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Society for Academic Emergency Medicine

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Unrestricted Educational Grants for this meeting generously provided by

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## Continuing Medical Education Information

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The **University of Illinois at Chicago College of Medicine** designates this education activity for a maximum of 6.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Learning Objectives: At the end of this session, participants will be able to discuss specific topics related to the general theme; "how to build interdisciplinary research in hypothermic resuscitation."

Purpose: To discuss the building of interdisciplinary research in the investigation of induced hypothermia in resuscitation of patients with several pathologies.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Illinois College of Medicine and FERNE. The University of Illinois College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

<b>Schedule</b>		
<b>2:30-4:30</b> <i>Salons C/D</i>	<b>SAEM State-of-the-Art Didactic Session – Resuscitative Hypothermia</b> session of the SAEM Annual Meeting with Fritz Sterz, MD, Guy Clifton, MD, Derk Krieger, MD, and Simon Dixon, MD	
<b>4:30-6:00</b>	Break – Social (Martinis and Educational Displays)	
<b>6:00-10:00</b> <i>Salons A/B</i>	<b>Resuscitative Hypothermia Academic Industry Roundtable</b> <b>How to build interdisciplinary research in hypothermic resuscitation.</b>	
<b>6:00-6:30</b>	Introduction and keynote	<b>Fritz Sterz, MD</b> , Vienna General Hospital
The following one-hour sessions will be led by a panel of speaker/facilitators. There will be one panel for each session. Panels will have 4-5 members each. The panel will make a brief presentation and then lead a discussion among all the participants of the meeting. The panels will include established experts in hypothermia research, representatives of emergency medicine, and representatives of industry or governmental agencies.		
<b>6:30-7:30</b>	<b>Session 1: Barriers</b>  Identification of the barriers to and opportunities for initiating multidisciplinary emergent hypothermic resuscitation research efforts.	<b>Guy Clifton, MD</b> University of Texas Houston <b>Celia Witten, MD, PhD</b> FDA, GRND <b>George Sopko, MD, MPH</b> NIH, NHLBI <b>Mike Sayre, MD</b> Ohio State University
<b>7:30-8:30</b>	<b>Session 2: Questions</b>  What are the critical questions of science to be answered in the next 5 years for hypothermia?	<b>W. Dalton Dietrich, PhD</b> University of Miami <b>Sam Tisherman, MD</b> University of Pittsburgh <b>Midori Yenari, MD</b> Stanford University <b>Clifton Callaway, MD, PhD</b> University of Pittsburgh
<b>8:30-9:30</b>	<b>Session 3: Collaborations</b>  What are the best models of collaborative research efforts in hypothermia? Is it valuable and feasible to develop consensus methodologies for effectiveness and safety endpoints, patient management strategies, data fields and timepoints? Do we need a consortium, a registry, a consensus conference, or something else?	<b>Derk Krieger, MD</b> Cleveland Clinic <b>Mary Ellen Michel, PhD</b> NIH, NINDS <b>Simon Dixon, MD</b> William Beaumont Hospital <b>Dave Wright, MD</b> Emory University
<b>9:30-10:00</b>	<b>Summation</b> and final open discussion.	

# Barriers

Mike Sayre, MD

Ohio State University

Guy Clifton, MD

University of Texas

Celia Witten, MD, PhD

Food and Drug Administration

George Sopko, MD, MPH

National Institutes of Health

This panel was asked to lead a discussion on:

**Identification of the barriers to and opportunities for initiating multidisciplinary emergent hypothermic resuscitation research efforts.**

What are the barriers to and opportunities for initiating multidisciplinary emergent hypothermic resuscitation research efforts? Does the need for early initiation of therapy make waiver of informed consent necessary, feasible, or worth the effort? What is needed to initiate hypothermia very early in a patient's treatment? What are the advantages and disadvantages of starting cooling in the emergency department versus the intensive care unit? What is the role of technology in cooling more rapidly? Is using new technology to cool patients ever a barrier to performing hypothermia research? Are we studying the devices or the concept of induced hypothermia? Does every study of hypothermia need a new IDE? Where should the funding for this research come from?

## BARRIERS

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### **Dr. Guy L. Clifton**

#### **What are barriers to multidisciplinary emergent hypothermic resuscitation research?**

Division of labor and responsibility between trauma service and Emergency Medicine

Medical control of EMS not with hospital-based services

Identification of eligible patients in the field.

