Canadian Blood Services
Société canadienne du sang

World Health Organization

International Guidelines for the Determination of Death – Phase I

May 30-31, 2012
Montreal
Forum Report

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FOREWORD: A GLOBAL CHALLENGE

Humanity has thoughtfully struggled with the concept and criteria for death for millennia and the 'line' between life and death continues to be debated. The profound changes brought about by organ failure support, organ replacement technology and transplantation continue to challenge our notions of life and death. While the discussions at this forum were about the determination of death, this focus was based on a desire to maintain a reverence for life and to further inform when life ends in view of the ongoing advances in biological insight and technology.

As with most discussions about death, the challenges are complex due to:

- Philosophical, religious, and cultural differences in the concept and definitions of death
- The difficulties in performing research in this field and the resultant deficits in information and evidence on a number of aspects of the dying process
- Controversies regarding the validity of death determination practices
- Lack of understanding and/or awareness by the public and health professionals
- The emotionally charged nature of the subject matter

Over the years, alarming language has emerged in the media and academic literature around death determination and deceased donation practices[1]. It is difficult to distinguish valid scientific critique from those criticisms based on the fear of death itself, the fear of a mistaken diagnosis or a premature declaration of death, or the fear of retrieving organs from the living. Responsible scholarship and the best available, evidence-informed policies are required to address these well-publicized concerns.

For the purposes of this forum, death was considered a biological event. Critical factors determining the success of this initial phase included the use of a common lexicon by all involved, a focus on the medical and physiological aspects of the dying process and determination of death, and emphasis on a global perspective rather than regional interests.

This forum did not include discussion or debate about ethics, law, religion or culture. The concept of death with its attending religious, spiritual, philosophical, and cultural aspects was out of scope. Instead, participants worked toward agreement based on clinical practice, informed evidence and expertise of international experts to focus on what is observable and measureable – the scientific, biological, medical aspects of the determination of death – in order to take steps towards building consensus in this important area.

To develop this consensus a common terminology was established to support clarity and precision in the language used throughout this forum and subsequent phases of work. The planning committee worked with participants to identify critical events that comprise the dying sequence with the understanding that death is a process based on cessation of function, and that the determination of death is an event (a moment in time) in that process. Tests required for a minimum acceptable clinical standard for determining death were identified, before coming to consensus on an operational definition of human

death. The final task was to develop a research agenda and initiate the development of a plan for next steps based on the architecture and outputs derived from this forum.

Future phases in this initiative will focus on resolving outstanding issues, addressing unanswered questions and developing leading practice based on the best available science. This will involve systematic reviews of the literature and the grading of available evidence. Guidelines for the determination of death must have application within a global perspective, with accessibility and utility in countries with diverse infrastructure and capabilities.

It takes experience, proficiency, collaboration and commitment by all involved to make an event like this a productive process. We gratefully acknowledge the efforts and invaluable contribution of our subject matter experts, delegates of medical professional societies, health organizations, and country-specific representatives.

Dr. Sam Shemie, Forum Chair

EXECUTIVE SUMMARY

Depending on the country and related professional societies, guidelines may or may not exist for the determination of death by neurological and/or circulatory criteria. If in place, these guidelines have not always been implemented or proven effective in alleviating concerns about legitimacy and conflicts of interest with deceased organ donation. The World Health Organization (WHO) and The Transplantation Society have had requests from various countries to provide guidance to inform leading practices and health policy in this area. Guidelines that are applicable in a wide range of global health care settings could provide many benefits, including promoting safe practices and assuring there are no diagnostic errors in the determination of death; protecting patients and health care professionals; improving public and professional confidence in the deceased donation process and; increasing the availability of organs obtained by ethically legitimate donation and procurement practices. In response, the WHO held an initial meeting in Geneva in December 2010 in an effort to generate interest in this global challenge in support of the Istanbul Declaration (May, 2008), the WHO Madrid Resolution (March 2010), and the World Health Assembly Resolution (May, 2010).

