just provide some clarification of this question,  
8 which is this specifically relates to surface cooling.

9 And I know in the last part of the discussion there  
10 was some discussion of endovascular and of surface  
11 cooling. But we have another question that's about --  
12 or our next two questions after this have to do with  
13 other methods of hypothermia. So this specifically  
14 relates to surface cooling devices.

15 ACTING CHAIRPERSON MAISEL: Henry.

16 DR. HALPERIN: Yes, I just wanted to make  
17 a comment about the issue of standard of care, and  
18 stifling further research and what have you. Because  
19 I think we're a little bit off the subject on that.  
20 Because although I've stated already that I think the  
21 two studies on hypothermia are important studies,  
22 they're hardly definitive for the role of hypothermia

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1 in cardiac arrest, because they apply to actually only  
2 at most 10 percent of the cardiac arrest population.  
3 I mean, these are comatose survivors of out-of-  
4 hospital witnessed ventricular fibrillation arrest. I  
5 mean, there's a lot of qualifiers to it. So all of  
6 the other cardiac arrest population are not covered at  
7 all by these studies. And that research is certainly  
8 wide open. So even if one accepted this as the  
9 standard of care, it would be a tiny patient  
10 population that it would apply to. And the study of  
11 hypothermia for cardiac arrest in general is still  
12 wide open.

13 ACTING CHAIRPERSON MAISEL: I'm not sure  
14 we've reached any consensus on this point. So maybe I  
15 can ask if we have any consensus regarding whether we  
16 feel comfortable with a blanket support of safety and  
17 effectiveness of surface cooling in general. There  
18 were a few people who seemed potentially in support of  
19 that concept. If so, can you speak up and maybe  
20 clarify your position? Are there people who feel that  
21 a blanket support of surface cooling is appropriate?

22 DR. YANCY: I think it has to be in the

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1 context of the clinical circumstances. The sentiment  
2 that I've perceived, at least, is that for patients  
3 that reflect the ones in which there are signals of  
4 benefit, it would be hard to say the answer is no,  
5 even if they aren't definitive trials. But to say  
6 that it is a global approach equivalent to restoring  
7 circulation and creating an airway, I don't think any  
8 of us can say that.

9 ACTING CHAIRPERSON MAISEL: What if we  
10 were more specific and said support -- are there  
11 people who feel comfortable supporting the safety and  
12 effectiveness of surface cooling for achieving mild  
13 hypothermia in the unconscious patient with  
14 spontaneous circulation after ventricular  
15 fibrillation. Are there people who would feel  
16 comfortable with that? I see a few. Are there people  
17 who are uncomfortable with that?

18 DR. NORMAND: Hello.

19 ACTING CHAIRPERSON MAISEL: Dr. Normand.

20 DR. NORMAND: No, I'm sorry to do this,  
21 but I think you're talking about the data based on the  
22 two trials, right?

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1                   ACTING CHAIRPERSON MAISEL: Correct.

2                   DR. NORMAND: And I'm uncomfortable with  
3 the information in the two trials. Obviously I'm not  
4 a clinician, but based on the data that are indicated  
5 in those two trials, with trending and with the way  
6 the trials were designed, I think the data would not  
7 make me feel comfortable with agreeing with that.

8                   ACTING CHAIRPERSON MAISEL: Okay. Well I  
9 think we have a good sense of what the panel feels.  
10 Dr. Weisfeldt?

11                  DR. WEISFELDT: I was going to try to go  
12 back to the question we were just asked about the  
13 trial design, what trial would you design. To be  
14 honest, I think I'd design the two studies that we  
15 just heard reviewed. Because you're talking about a  
16 metabolic intervention that is only going to improve  
17 the outcome of an organ that is recoverable from the  
18 point of view of the ischemic insult that occurred  
19 during the cardiac arrest. That's the intent. If you  
20 were to apply hypothermia to a broader population,  
21 then you're looking at mechanisms of failure to  
22 survival that have little or nothing probably to do,

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1 but have more to do with the intrinsic heart disease,  
2 or injury that's occurred somewhere else. So you come  
3 rather quickly, if you think about a study design  
4 where you have a half a chance of showing a favorable  
5 outcome from a metabolic intervention that's going to  
6 improve tissue survival, to a similar study, at least  
7 very similar, to this one.