#### **Waiver of informed consent is necessary.**

Timely initiation of experimental treatment

Sufficient patient accrual to conduct studies

Enrollment inclusion for all ethnic and economic populations

#### **What is needed to initiate hypothermia very early in a patient's treatment?**

Accurate determination of eligibility

Method of induction of hypothermia useable in ambulance or in emergency department

#### **What are the advantages and disadvantages of starting cooling in the ED vs. the ICU?**

Advantage of ED cooling—cooling within time window

#### **Is using new technology to cool patients ever a barrier to performing hypothermia research?**

Here discuss IND, risk, and new devices with use of waiver.

New technology may involve more layers of approval and additional planning, but should not be a barrier.

#### **We are simultaneously studying the devices used and the concept of induced hypothermia.**

#### **Does every study of hypothermia need a new IDE?**

If device is not FDA approved

If waiver of consent is used

#### **Where should funding come from?**

NIH

#### **References:**

Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar JP, Wagner FC, Marion DW, Luerssen TG, Chesnut RM, Schwartz M. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 344(8):556-563, 2001.

Markgraf CG, Clifton GL. Treatment window for hypothermia in brain injury. *J Neurosurg* 95:979-983, 2001.

Clifton GL, Knudson P, McDonald M. Waiver of consent in studies of acute brain injury. *J Neurotrauma* 19(10):1121-1126, 2002.

Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar, JP, Marion DW, Luerssen TG. Hypothermia on Admission in Patients with Severe Brain Injury. *J Neurotrauma*, 19(3):293-301, 2002.

**Regulatory Review: Pathways to Market**

Premarket Notification 510(k)

Premarket Approval Application (PMA)

Product Development Protocol (PDP)

Humanitarian Device Exemption (HDE)

De Novo Classification

**Premarket Notification 510(k): Substantial Equivalence**

Predicate Device (legally marketed, not subject to PMA)

Comparison

- same intended use and
- same technological characteristics or
- different technological characteristics and
- as safe and effective as predicate

**Premarket Application (PMA)**

... "reasonable assurance of safety and effectiveness"...

**Regulatory Path Examples**

**Hydrocephalus Shunts**

510(k) (substantial equivalence)

Comparison to predicate

Standards: ASTM F647, ISO 7197

Materials/biocompatibility

For new/unusual designs, may need a clinical study for infection or revision/causes or failures/failure modes

**Intracranial Neurovascular Stents**

Class III (PMA/HDE/PDP)

2 HDE's approved

**Deep Brain Stimulation**

Class III

PMA approval for essential tremor and Parkinson's disease symptoms

**Clinical Study Regulation: FFD&C Act gives FDA the authority to regulate investigational devices:**

To encourage the discovery and development of new devices

Maintain optimum freedom for scientific investigations

**Section 520(g) of the Act**

Requires IRB approval for all clinical investigations

Requires informed consent from all subjects unless emergency use

**IDE Regulation (Part 812) Allows an unapproved device to be shipped for clinical evaluation:**

Identifies sections of the Act from which IDEs are exempt

Identifies exempted investigations (e.g. cleared devices, IVDs)

Defines SR and NSR investigations

**Significant Risk (SR) Study**

Presents a potential serious risk to the health, safety, and welfare of a subject and is:

- an implant; or
- life supporting or sustaining; or
- of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health

FDA approval required

**Non-significant Risk Studies**

FDA approval not needed

Examples:

- MRI < 4 Tesla
- Urologic catheters
- Low level biostimulation lasers
- Laparoscopes

**NSR devices can be SR studies**

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**Informed Consent: Emergency Use**

Must be reviewed and approved by the IRB and the FDA prior to use

May be waived when there is a life-threatening situation

- the subject cannot communicate
- time is not sufficient
- no available alternative
- two physicians certify in writing

**Informed Consent: Emergency Research**

Certain studies may not require informed consent when IRB agrees that

- there is a life-threatening situation and current treatments are unsatisfactory
- no time
- can't identify subjects prospectively
- community consultation
- public disclosure

**When Are Clinical Data Needed?****To support:**

PMA, PDP or HDE (almost always), 510(k) (<10%)