On May 30-31, 2012, an invitational forum sponsored by Canada and Canadian Blood Services in collaboration with the WHO was held in Montreal, Canada, as a first step in the process of guideline development. In recognition of the manner in which scientific advances continue to inform our notions of life and death, the focus of this forum was to initiate the development of global medical and scientifically-based recommendations based on the cessation of biological/physiological functions in the dying process. While it was respectfully recognized that there are various legal, ethical, cultural and religious perspectives on death which can impact the utility of recommendations in the field, these perspectives were not a subject for debate or discussion at this initial meeting.

Thirty-two invited participants and delegates from a broad range of countries and professional societies participated in the forum. A comprehensive background package was provided to participants in advance including a selected bibliography of scientific, peer-reviewed articles related to death determination, a literature review on definitions of death, and a draft lexicon of medical terminology relevant to death determination policy and practice. At the meeting, international experts reviewed historical information and baseline knowledge and provided their perspectives on current issues and controversies. Participants then worked in small groups on specific challenge questions. Further plenary discussions and decision-making resulted in consensus in seven key areas as follows.

1. Death is first and foremost determined using clinical criteria based on direct, measurable observation or examination of the patient.

2. The physiological sequences of the cessation of circulatory and neurological functions leading to death were constructed to illustrate the critical events that occur when a catastrophic injury or illness occurs.

3. Clinical tests that fulfill the minimum clinical standard for the determination of death were defined for both the neurological and the circulatory sequences. Preconditions and confounding conditions that may impede or invalidate death diagnosis were also identified.

4. Certain ancillary and/or complementary laboratory tests may be useful in situations where clinical testing cannot be performed or where confounding or special conditions are present. It was recognized that there are limitations to the use of some of these tests and that further work is needed to identify reliability of these tests.

5. A precise terminology was reviewed and finalized in order to improve clarity in death determination discussions and debate.

6. Human death was defined based on measurable biomedical standards. Participants supported a movement away from anatomically-based terms such as brain death or cardiac death that erroneously imply the death of that organ. Emphasis was placed on the cessation of neurological or circulatory function and the predominance of brain function for determination of death.

   "Death occurs when there is permanent loss of capacity for consciousness and loss of all brainstem functions. This may result from permanent cessation of circulation and/or after catastrophic brain injury. In the context of death determination, 'permanent' refers to loss of function that cannot resume spontaneously and will not be restored through intervention."

   This definition is based on the cessation of function (the primary and fundamental purpose of an organ that can be assessed by observation and examination and is necessary for sustained life) rather than activities (physiologic properties of cells and groups of cells that can be measured by laboratory means).

7. The forum recognized that this report provides the architecture for future deliberations. Recommendations were made for further research to inform practice and address information gaps. The group also recommended a comprehensive review and grading of existing evidence related to the neurological and circulatory determination of death, as well as a review of qualifications for clinical and ancillary testing associated with death determination. The forum also recognized that order to further advance the development and implementation of comprehensive guidelines, work with a broader international group of stakeholders will be required.

1. FORUM OVERVIEW

1.1 Committees

Two committees were established to provide leadership and management for the development of the forum process. A Planning Committee met regularly for nine months prior to the forum to develop the agenda, the process, and the supportive background documents, and to manage the logistics. A Forum Advisory Committee of international experts was also created to review forum materials and provide their advice throughout the preparatory phase.

Forum Planning Committee

Dr. Sam Shemie, Forum Chair
- Professor of Pediatrics, McGill University, Montreal, Canada
- Division of Critical Care, Montreal Children's Hospital
- Loeb Chair and Research Consortium in Organ and Tissue Donation, University of Ottawa
- Executive Medical Director, Canadian Blood Services

Dr. Andrew Baker
- Canadian Critical Care Society Representative
- Chief, Department of Critical Care, Department of Anesthesia, St. Michael's Hospital, Toronto, Canada
- Professor of Anesthesia and Critical Care, University of Toronto, Canada

Ms. Laura Hornby
- Lead Project Manager, Determination of Death Practices in the ICU Research Program, Children's Hospital of Eastern Ontario Research Institute, Ottawa
- Loeb Research Consortium in Organ and Tissue Donation, University of Ottawa
- Organ Donation Research Program, Montreal Children’s Hospital

Ms. Dorothy Strachan
- Process Consultant and Facilitator, Strachan-Tomlinson Inc., Ottawa, Canada