8 I then go to the comments of several  
9 people that compared to other types of interventions  
10 and CPR, where we have no data, and I would want to  
11 correct for the record the amniodarone comment because  
12 it's not correct. There was no survival benefit to  
13 out-of-hospital cardiac arrest for two amniodarone  
14 studies. Here we have survival to discharge from the  
15 hospital in two studies, reviewed, claimed. And like  
16 so many other studies, if you dissect out details, you  
17 can find criticisms. And unlike a panel who is, let's  
18 say they were reviewing a surface device for cooling,  
19 there would be an advocate for the device that would  
20 have presented hopefully equally articulately and  
21 convincingly to the FDA representative what the  
22 deficiencies are. So I'm personally persuaded that

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1 the studies are not half bad, that there are better  
2 data, that one would certainly hope to see further  
3 data produced, but a judgment could easily be made  
4 here that in the subgroup of patients we're talking  
5 about, that this treatment is, by virtue of two  
6 randomized prospective controlled studies, safe and  
7 effective. In that population.

8 ACTING CHAIRPERSON MAISEL: Do we have  
9 other comments regarding the trial design, study  
10 endpoints, control groups? Dr. Brinker.

11 DR. BRINKER: Well, for these not half bad  
12 studies, I would at least, if they are to be labeled -  
13 - I mean, the issue is nobody's preventing them from  
14 being used. They could be used whenever they want.  
15 The issue is should that be a labeled indication based  
16 on the two studies. And I have my -- I still have my  
17 doubts that we need to label this so, because it sets  
18 up a straw man for other kinds of technology that  
19 would then warrant a less vigorous scientific study.  
20 All they would have to do is mimic their --  
21 potentially, at least -- their ability to cool to a  
22 similar temperature, and do it without introducing any

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1 excess adverse event.

2           So, but if one were to say that any  
3 cooling apparatus capable of dropping the temperature  
4 to X amount, that based on these studies should be  
5 labeled as indicated for cardiac arrest, which  
6 includes presumably bags of ice water, I would suggest  
7 that all the other issues that were controlled for in  
8 the two studies, namely temperature, core temperature  
9 -- assuming they measured core temperature -- but  
10 degree of temperature reduction, be cited as a goal,  
11 and the co-administration of paralyzing and sedative  
12 drugs, which may in themselves have a beneficial  
13 effect, be included as part of the labeling  
14 indications.

15           ACTING CHAIRPERSON MAISEL: Dr. Brott.

16           DR. BROTT: In terms of (c), as best I can  
17 tell these could be viewed as coma studies. And  
18 they're coma studies of small numbers of patients.  
19 And I think that if you have coma studies of small  
20 numbers of patients, you have to make sure that your  
21 endpoints are as unbiased as possible. And in the  
22 first study, there was a tremendous opening for bias.

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1       And I can't imagine that the person doing the  
2 assessments as to whether or not they could go home or  
3 not, or to rehab, had no idea as to which treatment  
4 group they were in.

5               The second study, we're not really told  
6 anything about how the CPC was carried out. We don't  
7 know if there was any Barthel, or any kind of  
8 assessment. So the assessments of small numbers of  
9 patients were really not described in detail enough  
10 for us to have confidence that they were unbiased.  
11 And so with regard to Question (c), I would think that  
12 since it's a coma study, the endpoints would have to  
13 be very carefully considered, to have not only a  
14 primary outcome that had to do with neurologic  
15 outcome, but then some secondary measures, since there  
16 would be small numbers of patients, to at least  
17 provide some support, or at least consistency, with  
18 the primary endpoints. So I could not accept (a), and  
19 I think the reasons are the suggestions for (c).

20               ACTING CHAIRPERSON MAISEL: Any other  
21 comments on surface cooling? Why don't we take a  
22 break for 15 minutes, and come back and finish up with

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1 endovascular cooling. So let's resume at 3:30,  
2 please.

3 (Whereupon, the foregoing matter went off  
4 the record at 3:14 p.m. and went back on the record at  
5 3:32 p.m.)

6 ACTING CHAIRPERSON MAISEL: So we'll turn  
7 our attention now to endovascular cooling devices.  
8 And why don't we read Questions 2 and 3, please.

9 MR. OGDEN: Thank you, Mr. Chairman.  
10 Question 2. Endovascular cooling catheters represent  
11 a new technology for achieving hypothermia. Please  
12 discuss whether or not you believe that surface-  
13 induced hypothermia is comparable to core-induced  
14 hypothermia in relation to safety and effectiveness  
15 measures. Is there literature to show that core- and  
16 surface-induced hypothermia are physiologically  
17 equivalent?

