

**SUMMARY MINUTES**

**MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL**

**OPEN SESSION**

**September 21, 2004**

**Gaithersburg Hilton  
Gaithersburg, MD**

*2004-4073M1*

## **CALL TO ORDER**

**Panel Chair William H. Maisel, M.D.**, called the meeting to order at 9:04 a.m. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. Full waivers had been granted for Drs. Becker, Hallstrom, Kato, Ornato, Weinberger, and Yancy for their interests in firms that could be affected by the recommendations of the panel. A limited waiver had been granted to Dr. Halperin, permitting him to participate in the panel's review and discussion but precluding him from voting. The Agency took into consideration certain matters concerning Drs. Becker, Brinker, Halperin, Ornato, and Yancy, who reported past or current interests involving firms at issue but in matters not related to the day's agenda. Dr. Weisfeldt and Halperin reported past or current interests in firms at issue; the Agency had determined that they could participate in the day's discussion. Ms. Wood noted that Dr. Maisel had consented to serve as chair for the duration of meeting.

## **FDA PRESENTATION**

**Randall Brockman, M.D., Medical Officer**, addressed important issues in clinical trial design for new devices for cardiopulmonary resuscitation (CPR) and provided a clinical summary of the history of CPR. The chain of survival is an important consideration in assessing outcomes with CPR devices, and it is important for trials to evaluate appropriate success endpoints. Success rates following in-hospital cardiac arrest have been essentially unchanged over the past 4 decades. Return of spontaneous circulation (ROSC) occurs in about 30 percent of patients, and approximately 15 percent of patients are discharged neurologically intact. A randomized controlled trial found that patients receiving interposed abdominal counterpulsation (IAC) had increased survival rates compared with standard CPR. Patients experiencing out-of-

hospital cardiac arrest have worse outcomes than those experiencing in-hospital arrest; they have hospital admission rates of 8 to 22 percent, and 1 to 8 percent survive to discharge with intact neurologic function. These outcomes remain largely unchanged despite multiple additions to the basic components of CPR.

Certain treatments, such as high-dose epinephrine, vest CPR, and transcutaneous pacing have been found to have no long-term benefit. Active compression-decompression CPR (ACD-CPR) has been found to have mixed outcomes compared with standard CPR; several studies found no improvement in long-term outcomes. Another study found improvement in several endpoints; however, a physician was present on scene, and emergency responders had been using the equipment for several years. Inspiratory impedance threshold devices combined with ACD-CPR showed some benefit. Automated external defibrillators and public access defibrillators appear to result in improved outcomes for some types of patients.

Choosing appropriate endpoints for clinical trials will be important to determining which devices will facilitate improvement in long-term outcomes. Fostering an environment to enhance clinical research in this field is important. Will one device improve outcomes, or should we improve each step along the chain?

**Elizabeth J. Tritschler, M.S.E., Reviewer, Circulatory Support and Prosthetics Branch**, presented information on the regulatory history of CPR devices. The first-generation devices, which were approved beginning in 1976, were external devices to mechanically assist in chest compression by reducing the work required to compress the chest and distributing the load evenly over the sternum. The devices are currently classified as Class III devices and are subject to the 510(k) process for approval. Submissions usually do not require clinical data.

Second-generation CPR devices include those providing audible indicators of compression rate and visual indicators of compression depth. As with first-generation devices, they are Class III devices that are regulated through the 510(k) process. Clinical data generally are not required for submissions.

Third-generation devices have focused on enhanced CPR hemodynamics. Examples include interposed abdominal compression (IAC) devices, ACD devices, circumferential chest compression devices, and minimally invasive open-chest cardiac massage. The Agency has determined that no preamendment or previously cleared predicate device exists for CPR devices intended to enhance hemodynamics and therefore requires clinical data to support such claims. Clinical study endpoints include survival to ICU admission and 24-hour survival, end-tidal carbon dioxide (EtCO<sub>2</sub>), presence of a pulse during CPR, and neurological evaluations at 30 days or 1 year based on CPC, Glasgow Coma Score, or quality-of-life assessments.