Dr. Jeanne Teitelbaum
- Neurologist and Neuro-Intensivist, Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University Health Centre, Montreal, Canada
- Program Director for Neurocritical Care, Montreal Neurological Institute
- Associate Professor of Neurology, McGill University

Ms. Sylvia Torrance
- Director, Strategic Planning, Organ Donation and Transplantation, Canadian Blood Services, Ottawa, Canada

Ms. Kimberly Young

- Executive Director, Organs and Tissues, Canadian Blood Services

Forum International Advisory Committee

Dr. James Bernat

- Professor of Medicine and Neurology, Dartmouth Medical School
- Director, Clinical Ethics Program, Dartmouth-Hitchcock Medical Center, Department of Neurology, Dartmouth-Hitchcock Medical Center, USA

Professor Alexander Capron

- Vice Dean, Faculty and Academic Affairs, University of Southern California (USC)
- Scott H. Bice Chair, Healthcare Law, Policy and Ethics
- Professor of Law and Medicine, Keck School of Medicine, USC
- Co-Director, Pacific Center for Health Policy and Ethics, USC Gould School of Law, USA

Dr. Frank Delmonico

- Professor of Surgery, Harvard Medical School
- Massachusetts General Hospital, Emeritus Director of Renal Transplantation
- President-Elect, The Transplantation Society
- Advisor, WHO, Organ Donation and Transplantation
- Medical Director, New England Organ Bank, USA

Dr. Luc Noel

- Coordinator, Clinical Procedures Department for Health Systems and Policies and Workforce, World Health Organization, Switzerland

1.2 Background

Depending on the country and related professional societies, guidelines may or may not exist for the determination of death by neurological and/or circulatory criteria. If in place, these guidelines have not always been implemented or proven effective in alleviating concerns about legitimacy and conflicts of interest with deceased organ donation. Country and professional society perspectives and interests are likely to vary depending on the stage of development of deceased donation programs. The significant diversity in health services and standards of care worldwide is an additional complicating factor.

Both the World Health Organization (WHO) and The Transplant Society have had requests from various countries to provide guidance in the area of death determination, as any international initiative to improve deceased donation is fundamentally predicated on a common understanding and best practices for the determination of death. The WHO held an initial meeting in Geneva in December 2010 in an effort to generate interest in this global challenge.

The purpose of this forum was to initiate the development of medical and scientifically-based guidelines and recommendations to inform health policy regarding leading practices for the determination of death. It was developed and sponsored by Canadian Blood Services in partnership with the WHO.

Forum objectives were:

1. To consult with forum participants and other key stakeholders prior to the forum about the current situation of countries and professional associations with respect to the determination of death in their domains,
2. To develop background documents in support of forum discussions and decision-making,
3. To discuss and come to agreement on a shared understanding of how to accomplish the purpose of this initiative,
4. To create a plan for moving this initiative to the next stage, and
5. To create mutual support, collaboration and education in support of the Istanbul Declaration[2] (May 2008), the WHO Madrid Resolution[3] (March 2010), and the World Health Assembly Resolution[4] (May 2010) and related strategic issues affecting global alignment on death determination and deceased donation.

This forum took an initial step – developing consensus on the determination of death based on neurological and circulatory criteria – in a longer journey that is directed toward facilitating and enhancing regional and international practices. Such a consensus can provide many benefits:

- Promoting safe practices and minimizing diagnostic errors in the determination of death,
- Protecting patients and health care professionals,
- Improving public and professional confidence in the deceased donation process,
- Upholding the "Dead Donor Rule",
- Increasing the availability of organs obtained by ethically legitimate donation and procurement practices.

1.3 Scope

For this forum, the following items were identified as being within scope for discussion.

- Discussions were focused on the biological/medical aspects of death determination. It was respectfully recognized that there are various legal, ethical, cultural and religious perspectives on death. However, while these perspectives must be considered in terms of implementation, they were out-of-scope and not subject for debate at this forum.
- A critical success factor for the meeting was decision making based on scientific evidence. A selected bibliography was provided ahead of the meeting for participants. However, a comprehensive review of scientific information and grading of evidence was beyond the scope of this meeting.
- The forum included consideration of both neurological and circulatory death determination.
- The forum included consideration of both adult and pediatric patients.
- The recommendations provide a global perspective, i.e. the recommendations need to be applicable across the world, regardless of technology available.