18 Question 3. Please discuss an appropriate  
19 study design to evaluate safety and effectiveness of  
20 endovascular cooling catheters for patients following  
21 cardiac arrest. For example, please address the  
22 appropriate control group and endpoints for this

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1 study.

2 ACTING CHAIRPERSON MAISEL: Discussion.  
3 Dr. Weinberger.

4 DR. WEINBERGER: Alright. I think that we  
5 couldn't even all agree on whether we thought surface  
6 cooling was appropriate therapy for a more general  
7 class of patients. So I think asking whether  
8 endovascular catheters might be equivalent is sort of  
9 premature.

10 But on a more serious note, I think I'd  
11 have to know quite a bit more about the nature of the  
12 device in order to specify what sort of controls I  
13 would want. For instance, are we talking about an  
14 endovascular device that requires a large hole in a  
15 vein or a small hole? Is the patient heparinized  
16 during this process or not? There are potentially  
17 interesting complications that one can envision from  
18 this process that are very unique to an endovascular  
19 location that wouldn't be expected to be seen in a  
20 surface cooling methodology. So without the  
21 appropriate details of the device, and some  
22 consideration of the expected complications, including

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1 local bleeding, including hypercoagulable states,  
2 because you're putting a device of unknown size into  
3 the IVC where flow is sluggish, and you know, to be  
4 cooling the blood, presumably we don't know what the  
5 surface temperature of the coil is going to be. We're  
6 presumably shooting for a core temperature of 33, but  
7 what's the temperature on the surface of the coil? Is  
8 that at 30 or below, and what is that doing to the  
9 coagulation system? Certainly in the COOL-MI trial  
10 there were some interesting events that happened in  
11 relation to people who were cooled. There were events  
12 of pulmonary edema, and pulmonary emboli. I think  
13 that it really deserves a much more careful kind of  
14 thought than -- and treating this like a convention  
15 PMA-type trial. That is, a randomized control trial  
16 which might potentially require even three arms if the  
17 device itself is problematic even without its use. So  
18 I think that the discussion is predicated on knowing a  
19 bit more about the device, and at least seeing some of  
20 the animal data that is motivating use of this  
21 particular device.

22 ACTING CHAIRPERSON MAISEL: Everyone

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1 agrees with Judah? Dr. Becker.

2 DR. BECKER: I pretty much do. I guess my  
3 major concern is really one of safety more so than the  
4 cooling aspect of it. That it would seem to me that  
5 there would be different safety issues, and that that  
6 would sensibly be the focus of a review from my  
7 standpoint; that I think they are not the same in  
8 terms of potential safety. And certainly we haven't  
9 seen any data here at least to indicate that there is  
10 safety. There may be data out there, but you know,  
11 we've not seen that today.

12 ACTING CHAIRPERSON MAISEL: Could you be a  
13 little more specific about what sort of safety  
14 endpoints, you know, what time you would like those  
15 safety endpoints?

16 DR. BECKER: Well, I agree with many of  
17 the things that were said in terms of the temperature  
18 effects, local effects, bleeding kinds of effects, you  
19 know, just trauma to the vessel, incidence of if you  
20 poke something in the femoral vein, how often do you  
21 go through the vein, end up in the retroperitoneal  
22 space. You know, there really are safety kinds of

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1 concerns when you become invasive that I think are  
2 potentially important. And in the absence of seeing  
3 that, I think that those would have to be satisfied.  
4 But I guess I'd say then beyond that, I think that if  
5 the safety concerns were satisfied that they appear to  
6 be as safe, I would tend to think that then cooling is  
7 cooling at some point; that effects on the brain in  
8 terms of neurologic long-term recovery, I have no  
9 reason to think that they would be substantially  
10 different between surface cooling and endovascular  
11 cooling beyond the safety issues.

12 ACTING CHAIRPERSON MAISEL: Clyde.

13 DR. YANCY: Well, that would be with one  
14 caveat. I mean, we do recognize the clinical syndrome  
15 of hypothermia that in some circumstances can be an  
16 important clinical situation that has to be addressed.