New indication for an *approved* device (e.g., BPH for a urologic laser)

Significant change to device, especially Class III devices

**Types of Studies**

Sponsor-investigator or manufacturer-sponsored

Feasibility

Pivotal, including sites outside the US

Post-approval

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**Feasibility Trial**

Answer design-related questions that cannot be addressed by bench/animal testing

Modify device design &/or instructions for use

Preliminary safety data

No control

Limited # pts/limited follow-up

**Pivotal Trial**

Final design, indication for use, and protocol

Controlled and masked, if possible

Primary/secondary endpoints

Develop information for labeling

Statistical validity to show S & E

**Post-Approval**

May be required for PMA approval

Designed to address specific question

# of patients and duration specified by FDA

**Cooling Devices: Clinical Study Questions**

How soon? How cold? How fast? How long?

How measured? Speed of rewarming?

Other treatments provided? Local versus systemic?

**Temperature Control Devices**

Tool?

Treatment?

**Temperature Control Devices**

Cooling Blankets

Endovascular Devices

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**Dr. George Sopko**

**Definition of hypothermia**

How cold? How long? How fast? When? Where?

**Other hypometabolic strategies**

Uncontrolled vs. controlled hypothermia

Self-induced hypothermia - role of hibernation

**Aim of hypometabolic strategies**

Prevention of critical organ/system injury – “ranking”

Prevention of hyperthermia

**Aim of hypometabolic strategies**

Role of new technologies: development and testing

Utilization of technologies: when, where, and by whom

**Hypometabolic strategies: clinical application**

Definition of outcomes

Choice of relevant outcomes

Role of biomarkers as a target for initiation and monitoring of interventions

Identification of target population: single vs. multiple organ disorder(s)

Conduct of clinical studies: existing vs. optimal infrastructure

Available models

Consent: role of community, medical and professional organizations

IDE/IND: when old becomes new therapy

Unified scientific agenda: development & implementation, timeliness, flexibility, practicality, and scientific review

Funding: industry, government, foundations

NIH: typically mechanistic or hypothesis driven

# Questions

Clifton Calloway, MD, PhD	University of Pittsburgh
W. Dalton Dietrich, PhD	University of Miami
Samuel Tisherman, MD	University of Pittsburgh
Midori Yenari, MD	Stanford University

This panel was asked to lead a discussion on:

What are the critical questions of science to be answered in the next 5 years for hypothermia?

What are the critical questions of science to be answered in the next 5 years for hypothermia? Should the focus be on mechanisms of action? Can we define optimal temperatures, durations of therapy, and rates of re-warming? Do these differ from one disease state to another or from one patient to another? Can hypothermia be induced or supplemented pharmacologically? Can cooling be performed non-invasively? Are there important questions of genomics and proteomics related to hypothermia?

## QUESTIONS

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**Dr. Clif Calloway,**

### ***General Questions.***

The practical questions about the implementation of therapeutic hypothermia can provide clues and a plan for investigating the underlying mechanisms of therapeutic hypothermia. Specifically, practical implementation requires one to know (1) what temperature range is most effective, (2) how quickly must hypothermia be induced to be effective, (3) how long should hypothermia be maintained. Separately, we must determine whether the answers to these three questions are different for different disease states, such as traumatic brain injury, cardiac arrest (global brain ischemia), and stroke (focal brain ischemia).

#### **What degree of hypothermia is optimal for improving outcomes after cerebral injury?**

Almost all physiological processes are affected by hypothermia. Reduced temperature will reduce the metabolic demands of the brain, presumably improving mismatch between substrate supply and demand in low-flow states. Inasmuch as reduced metabolism contributes to the beneficial effects of hypothermia, the lower the temperature the better. For global brain ischemia, this central role for lowered metabolism is supported by data about intransischemic hypothermia, but it is not supported by the beneficial effects of hypothermia induced after reperfusion. Post-reperfusion hypothermia may provide its maximal benefit at a level of 32-34°C. This observation suggests that post-reperfusion cooling may alter the balance between specific metabolic pathways that have a differential sensitivity to temperature. If cooling proceeds too far, all processes are inhibited without any additional benefit. Mechanistic studies should look for candidate processes that are affected over this temperature range.