- The recommendations identify the minimum criteria (lowest acceptable standard) for the determination of death, i.e. what constitutes acceptable medical practice in this area.

1.4 Forum Process

The forum process brought together a group of international subject matter experts and representatives from professional organizations and countries to build an initial understanding and consensus on a variety of topics related to death determination (Appendix C: Forum Participants). Professional organizations were selected based on their involvement in the care of patients who may die after catastrophic brain injuries and/or circulatory arrest.

In preparation for the meeting, a comprehensive background package was provided to participants in advance of the forum. This included a selected bibliography of scientific, peer-reviewed articles related to death determination (Appendix A), a literature review on definitions of death, and a draft lexicon of medical terminology relevant to death determination. A survey was also distributed to participants prior to the forum, to establish what practices and guidelines related to both circulatory and neurological death determination were available in various countries and to identify concerns and issues related to death determination.

Because of the challenging and sensitive nature of the subject matter, as well as the international nature of the group, the approach at the meeting was to deconstruct the dying process and reach consensus on foundational building blocks before proceeding to more difficult and controversial topics. The first steps included:

- Establishment of a common terminology to ensure shared understanding during discussions
- Identification of the neurological sequence leading to death after catastrophic brain injury
- Identification of the circulatory-respiratory sequence leading to death after cardiac arrest
- Identification of criteria, preconditions and confounding factors for the critical events along those pathways,
- Determination of the point of death along those sequences,
- Development of an operational definition of human death,
- Development of a research agenda to identify gaps in knowledge.

Each section of the meeting began with an international expert speaker to provide historical information, review baseline knowledge, and provide an expert's perspective on current issues and controversies. After each presentation, plenary discussions provided an opportunity to interact with speakers and ask questions. Participants were provided reference sheets as condensed summaries of existing evidence and then divided into groups with extensive discussions around each challenge question. Group results were discussed in plenary sessions, with outputs being reworked until consensus was reached. Consensus was defined as meaning substantial agreement and was based on participants stating that they agreed with or could live with the proposal, and would support the decision both within and outside the meeting. The reference fact sheets were revised and confirmed as part of the table and plenary discussions during the forum process.

At the end of the first day, the Forum Planning Committee met to review conclusions generated through small group discussions and developed a report for consideration the following morning. Given that this forum was an initial step in the development of death determination guidelines, discussions on the second day also focused on next steps related to the further development and implementation of related practice guidelines. Plans are in progress for subsequent work in future phases to further develop and implement these guidelines.

1.5 Forum Agenda

Introduction

Kimberly Young, Executive Director, Organs and Tissues, Canadian Blood Services, welcomed participants, describing the substantive contributions of the Canadian Council for Donation and Transplantation and Canadian Blood Services in collaborative policy development related to ICU-based care in organ and tissue donation. She commented that Canadian Blood Services is proud to host this forum as an initial phase in a longer process focused on global consensus building, and to co-sponsor the event with the WHO.

Challenge Address

Dr. Sam Shemie, Forum Chair, provided a dynamic challenge address to set the stage for expert forum presentations and discussions. In his remarks, Dr. Shemie emphasized the critical success factors for the meeting which included using common terminology, focusing on medical and biological aspects of death determination, using evidence-informed clinical expertise and an international perspective, and thinking globally rather than focusing on regional interests.

Dr. Shemie also reviewed the evolution of the understanding of death and the impact of new technologies and procedures that challenge traditional concepts of irreversibility, including extracorporeal technologies and decompressive craniectomy. He described the forum approach and outlined what forum participants would be doing and how they would build consensus on various aspects of death determination. Dr. Shemie concluded by thanking forum participants and the organizations and countries they represented for their support.

International Perspectives

Dr. Luc Noel, Coordinator, Clinical Procedures Department for Health Systems Policies and Workforce at the WHO, provided a WHO and international perspective on the purpose of the forum. He pointed out that the need for international guidelines on death determination arose out of a request by member states at the 65th World Health Assembly. Dr. Noel explained that rigorous and systematic guidelines that are based on the best science available and are respectful of global diversities can provide a credible and well-organized reference for use by all countries. He concluded by commenting on the importance of placing death and deceased donation in the context of common experience.