In June 1998, the panel met to discuss a PMA for an ACD device and recommended that the device was not approvable. To date, more than 30 external cardiac compression devices have been cleared for marketing, and a small number of CPR aid devices have been cleared for marketing. No devices intended to enhance CPR hemodynamics have been approved for marketing in the United States.

**Ronald M. Lazar, Ph.D., Division of Stroke and Critical Care, Neurological Institute of New York**, provided data on neural events and outcomes in cardiac arrest clinical trials. The physiological impact of cerebral anoxia following cardiac arrest is well documented, and effects can be transient or permanent. During cardiac arrest, brain cells begin to degenerate after 4 to 6 minutes if circulation is not restored. A 1993 study by Roine et al. found that at 1 year, 48 percent of survivors experienced moderate to severe neuropsychological deficits, including

delayed memory recall and problems with manual dexterity and skilled motor movement. Many European researchers have used the Cerebral Performance Categories (CPC) as a means of assessing post–cardiac arrest neurological outcomes. According to the CPC, patients in the first two of the five CPC categories are considered intact, but even a rating at the highest CPC category can involve mild dysphasia, nonincapacitating hemiparesis, or minor cranial nerve abnormalities. The CPC has limited utility because it is subjective, its categories are poorly defined, it is frequently used only at hospital discharge, and it has never been validated or compared with other measures.

Even mild neurological deficits can be permanent and can make a difference between patient competence and futility. Objective measures of brain function that include physiological and cognitive outcomes need to be developed; in research, they should be performed by clinical neurologists who are blinded to treatment. The CPC lacks the sensitivity and specificity to fill this role. Neural endpoints need to be obtained in the acute period, at discharge, and at long-term follow-up to ensure meaningful patient outcomes.

**Elisa D. Harvey, DVM, Ph.D., Acting Director, IDE Program**, provided an overview of the regulations governing exception from informed consent. Informed consent is a fundamental element of human subject research protection in clinical research. The Declaration of Helsinki and the Belmont Report are international documents governing research involving human subjects. Consent by a legally authorized representative (i.e., a “proxy”) has long been accepted for research populations incapable of providing informed consent (e.g., children and cognitively impaired populations). Research involving situations in which the patient is unconscious or otherwise unable to provide consent is urgently needed.

Before 1996, no provision in the regulations governed any exception from the informed consent requirement (either individual or by proxy). In 1996 a new FDA regulation addressed the need to permit exception from informed consent requirement in specific situations. It also recognized the need for additional protection of patients' rights when research is undertaken with consent waived. The regulation (codified at 21 CFR 50.24) was developed with substantial input from medical community. It identifies criteria for studies that may be conducted with exception from informed consent, establishes requirements for study conduct, and specifies additional steps sponsors must take to ensure patient protection.

According to the regulation, to conduct studies with exception from informed consent, the following criteria must be met: Subjects must be in a life-threatening situation, available treatments must be unproven or unsatisfactory, participation in the study must offer the prospect of direct benefit to patients, and the study may not be feasible without exemption from the informed consent requirement. In addition, the situation under study must be one in which too few patients would be able to provide consent or would have an acceptable proxy available to provide consent within a reasonable time interval. It must not be possible to prospectively identify the population from which study patients would likely be drawn. Investigators must make every attempt to obtain consent from the patient's legally authorized representative within a specified time interval before proceeding to enter the patient in the study.

Dr. Harvey reviewed the IDE requirements for such studies and noted that institutional review boards (IRBs) must consult with the communities in which such a study would be conducted. The study must be publicly disclosed to these communities prior to initiation, and results must be publicly disclosed when study completed. The study must be overseen by an independent data safety monitoring board. IRBs for study sites must be notified of concerns

raised by the IRBs of other participating sites. The Public Access Defibrillation (PAD) Trial (*NEJM* 2004;351:637–46) is an example of a trial conducted with exception to informed consent requirements.