17 And we don't know that there's one threshold above  
18 which everyone is safe and below which people at risk.

19 There may be a continuum that turns on gender, age,  
20 body mass, et cetera. So understanding so little  
21 about the implications of endovascular cooling and how  
22 that affects core temperature, the rapidity to which

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1 you are cooled, all of these dynamics are, at least in  
2 my mind, so unclear that I think the overwhelming  
3 answer to the question is that we cannot believe that  
4 surface and core are identical until we see more data.

5 And the safety issues I think have to go beyond the  
6 procedural things which admittedly are a concern, and  
7 have to deal with the very issue of generating  
8 hypothermia systemically and what's associated with  
9 that.

10 ACTING CHAIRPERSON MAISEL: Lance.

11 DR. BECKER: Just one follow-up on that,  
12 because I think Clyde raised an important point. And  
13 maybe we should've mentioned this with surface  
14 cooling, that I have some concerns over safety with  
15 surface cooling. I think that in terms of warnings  
16 and things like that on the labeling, I think there  
17 has to be very early on attention to sort of what is  
18 the monitoring so that you don't over-cool an  
19 individual. That is, too much cooling we know can be  
20 lethal. Now, that's true in many things that we do in  
21 medicine. Too much of many things can ultimately be  
22 lethal. But I think that needs to be -- I think we

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1 need, actually, a little better handle on that.

2           Because I can tell you now that we are  
3 doing surface cooling that issues with respect to the  
4 actual control of an individual patient are not  
5 trivial. What I mean by that is it's actually, over-  
6 shoot is very common in trying to cool an individual  
7 down. And I have heard at least at one national  
8 meeting of at least one death that's been attributed  
9 to over-shoot in the attempt to cool someone. This is  
10 with surface cooling. And so I think that the issue  
11 of monitoring of the therapy is something that  
12 probably does need to be addressed.

13           And it's sort of interesting to come back  
14 to how the endovascular may or may not just fit into  
15 this. It may turn out that endovascular has an  
16 advantage because it has the ability to both cool and  
17 to warm, for example. I mean, it may ultimately turn  
18 out to be a safer device. But again, I think we need  
19 to see that data in order to really make that  
20 judgment.

21           ACTING CHAIRPERSON MAISEL: And what would  
22 the control group be for these studies of endovascular

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1 devices?

2 DR. BECKER: My thought would be that --  
3 this is really a tough one. Because what you're  
4 really asking is could you ethically have a non-cooled  
5 group, I think, or at least that's what I struggle  
6 with. And I'm not sure that I know the answer. I  
7 think that if you are using one of the groups -- you  
8 know, we have a very, very narrow group for surface  
9 cooling that we -- or at least that some of us believe  
10 that there's a clear indication for. I think that if  
11 you're outside that group, there would be no question  
12 that an appropriate control group would be a control  
13 group that was normothermic. And I don't think anyone  
14 would have too much difficulty with that. So if you  
15 were looking at asystole, or PEA, or some of the  
16 conditions where we really don't have any data, my  
17 thought would be that an appropriate group would be a  
18 normothermic group.

19 ACTING CHAIRPERSON MAISEL: Dr. Brinker.

20 DR. BRINKER: Lance, I think it would be  
21 hard to get a sponsor to take a group that --  
22 basically they would have to establish superiority

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1 under no cooling, and the group that is arguably at  
2 higher risk of not benefiting from any type of  
3 cooling. So it'd be a high-risk study for anybody to  
4 undertake, although it could be an important one in  
5 terms of knowledge because it fills in the gap of what  
6 we don't have with the surface cooling studies. On  
7 the other hand, if you don't mandate that, that is all  
8 you have to do is to show you're as good as the  
9 surface cooling study, then you have to compare it to  
10 surface cooling, and you'd get some interesting data  
11 about the ease of achieving cooling and maintenance of  
12 that degree of hypothermia. But what you wouldn't get  
13 is any difference in, presumably at least, it's  
14 unanticipated that you would get any difference in  
15 mortality, or I should switch it around, in survival.

16 And in fact, the survival rates since it's not quite  
17 clear what they would be -- what's the normally  
18 anticipated survival rate with cooling. It could be  
19 anywhere over the place. And it'll be hard. It'll be  
20 hard no matter what the sponsor of these devices do.  
21 But I don't think that, unless they had some out-of-  
22 U.S. experience leading them in a certain way that

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1 they could afford to do anything but compare it to  
2 surface cooling. Which wouldn't give us all the  
3 information we'd like to see from such a study.