Assumptions and Key Considerations

Facilitator Dorothy Strachan reviewed the core assumptions and key considerations for the meeting. The group reaffirmed the following as being critical for discussions throughout the forum:

- Protecting the interests of dying patients overrides facilitating deceased donation for the purposes of transplantation.
- The scope of this work will be restricted to the scientific, medical and biological basis for the determination of death.
- The principle of the 'dead donor rule' applies to deceased donation practices.
- The best scientific and medical evidence available should be used to inform decisions.
- Agreement on terminology for the purposes of the forum is essential to support discussion.
- The guidelines and recommendations must have utility, applicability and be workable in a wide range of global health care practice settings.

Presentations

Expert speakers (in order of presentation) included:

Death and the Brain: A Clinical Assessment (and Nothing Else)
Dr. Eelco Wijdicks, Professor of Neurology, Mayo Clinic College of Medicine

In his presentation Dr. Eelco Wijdicks provided a comprehensive history of the controversies and milestones related to practices regarding the determination of death based on neurological criteria - "brain death". In his overview he referred to key papers and guidelines that have informed the state of the field today, focusing on the 2010 guidelines from the American Academy of Neurology (AAN)[5]. He then reviewed the use of the apnea test and various confirmatory tests, discussing some of the associated issues.

Dr. Wijdicks also described a survey of 80 nations regarding brain death criteria[6]. While the fundamentals of clinical testing for brain death are remarkably similar, there are substantial differences between countries that are generally related to the time of observation, the qualification of the examiner, and the use of confirmatory tests. He also noted that mistakes in death determinations were generally the result of inexperienced physicians, misjudgment of confounders, and/or misapplication of criteria. To close his presentation, he provided advice to participants in coming to consensus on the determination of death based on neurological criteria:

- Focus on the brainstem ("look below the tentorium").
- Accept a clinical dividing line - once all is lost, nothing returns; when some function is preserved recovery may occur.
- Ask 'why should this patient not be brain dead'
- Stick to the essentials: etiology, preconditions, confounders and the clinical neurological examination.
- The 2010 AAN guideline is a reasonable start for discussion.

Death and Circulation: History and Current Concepts
Dr. James L. Bernat, Louis and Ruth Frank Professor of Medicine, Dartmouth Medical School, New Hampshire

Dr. James L. Bernat opened his presentation by commenting that traditional death determination – both in current practice and prior to cardiopulmonary resuscitation (CPR) and mechanical ventilation – is the cessation of circulation and respiration, and this determination remains useful for the majority of deaths.

Speaking to the wide variation in medical and legal language to describe death, Dr. Bernat noted that there was a need for greater uniformity within and among countries to ensure better public trust. In discussing the situation in the United States, he explained the confusion arising from the terms "permanent" cessation of circulatory function (will not be restored spontaneously or through intervention) and "irreversible" cessation (cannot be reversed using current technology). He emphasized that, despite the use of "irreversible" in statutes of death, the traditional standard of death always has been the permanent cessation of circulation. Dr. Bernat also discussed donation after cardiocirculatory death (DCD) and issues surrounding auto-resuscitation and use of extracorporeal membrane oxygenation (ECMO) after death.

Historical Review of the Definition of Death: Evolving Towards an Operational Definition of Human Death
Prof. Alexander M. Capron, Professor, University of Southern California

Dr. Alexander Capron began this session by providing a brief history of the medical understanding of death. He noted that people had different ideas of what a "definition" of death encompassed, ranging from a spiritual understanding to clinical and laboratory tests to determine death. Dr. Capron suggested that a new, uniform and universal approach to death definition was needed – one that was applicable to all people regardless of jurisdiction or circumstances. This was driven by the technological advances in ventilation support for patients, the improved success rates of transplantation, as well as the movement of persons among jurisdictions.

Dr. Capron also discussed the different groups that potentially had death determination decision-making authority: the physician (individual clinical judgment); a group of experts (decision through professional guidelines); the patient or family (based on preference or religious exemptions); and/or decision by society through legal authority and legislation. Understanding these decision-making powers and how to exercise them when implementing an operational definition of death is essential to supporting effective practice.