A draft guidance document was issued in 2000, and revisions to it are underway. The revision will incorporate public comments and provide clarification on some points. Past experience should facilitate increased efficiency in future investigations carried out under this regulation. Sponsors, investigators, IRBs, and FDA reviewers are all still in learning mode with regard to “best practices.”

### **Panel Questions for FDA**

Panel members noted the importance of assessing neurological endpoints in evaluating the success of CPR devices; in response to a panel member’s question, Dr. Lazar suggested that the NIH Stroke Scale, the modified Rankin Scale, and the Bartel Scale could be useful. Panel members also asked about the existence of postmarketing data on currently approved CPR devices and the ability to use data from outside the United States in evaluating devices. In response to various questions, FDA representatives clarified the 510(k) process and the relation of superiority and equivalence claims to that process. Devices that make claims for improving hemodynamics, as opposed to simply assisting CPR, are subject to the PMA process, not the 510(k) process.

### **OPEN PUBLIC HEARING**

Dr. Maisel read the Agency’s statement on transparency of the device approval process.

**Kenneth Collins, Executive Vice President, Alsius Corporation, Irvine, CA,** noted that his company has a 510(k) pending for an endovascular system for hypothermia. He noted that persuasive data demonstrate benefit of induced hypothermia in humans. In light of the clinical data already available, there is no reason to require individual hypothermia devices to bear the burden of randomized controlled trials to demonstrate clinical utility. Survival after cardiac arrest involves a chain of survival, and no one link in the chain can be successfully submitted to the scrutiny of randomized controlled trials and result in replicable results. The issue for FDA is not whether hypothermia devices improve survival but whether they introduce new questions of safety or efficacy and whether the questions should be addressed by clinical data. The Agency should adhere to the least burdensome approach.

**Keith Lurie, founder, Advanced Circulatory Systems, and Professor of Medicine, University of Minnesota, Eden Prairie,** noted that despite the widespread practice of CPR, its inefficiencies contribute to death for victims. Even after survival to the hospital, 75 percent of patients die before discharge. In determining safety and effectiveness of new CPR devices, it is important to use the current standard of care for comparison. In addition, studies must be consistent with the American Heart Association (AHA) chain of survival approach. Given the nonstandardized care of patients once they are admitted to the hospital, it is difficult to control for many variables that affect the value of CPR devices. Each new technology should be required to be safe and effective only for what it was designed to do. If long-term patient outcomes are required prior to clearance of CPR devices, little progress will take place; for example, no biphasic defibrillator has ever been shown to improve survival, but they are the standard of care. Long-term survival goals are not achievable without an enormous number of patients, which is associated with tremendous expense. Finally, the appropriate control group for CPR studies

consists of patients receiving the AHA standard of care. The gold standard is conventional manual CPR, not a device. We are at a crossroads in CPR research that requires a lowering of regulatory barriers. The FDA can continue to play a leadership role by recognizing that regulatory barriers have prevented progress and developing creative ways to remove those barriers.

Geretta Wood read into the record a statement from **Terri Schmidt, M.D., M.S.**, which urged the Agency to further study the process of protecting human subjects while moving forward with well-designed studies. The nature of cardiac arrest makes it difficult to obtain informed consent from patients before enrolling them in studies of new treatments. The new regulations governing informed consent created two new safeguards: community consultation and community notification. Little is known about the effectiveness of these processes and subjects' actual experience in studies using these safeguards. We need objective data about how the rules are affecting both the ability to perform research and the subjects the rules are intended to protect. Finally, establishing a central IRB could help improve consistency in implementation of the rules governing informed consent.