#### **How quickly must hypothermia be induced to be effective?**

The therapeutic window for induced hypothermia should help identify critical mechanisms for neuronal recovery. Hypothermia induced during brain injury effectively reduces the magnitude of the injury. However, hypothermia induced after a given injury can only interfere with those processes occurring during that time window. Using the example of global ischemia, mild hypothermia is known to be beneficial when initiated up to several hours after reperfusion. Because the most severe oxidative stress, excitatory amino acid release and energy failure occur during ischemia and the first 30-60 minutes of reperfusion, these processes are probably not the ones targeted by cooling. Therefore, mechanistic inquiries should focus on later events in the cascade leading to neuronal death or survival.

#### **How long should hypothermia be maintained?**

Again, the therapeutic window for induced hypothermia can provide important clues about the mechanisms that it affects. For global ischemia, brief hypothermia (1-2 hours) only proved effective if it began immediately. In fact, brief hypothermia is best if it begins to overlap the ischemic period itself. Thus, the free radical burst, excitatory amino acid release and energy failure that occur during that period are likely targets for brief hypothermia. Strangely, the beneficial effects of brief hypothermia may not be permanent, and may only delay neuronal degeneration. Prolonged hypothermia (6-36 hours) appears to be effective even if initiated much later (up to 6 hours after reperfusion), suggesting again that other more protracted processes are affected. Intracellular signaling, new gene expression and protein processing are possible target mechanisms. Importantly, the beneficial effects of prolonged hypothermia appear to be more permanent. Understanding what cellular processes are affected could help guide how long to maintain hypothermia in clinical settings.

Because different cellular events occur after different types of brain injury, practical application of hypothermia must develop an appreciation of these differences, rather than assuming that one regimen fits all. For example, traumatic brain injury seems to have a burst of high intensity events that progress rapidly after the insult. However, survivable global brain ischemia appears to initiate a smoldering cascade of cellular events leading to protracted cell death. Therefore, rapid induction of hypothermia may prove more important after traumatic brain injury than after cardiac arrest. Appreciation of these different mechanisms could help interpret the different success observed in clinical trial for different diseases. Furthermore, understanding these cascades may help clinicians to identify which patients are most likely to benefit from induced hypothermia.

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**Dr. W. Dalton Dietrich,**                    **General questions continued.**

Methods of inducing hypothermia: Endovascular catheters or external cooling devices?

Rewarming phase: How fast to rewarm; what can go wrong?

Gender questions: Are females protected by hypothermia?

Mechanisms of hypothermic protection: Temperature as an experimental tool?

Pharmacotherapy plus hypothermia: Better protection with combination therapy?

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**Dr. Mimi Yenari,**                    **Questions regarding hypothermia in patients with stroke.**

**Is hypothermia protective against experimental stroke in the absence of reperfusion?**

Is it protective? (Experimental literature is conflicting)

What is the optimal duration of cooling?

What is the temporal therapeutic window?

**What are the interactions between hypothermia and thrombolysis?**

What is the influence of temperature on thrombolysis in in-vivo models of stroke?

Are hypothermia and thrombolysis synergistic, or can hypothermia prolong the time window for rt PA use?

Can hypothermia reduce the risk of BBB disruption and hemorrhage that can result from rt PA use?

**Can hypothermia help us identify other therapeutic targets for neuroprotective stroke treatment?**

**Can hypothermia work as a part of "Cocktail" approaches with other neuroprotectants?**

For example, hypothermia may be used in combination with gene therapy.

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**Dr. Samuel Tisherman,**                    **Questions regarding hypothermia in patients with hemorrhagic shock.**

A much more controversial area of interest is the effect of mild hypothermia during hemorrhagic shock. There is an ever increasing body of laboratory research suggesting that mild (33-36°C.) to moderate (28-32°C.) hypothermia improves survival from hemorrhagic shock. In some preliminary studies, this does not seem to be related to changes in systemic cytokines or in free radical production. The benefits seem to be more related to cardiovascular support, i.e., maintaining blood pressure and preventing cardiac arrest. This is even true if hypothermia is not initiated until the end of shock and start of full fluid resuscitation.