4 ACTING CHAIRPERSON MAISEL: Norm.

5 DR. KATO: From what I've read, I still  
6 have a problem with what the definition of  
7 normothermia is. And the reason why I bring that up  
8 is because our experience in the operating room with  
9 surgical patients is that within about an hour, hour  
10 and a half, core temperature drops from normal down to  
11 34, sometimes 33 degrees Centigrade. Given that many  
12 of our ICUs are air conditioned, and we like to work  
13 in air conditioned settings, you know, is it  
14 reasonable just to allow a patient to equilibrate to  
15 ambient temperature as a control? Although, I have to  
16 tell you, they're going to cool off anyway. Is that  
17 what normothermia should be? Because I think the  
18 converse, which is to try to maintain a body  
19 temperature of 37-38 degrees, in the cardiovascular  
20 field we've also learned that when you're warming  
21 somebody up from even 33-34 degrees, you basically  
22 have to stop at 35 because they will, you know, much

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1 like a turkey coming out of the oven, they will  
2 continue to cook until they hit 37-38 degrees. So  
3 that's the other part of the problem with that. So I  
4 echo the comments about over-shoot. But again, I'd  
5 have to look at some more data to get a comfort level  
6 with that definition of normothermia.

7 ACTING CHAIRPERSON MAISEL: John.

8 DR. SOMBERG: Well, when comparing surface  
9 to core cooling, I think it's important to how you  
10 measure the temperature of the body as well. There  
11 wasn't any material in the handout. I didn't do any  
12 research on this, but in both studies they used first  
13 tympanic membrane temperature and then they used  
14 bladder temperature. And in fact one did used a Swan,  
15 I think one Australian one used a Swan temperature as  
16 well of the heart. But there are different ways to  
17 measure temperature. And if one was comparing surface  
18 with catheter cooling, I think one would first want to  
19 see if you'd get similar readings on that. And I  
20 didn't see anything in the literature, but maybe there  
21 is literature on this.

22 ACTING CHAIRPERSON MAISEL: Clyde?

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1 DR. YANCY: Yes, one practical issue is if  
2 you talk a little bit more about trial design and  
3 think this through. I'm not sure how you stand at the  
4 bedside with a patient who's comatose and present  
5 three options to a family: normothermia, surface  
6 cooling, and endovascular. And do that without some  
7 major conflict internally. You're talking about a  
8 desperate situation where you feel compelled to do as  
9 much as possible. And I think even though we can  
10 sketch out an ideal design, I think making it happen  
11 and overcoming the informed consent barrier, I think I  
12 really struggle with that.

13 ACTING CHAIRPERSON MAISEL: There was a  
14 comment from Dr. Becker earlier that, quote, "Cooling  
15 is cooling." And I just wanted to get a sense of  
16 whether we feel that endovascular -- recognizing the  
17 safety issues, that we feel that endovascular cooling  
18 is likely to be the same and have the same effects, or  
19 whether we think it's different and needs to be  
20 studied with separate clinical endpoints, et cetera.

21 DR. SOMBERG: Can anyone answer my  
22 question, or maybe the FDA who's looked at this issue

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1 more, about the measuring the cooling before we vote  
2 on is cooling the same? In other words, if you cool  
3 using those two methods, do you get similar core  
4 temperature, brain temperature, cardiac temperatures?

5 DR. WITTEN: Are you asking whether if you  
6 cool with surface cooling or endovascular cooling you  
7 get similar temperatures?

8 DR. SOMBERG: Yes.

9 DR. WITTEN: Well, it's hard to give a  
10 simple answer to that, because usually in the kinds of  
11 studies that we've seen, the sponsors try to achieve a  
12 certain temperature. And you could achieve it. But  
13 there are the issues that were discussed a little bit  
14 earlier about how long it takes, and whether there's a  
15 problem with over-shoot, whether there's a problem  
16 with re-warming. And so I think those are all  
17 questions. With all these technologies, it's exactly  
18 how well you're able to control what you're doing. It  
19 depends on the specific device and the specific  
20 technology, certainly, that's true.

21 DR. SOMBERG: But there are different ways  
22 to measure the temperature. You know, we're saying

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1 cooling is cooling, but what's the point of  
2 measurement? Where are you getting it?