## **OPEN COMMITTEE DISCUSSION**

Panel members noted the difficulty of limiting inclusion criteria to a specific condition, such as ventricular fibrillation, particularly under emergency conditions, which do not provide much flexibility for inclusion and exclusion criteria. They suggested that it would be easier to design trials to include all cardiac events, then conduct subgroup analyses by event type. They emphasized the importance of knowing how long the patient has been down in order to provide the correct intervention and the possibility of using ventricular fibrillation as a surrogate for time

down. Other difficulties with research on CPR devices are the lack of data on patient comorbidities and the fact that out-of-hospital patients have many confounders. In addition, some patients simply are not viable. The data that are available reflect the heterogeneity of the patient population. Unless the research involves a specific device for a specific scenario, it is best to use a broadly inclusive patient sample.

## **FDA QUESTIONS**

**Questions 1a and 1b: Should the study exclude non-witnessed arrests, or should the study include both witnessed as well as non-witnessed arrests? Should the study only include those patients with documented ventricular fibrillation?**

The panel concurred that it did not want to see important patient populations excluded from study but that without knowing the endpoints, it was difficult to answer the question. Both witnessed and nonwitnessed arrests could be studied, but it may not be appropriate to do in the same trial. In out-of-hospital situations, it will be difficult to implement complicated inclusion and exclusion criteria. The primary comparison group will have to be defined on the basis of criteria determined before the intervention. Panel members noted that “casting a wide net” increases the potential for higher costs and the need to increase the number of patients in order to see effects; however, exclusion criteria do not simplify analysis as much as one might think and might discourage participation. Little is to be gained in power or lowered costs by excluding patients. Panel members noted that rigid requirements for intent-to-treat analysis can present barriers to research. Lack of intent-to-treat analysis can interfere with preserving randomization; it can be useful for generating hypotheses, but not for determining safety and effectiveness.

**Question 1c: 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?**

Panel members concurred that it is important to document the time elapsed as accurately as possible, using medical records, if they are available. It is important to set limits on the time elapsed. For most studies, however, it is not possible to know how much time has elapsed.

**Question 1d: Should the study patients be limited to patients who have arrested in the field, or should the study also include in-hospital cardiac arrest patients?**

The panel felt that it had addressed the question in its earlier discussion; both populations should be studied, but separately.

**Question 1e: If field patients are to be included, should CPR be initiated by professionals only, or can patients be enrolled if timing is recorded by, and CPR is initiated by bystanders?**

Again, the panel concurred that it was better to be inclusive, recognizing that there may be important differences in outcomes. Prespecified subgroup analyses are important.

**Question 1f: Do you have any other suggestions regarding the inclusion/exclusion criteria?**

Panel members had no further suggestions.

**Question 2a. What would appropriate clinical endpoints be for efficacy in a cardiac arrest study? Survival? If so, how would “survival” be defined? E.g., Would functioning in a vegetative state be considered “surviving”?**

Panel members concurred that survival to different times is an appropriate endpoint, but they were divided as to the appropriate use of surrogates. Many panel members stated that surrogates should relate to the specific issues under study. Several panel members favored taking a narrow approach to endpoints; thus, for a device that augments bloodflow, the focus should be bloodflow, not survival. Several panel members urged a systems approach because it is difficult to attribute any one element of the chain of survival to patient outcomes. It was noted that outcomes may be related to patient viability independent of the intervention: The best CPR can do is to return the patient to the pre-CPR state, but if his or her pre-CPR state made it unlikely

that the patient would leave the hospital anyway, the best intervention in world would not help. Other possible endpoints include heart MRI and tissue-based measures of brain injury.

**Question 2b. What are meaningful neurological endpoints and how should they be evaluated? Is a composite endpoint acceptable?**

Panel members concurred that MRI may become a meaningful endpoint. In addition, measures such as the NIH Stroke Scale and the Rankin Scale could be useful. Measurement of major loss of neurological function is the primary concern. It is important to view neurological function as a continuous variable. Any neurologic endpoint is a composite of several measures.

**Question 2c: Are there clinically acceptable surrogate endpoints that can be used? E.g., Return of spontaneous circulation, 24 hour survival, hemodynamic improvement, quality of life, work status/functional status, etc. Should these surrogates be primary or secondary endpoints?**

The panel was not in consensus on this issue. Some panel members felt that surrogate endpoints such as ROSC and hemodynamic improvement were appropriate, others did not.