In contrast, retrospective clinical studies of trauma patients have correlated hypothermia with increased mortality. The studies are compounded by the fact that the most severely injured patients are the ones who become hypothermic as a result of exposure, shock, administration of cold fluids, intoxication and analgesia/anesthesia. One prospective study comparing a more rapid rewarming technique (continuous arteriovenous rewarming) with standard rewarming procedures showed some physiologic benefits of more rapid rewarming, but no overall survival benefit. Unfortunately, this study did not compare totally equivalent groups of patients. More importantly, no studies have explored the effects of controlled, resuscitative mild hypothermia in this patient population.

In trauma patients, one of the main concerns regarding hypothermia is coagulopathy. There is some data, mostly in vitro, suggesting that clinically important coagulation changes do not occur above 34°C. In a trauma patient with significant tissue trauma, massive blood loss, shock, and massive transfusions, it is difficult to determine the direct effects of temperature. Also, novel hemostatic agents may make these issues less important.

Only a prospective, randomized clinical trial, with precise control of temperature and prevention of shivering and sympathetic response, will be able to clearly answer these questions.

# Collaborations

Derk Krieger, MD

Mary Ellen Michel, PhD

Dave Wright, MD

Simon Dixon, MD

Cleveland Clinic

National Institutes of Health

Emory University

Beaumont Hospital

This panel was asked to lead a discussion on:

## **What are the best models of collaborative research efforts in hypothermia?**

What are the best models of collaborative research efforts in hypothermia? Is it valuable and feasible to develop consensus methodologies for effectiveness and safety endpoints, patient management strategies, data fields and timepoints? Do we need a consortium, a registry, a consensus conference, or something else? Is it best to create multi-center efforts de novo for each study, or would it be valuable to have an ongoing hypothermia research network? Is it realistic to expect centers to be able to perform hypothermia research across several disease states, or are centers too dependent on individual investigators with a specialized interest to make crossover feasible? How should funding of collaborative efforts be obtained?

### **Public Resource or Corporate Commodity?**

The costs of medical research have increased to levels that even the wealthiest universities can no longer afford. Private industry, driven by the public's appetite for innovation, has begun to assume the lion's share of those costs, and a formidable share of control. The boundaries between new science and applicable technologies, and hence between knowledge as a good and knowledge as a commodity, have become blurred. Some argue that the marriage of academic research with private funding will be repented because the incompatibility of commercial and scientific goals is so profound, that control over virtually all research into human health should be restored to academia. Others, particularly those working in technologically intensive fields, argue that public funds cannot do the job.

### **How Can These Efforts be Orchestrated?**

Most members of the research community agree that partnerships with industry are essential to propel research but must be managed with care. An increasing number of trials are being conducted by private industry, either alone or in partnership with other funding bodies. There is an alleged hierarchy of trial credibility ranging from purely investigator-driven and national research body funded trials to in-house industry trials. A pragmatic interaction between investigators and industry may help to raise the standards overall. Issues concerning quality and independence of the investigators have raised levels of concern among physicians. Particular concern has been expressed about conflict of interest in trial interpretation and the writing of guidelines. Standards concerning the relationship between companies and investigators are being established. In order to protect patients' rights and to honor society's need for unimpeded scientific inquiry and dissemination of results, recognized leadership associated with a national organization is needed to promote unequivocal standards and monitor ethical behavior in this research.

### **What Are The Gains of Collaboration?**

To effectively address these matters, an academic alliance committed to the pursuit of therapeutic hypothermia in design and conduct of research projects and clinical trials is imperative. Such an alliance of opinion leaders in research, clinical practice and industry may perhaps best support therapeutic hypothermia as an emerging therapeutic concept. A consortium in conjunction with national or international organizations can promote and monitor ethical behavior in research and set unequivocal standards to protect the rights of patients involved and to honor society's need for unimpeded scientific inquiry and dissemination of results.

### **What are the Goals of a Consortium?**

There are a number of trial networks that may serve as models for such a collaborative partnership. A therapeutic hypothermia research network may in the beginning be established as a multidisciplinary consortium of research consultants and members of various medical subspecialties affiliated with national or international organizations. It should primarily be build around a clinical trial to align centers and demonstrate authenticity. At a later stage, competency, knowledge, and clinical expertise of the membership may be contributed to industry and philanthropy across a spectrum of initiatives, including clinical trial preparation and review, registries, surveys, systematic reviews, and writing guidelines. The success of the consortium will be determined by the amount of inquiries and the size membership. Primary source of funding should be client sponsorship agreements rather than membership fees.