3 DR. WITTEN: Yes, well we've had different  
4 measurements we've seen. I mean, the answer's the  
5 same in terms of what you get, but bladder  
6 temperature, tympanic membrane temperature, those  
7 would be two of the places that we've seen  
8 measurements taken during studies. Rectal  
9 temperature.

10 ACTING CHAIRPERSON MAISEL: So it sounds  
11 like we're saying endovascular cooling techniques are  
12 different. They certainly raise their own safety  
13 issues. I don't think it's clear that brain cooling -  
14 - I don't know that we know whether brain cooling is  
15 the same based on a temperature in IVC versus surface  
16 versus bladder, what have you. I think we'd ideally  
17 like to see randomized trials. I don't know how  
18 realistic that is. The comparison group, certainly in  
19 groups that have already been studied it sounds like  
20 should be surface cooling. And for groups that have  
21 not been studied it could probably be either control  
22 groups or surface cooling, perhaps. Anyone have any

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1 additional comments on endovascular cooling?

2 DR. SOMBERG: I just want to stand  
3 corrected. He just gave this to me, that it has been  
4 looked at, and there doesn't seem to be variance for  
5 the two methods in terms of the core temperature one  
6 reaches. That's in that summary article.

7 DR. NORMAND: It was summarized in the  
8 article. I just couldn't interpret it.

9 DR. WITTEN: May I ask one follow-up  
10 question, which is I think there was a nice discussion  
11 on both local and systemic adverse events that one  
12 might conceivably be concerned about. And I'd like to  
13 know if there are any specific adverse events in this  
14 particular population that you'd want to pay attention  
15 to if you were doing a study of endovascular cooling.

16 In other words, we have the general systemic and  
17 local safety concerns, but in this particular  
18 population, is there a specific category or type of  
19 adverse events that we particularly would want to note  
20 in a study?

21 ACTING CHAIRPERSON MAISEL: Judah?

22 DR. WEINBERGER: I was having a discussion

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1 with Dr. Weisfeldt during the break. I think patients  
2 who have low flow states, particularly in the IVC,  
3 people who survive cardiac arrest, even if they have  
4 the circulation, some of them have poor pump function  
5 and low cardiac outputs. Those are people if you put  
6 a device into the IVC, and you have slow flow, are  
7 more likely to thrombose. And thrombosis might appear  
8 as an IVC thrombosis, it might appear as pulmonary  
9 embolus. And I think that class of complications is  
10 one you're probably want to be sensitized to.

11 DR. WITTEN: Thank you.

12 DR. KATO: The other general complications  
13 from cooling can be ventricular fibrillation, DIC,  
14 bleeding problems. Basically just talk to any  
15 cardiovascular surgeon who performs deep hypothermic  
16 circulatory arrest and they'll tell you it can be  
17 virtually anything. And the re-warming process can be  
18 a disaster too. You know, gas can come out of liquid.  
19 You can get air emboli. A whole host of metabolic  
20 derangements, not to mention differences in splenic  
21 blood flow causing sudden acidosis as circulations are  
22 restored in terms of perfusion. So there can be a

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1 whole host of problems with endovascular cooling.

2 ACTING CHAIRPERSON MAISEL: Any additional  
3 panel comments? Dr. Witten, any other comments or  
4 questions?

5 DR. WITTEN: No. I'd like to thank the  
6 panel for this really helpful discussion this  
7 afternoon. Thank you.

8 ACTING CHAIRPERSON MAISEL: Dr. Zuckerman,  
9 any comments or questions for the panel?

10 DR. ZUCKERMAN: Again, on behalf of the  
11 agency we found this whole discussion to be extremely  
12 productive and thank the panel members.

13 ACTING CHAIRPERSON MAISEL: I'd like to  
14 invite our industry representative Michael Morton to  
15 make any comments.

16 MR. MORTON: Thanks, just a couple of  
17 quick comments here. I appreciate many of the  
18 comments that the panel has made today regarding the  
19 size and design of studies, acknowledging the  
20 challenges of this patient population, and informed  
21 consent, realizing that if the expectations become too  
22 high for these studies the cost of the studies could

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1 preclude a sponsor from bringing them to market. So  
2 thank you.

3 ACTING CHAIRPERSON MAISEL: Thank you.  
4 And I'd like to invite our consume representative  
5 Linda Mottle to make any comments.