**Question 3: Based on the clinical endpoints discussed above, what length of follow-up should be considered for the efficacy endpoints? E.g., If a device was associated with a 24 hour survival advantage but did not improve hospital mortality, would this device be considered efficacious?**

Panel members concurred that studies can use numerous endpoints, such as ROSC and hospital admission and discharge. Discharge alive is important. Members noted that under certain circumstances, short-term (1-hour or 24-hour) survival might be important; such endpoints might support efficacy, but not for long-term outcomes.

**Question 4: What should the primary composite safety endpoint include?**

The panel concurred that safety endpoints would be device specific. In general, a device should not cause increased damage compared with control, assuming equal or superior efficacy in the study arm. Data through the hospitalization period are needed. Safety issues require more than 24-hour follow-up. Neurological outcomes—including performance and functional status—should be viewed as a safety measure. A paradigm shift to a neurological scoring system may be

needed. Learning curves are also an issue: Any device platform that is developed will be widely distributed to people with widely disparate skills.

**Question 5: What length of follow-up should be considered for the safety endpoint?**

Panel members concurred that follow-up should continue at least through hospitalization.

**Question 6: Can a scientific study be performed using a single arm study with historical controls (US 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?**

Panel members concurred that historical controls cannot be used effectively. U.S. and OUS data sets are too disparate. Prospective nonrandomized studies may be appropriate.

**Question 7: If the study is unblinded, do you expect any substantial positive or negative placebo effect, or an effect of investigator bias on patient selection or endpoint evaluation? If so, how can these problems be minimized?**

The panel noted that although most studies have to be unblinded, studies should be blinded to the extent possible. Investigators could blind for certain outcome measures, such as neurological function. It is not possible to do a double-blind CPR study. Randomization can help lessen the impact of bias. In response to a question from Bram Zuckerman concerning how to assess CPR quality and control group quality, panel members suggested third-party observation or historical controls.

**Questions 8a-c: Should the trial design be a non-inferiority (i.e., equivalence) or superiority study for safety and efficacy? Under what conditions could an equivalence trial be acceptable? E.g., limited labeling/claims? If non-inferiority, what equivalence delta(s) would be clinically acceptable for the safety and effectiveness endpoints discussed above? If superiority (i.e., new technology would need to demonstrate improvement over current technology), are there new clinical trial designs that can be considered, e.g., superiority for surrogate endpoint and equivalent hospital discharge rates; or additional post-market studies on devices/technologies to supplement initial pre-market approval safety/effectiveness data.**

Panel members concurred that historical controls were generally not acceptable. Other trial designs are possible but could require large sample sizes.

**Question 9: 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.**

Panel members noted that the data must be auditable. It also must be collected in detail, including potential confounders, such as time of entry and time on market. Patient and operator characteristics are important, as is information on the time frame in which the treatment is undertaken. Elements that one would not normally think of including must be included, such as data related to who got what treatments. One potential role of a registry is to look at nonobvious adverse events. They are useful for devices with narrow indications, such as pediatric defibrillator pads.

One panel member noted that registries do exist, but the problem is not in defining datapoints—rather, data are biased; are numbered in terms of the number of cases; and tend to draw on a small, fairly biased group of sources. Out-of-hospital registries are struggling with the HIPAA issue. A broader issue is one of society figuring out whether it wants cardiac arrest treatment to move forward like cancer and trauma treatment have. Another issue is that of government choice—should an agency like the Centers for Disease Control and Prevention (CDC) champion the idea that cardiac arrest should be reportable? Doing so would tear down a lot of the HIPAA problems.

**Question 10: Can uniform definitions of adverse events be created? If yes, by whom?**

Panel members concurred that such definitions can be created; a registry or independent entity (perhaps the CDC) would have to create them.

**FDA PRESENTATION**

**Richard P. Felten, Medical Officer, General Surgical Devices Branch,** presented an overview of existing devices for inducing hypothermia, including cooling blankets, cooling surfaces, cold packs, external heat exchangers, and endovascular cooling systems. The most

common devices are cooling blankets. When endovascular cooling systems were introduced, the Agency was concerned that internal and external devices may have different safety profiles. As a result, these devices have very specific indications for use.

**Julie Swain, M.D., consultant to FDA,** discussed several studies of postevent induced hypothermia. The Post-Event Hypothermia in Myocardial Infarction (cool-MI) study was a prospective, randomized control study comparing cooling with inferior vena cava (IVC) catheter to normothermia during percutaneous coronary intervention. The study found no difference in outcomes between the group receiving hypothermia and the control group. The study was not powered to detect individual safety events, but there was a trend toward a higher death rate in the hypothermia group.

Clifton et al. (2001) conducted a prospective, randomized trial comparing normothermia and hypothermia from surface and gastrointestinal cooling in patients following brain injury. The primary endpoint was the Glasgow Outcome Score at 6 months; the numerous secondary endpoints consisted of psychometric tests. Outcomes were almost identical in the treatment and control groups for all endpoints, and the rate of complications was higher in the group receiving hypothermia.

Two studies of hypothermia following cardiac arrest, Bernard et al. (Australia) and The Hypothermia After Cardiac Arrest Study Group (Europe), led the International Liaison Committee on Resuscitation (ILCOR) to recommend that unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm is ventricular fibrillation. ILCOR stated that such cooling also may be beneficial for other rhythms or in-hospital cardiac arrest.

Both studies were located outside the United States in countries with different emergency response systems; 911 response time averaged 2 minutes. As a result, the studies are not directly comparable to each other and are not applicable to U.S. populations. For example, the primary endpoint in the Europe study was survival to hospital discharge with neurological function allowing home or rehabilitation; the primary endpoint for the Australia study was a CPC rating of good or moderate disability at 6 months. In the European study, 91 percent of participants were ineligible according to the inclusion criteria. Dr. Swain summarized the methodological problems with each study.

In the Australian study, neither group experienced clinically significant infections, but the study does not mention any other adverse events. In the European study, three patients had hypothermia stopped because of arrhythmia or hemodynamic instability. Complications during hospitalization were not reported. Patients receiving hypothermia in the European study experienced a greater rate of complications in the first 7 days than the normothermia patients, although the differences were not statistically significant.

Dr. Swain listed the many available cooling methods and asked whether efficacy would be the same for all methods. She noted that the ILCOR recommendations state, "Future research is needed to determine optimal duration of therapeutic hypothermia, optimum target temperature, and rates of cooling and rewarming." She asked the panel the following questions: (1) Is post-event hypothermia the standard for treating out-of-hospital arrest patients in the U.S.? (2) Is surface-induced hypothermia comparable to endovascular hypothermia in safety and efficacy?

Dr. Witten joined the panel, replacing Dr. Zuckerman.

## OPEN PUBLIC HEARING

No comments were made.

## FDA QUESTIONS

**Question 1a and 1b: Are the existing data adequate to support the safety and effectiveness of surface cooling for achieving mild hypothermia in unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest? If you believe the existing data are adequate to support such a labeling indication for blankets and other surface cooling devices, please discuss any recommendations for the instructions for use.**

The panel was not in consensus about the safety and efficacy of surface cooling following cardiac arrest. The panel concurred that the data are interesting but would not support an application for a particular device or therapeutic approach. The number of patients studied is small, and it is difficult to demonstrate success. Larger studies are needed that include composite endpoints. It is unclear which patient populations will benefit most from hypothermia treatment. It is also unclear whether hypothermia should be the standard of care; many physicians who work in this area feel compelled to apply hypothermia (at least as narrowly defined as it is in the two studies) because animal models do support doing so. Panel members discussed the possibility of examining hospital billing data to find more data on patients receiving hypothermia treatment. It was noted that the ILCOR recommendations are for a limited group of patients. Hypothermia treatment at this point is more difficult than it would seem; considerations include medication metabolism and maintenance of temperature, particularly with surface cooling methods. Panel members raised safety concerns, noting that issues with respect to temperature control of patients are not trivial; “overshoot” is not uncommon.