6 DR. MOTTLE: Thank you, Dr. Maisel. I'd  
7 like to echo some of that same thought. The  
8 deliberations have been very forthcoming. Some of the  
9 things that I still am concerned about are some of the  
10 ethics dealing with our implementation of new  
11 technologies into our public health system, and that  
12 we do not stifle those developments. We've heard many  
13 comments that many of our ACLS algorithms now don't  
14 have a lot of wonderful clinical studies behind them,  
15 and yet they are standards of care. We have new  
16 technologies emerging with some quasi-studies to back  
17 them up, and yet we have hundreds of thousands of  
18 deaths. We also have other precedents in the clinical  
19 trial arenas, such as with cancer, AIDS, where not the  
20 tightest of scientific study results are often used,  
21 and yet the progress continues to develop and  
22 implement new treatment modalities. And I'd like

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1 those to be considered also in this arena.

2 ACTING CHAIRPERSON MAISEL: Thank you.  
3 Any other final comments or recommendations from the  
4 panel? Dr. Weisfeldt.

5 DR. WEISFELDT: The last comment, Dr.  
6 Mottle, and the letter from Dr. Schmidt point to the  
7 issue that I think everybody is aware of, that the  
8 FDA-initiated regulations on the waiver of informed  
9 consent does create significant impediment to doing  
10 studies. We've seen several publications that have  
11 documented the decline in resuscitation research in  
12 this country, and there are European issues that are  
13 coming to the fore that are parallel.

14 But there's one comment that at least to  
15 me has come up a couple of times when the waiver has  
16 been discussed, and that is whether -- you cannot have  
17 a national IRB because IRBs are regulated in local  
18 fashion. But the agency, the FDA, could decide to  
19 create a national advisory board on resuscitation  
20 research that would constitute, if you will, advisors  
21 to the agency, much like if you will the gene therapy  
22 advisory board creates advice to the NIH and the NIH

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1 director about clinical trials. If there were such a  
2 body that advised the FDA on the appropriateness and  
3 ethics of resuscitation research, testing of specific  
4 devices, my sense is that local IRBs would find some  
5 cover, some support for making difficult decisions  
6 that they now have to make essentially individually  
7 based upon whatever expertise they may have, which is  
8 oftentimes not very much in the area that we're  
9 talking about.

10 The IDE, we understand, is the agency's  
11 major way with devices for giving approval for  
12 research. But in truth, the IDE is a technical issue,  
13 and it doesn't come with a lot of deliberation about  
14 the appropriateness of the research. So, I mean some  
15 of the problems we have here in the area we're talking  
16 about clearly deal with the sample size, ability to do  
17 research in this arena. And one of the major  
18 perceived impediments to more and better research, I  
19 believe, is the waiver. And at least that suggestion  
20 might be something the agency could consider, and in  
21 its wisdom see whether they believe that this might  
22 help. And obviously, any panel member, I would love

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1 to hear comments.

2 ACTING CHAIRPERSON MAISEL: Any other  
3 additional comments from the panel? Dr. Becker.

4 DR. BECKER: Yes, I'd like to just sort of  
5 thank the agency for holding this panel. I've had  
6 sort of the opportunity to be involved in this  
7 research for a long time, and this is one of the first  
8 times that I've been aware of a panel with no sponsor  
9 where sort of a real airing of a number of difficult  
10 issues could take place in this kind of a setting.  
11 And I'd like to compliment the directors and the  
12 individuals who have put this together and pulled all  
13 the people together.

14 And I guess my one recommendation would be  
15 that, you know, a venue like this would be considered  
16 in the future. Because I think this is a very  
17 different dynamic area of science. I think that what  
18 we have today, I hope, will not be what we have in  
19 five years, and not what we have in five years after  
20 that. And so I think the notion of sort of revisiting  
21 this very dynamic issues around the appropriate  
22 controls and consents and devices is really one that

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1 warrants sort of this kind of attention. And I would  
2 like to just personally thank the agency for their  
3 efforts to have this be an open and very welcoming  
4 sort of venue.

5 ACTING CHAIRPERSON MAISEL: Seeing no  
6 additional comments, this concludes the  
7 recommendations of the panel regarding the type of  
8 data required to effectively evaluate the performance  
9 of CPR in hypothermia devices, and I'd like to thank  
10 the panel members for attending.

11 (Whereupon, the foregoing matter went off  
12 the record at 4:01 p.m.)  
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