**Question 1c: If you do not believe the literature supports an indication in the labeling for surface cooling for achieving mild hypothermia, please discuss an adequate study design to demonstrate that these are safe and effective for achieving mild hypothermia in patients with cardiac arrest.**

Many panel members felt that surface cooling to achieve mild hypothermia might be appropriate in certain contexts but is not a global approach comparable to restoring circulation and creating airway. The studies to date cover a small population. Endpoints for studies must be carefully considered, and neurological and secondary measures must provide some support for primary endpoints. One cannot say that any cooling apparatus capable of dropping body temperature to a certain point should be labeled as indicated for cardiac arrest.

**Question 2: Please discuss whether you believe that surface-induced hypothermia is comparable to core-induced hypothermia in relation to safety and effectiveness measures. Is there literature to show that core and surface-induced hypothermia are physiologically equivalent?**

The panel concurred that endovascular techniques raise a different set of safety issues from surface-induced hypothermia. Randomized controlled trials would be helpful but may not be realistic. The panel was not in consensus as to the safety and effectiveness of core-induced hypothermia. Without details of the process by which hypothermia was induced and some consideration of expected complications (e.g., hypercoagulable state), the question cannot be answered. A study to evaluate safety and effectiveness would need to have several arms: device, control and, perhaps, blanket. Animal data are important. Many safety issues that are related to invasive processes would have to be addressed, such as local effects, bleeding, and vessel trauma. The methodology for examining neurological long-term recovery would not be significantly different from that used in studies of surface cooling, however. In addition, the existence of a cooling threshold above which everyone is safe has not been demonstrated. Safety studies have to address the issue of hypothermia itself. Endovascular devices may be superior because they can better regulate temperature.

With regard to study design, panel members discussed whether it was ethically appropriate to have a noncooled group. Outside of the narrow group for which there is a clear indication for the use of surface cooling, the appropriate control group would consist of normothermic patients. Otherwise, the appropriate group would be surface-cooled patients. Panel members also noted that normothermia is not well defined; in air-conditioned operating rooms, patient core temperature drops within 60 to 90 minutes. Again, overshoot—for both cooling and warming—is a concern. Other issues include informed consent procedures; appropriate measurement of temperature; effects in patients who have low flow states, have poor pump function, and low output because they are more likely to thrombose; and adverse effects associated with rewarming, such as air emboli and sudden acidosis.

**Michael Morton, Industry Representative**, expressed his appreciation for the panel's many comments concerning the size and design of studies and their understanding that if expectations become too high, cost could preclude a sponsor from bringing devices to market.

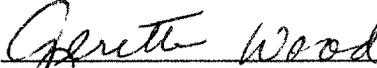
**Linda Mottle, Consumer Representative**, noted the ethical issues around implementation of new technologies. Many of treatment algorithms do not have many clinical studies to support them but are nevertheless the standard of care; fields such as cancer and AIDS have made progress despite flaws in the research.

Dr. Weisfeldt urged FDA to create a national advisory board on resuscitation research that would function much like the gene therapy advisory board. Such a body could provide support for local IRBs making difficult decisions

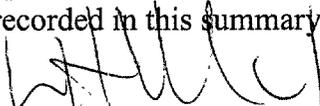
## **ADJOURNMENT**

Dr. Maisel thanked the participants and adjourned the meeting at 4:00 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on September 21, 2004, and that these minutes accurately reflect what transpired.

  
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Geretta Wood  
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

  
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William H. Maisel, M.D.  
Chairperson

*Summary prepared by*  
Caroline G. Polk  
Polk Editorial Services  
PO Box 2761  
Charlottesville, VA 22902  
(434) 244-0657  
cpolk@earthlink.net