As advice to forum participants for their deliberations, Dr. Capron noted that any definition of death should:

- Be defined as a single phenomenon

- Describe the death of the organism as a whole (not the whole organism)- destruction or disintegration is not required
- Be relevant to most prevalent situations and practices
- Be uniform among people and situations
- Be adaptable to advances in technique
- Be reliable in application
- Be acceptable to practitioners and the public

Building Global Agreement around Complex Practices: Lessons Learned
Professor Charles L. Sprung, Director, General Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center, Jerusalem

Dr. Sprung shared lessons learned from his experiences in international consensus building in both research and clinical practice, initially from the Ethicus Study[7] and in particular from the Welpicus study (Consensus Guidelines for Worldwide End of Life Practice for Patients in Intensive Care Units). He noted that broad representation and diverse opinions were required for international consensus. Dr. Sprung identified some of the tools that had been successful in achieving consensus on end-of-life-care issues: a modified Delphi process for identification of issues for inclusion in the study, use of coordinating centres for issue review, a web site and translation for sharing and reviewing of documents, and an expert steering committee to guide the process. He also emphasized that decisions must make sense at a practical level across cultures and professions, being sensitive to the different ways and means of communication to support long-term engagement.

Dr. Sprung ended his presentation by summarizing his recommendations:

- Prospectively involve as many stakeholders as possible – health care professional organizations, patient advocate groups, etc.
- Make stakeholders part of the process from the beginning.
- Define the key issues, especially controversial ones.
- Develop a process for defining and developing consensus for these issues.
- Determine the reasons for the lack of consensus, and try again.
- Develop a process for communication and dissemination of literature.
- Provide periodic reminders to professional societies to sustain engagement and facilitate support.
- Develop protocols and standard operating procedures where there is consensus.

WHO Guidelines Development Process
Dr. Margaret Harris, Guidelines Review Committee (GRC) Secretariat, WHO

Dr. Harris outlined the history and requirements of the WHO guideline development process which has been evolving since 1947 to its current state. She supported Dr. Sprung's comments regarding the need to engage individuals with a broad range of expertise and experience, e.g., medical, scientific, legal, economic, ethical and patient perspectives from both countries and professional societies. Dr. Harris

also stressed that development of guidelines needs to be transparent, evidence-based and unbiased. "Transparency and consistency in relation to how the guidelines are developed is essential to reduce bias and skepticism and support implementation." Peer-review and grading of evidence were also key components in the WHO guideline development process.

Forum Research Group: Dr. Andrew Baker, Canada (Lead); Ms. Laura Hornby, Canada; Dr. Tong Kiat Kwek, Singapore; Jeanne Teitelbaum, Canada; Dr. Alexander Manara, United Kingdom

One important outcome of this forum was the development of a research agenda to support discussions in the next phases of this initiative. To this end, a Forum Research Group was formed to identify during the meeting:

- Relevant research that is currently in progress or in planning,
- Specific topic areas of existing evidence required to be assembled to inform practice and policy decisions subsequent to this meeting, and
- Major gaps in existing or planned research.

The Forum Research Group was asked to focus on the questions that are realistically answerable (feasible and fundable) within a reasonable timeframe. The Group's findings were presented and discussed on the second day.

Consensus Discussions

After each presentation, group results were discussed in plenary sessions, with outputs being reworked until consensus was reached. The outcomes and consensus from these discussions are presented in Section 2 of this document.

Closing Remarks

Dr. Sam Shemie, Forum Chair, closed the meeting by thanking the participants, as well as the Planning and International Advisory Committees, commenting that not only had the expressed objectives been achieved for this meeting, they had been surpassed. Participant evaluations of the meeting design, process and outcomes rated the forum as excellent.

Dr. Luc Noel (WHO) highlighted the quality of both the group and the organization of the event. "We have a fantastic starting point and need to bring the results of this forum to those who also need to be at the table to support a global implementation process in the future."

Dr. Shemie committed to providing a forum communiqué and forum report to the participants, as well as to keeping the group informed of future developments and next steps in the process.

2. FORUM OUTCOMES

2.1 Terminology

Participants agreed to the following terminology, in order to improve the clarity of discussions and debate, for use during and subsequent to this forum.

Term	Definition
Activity	Physiologic properties of cells and groups of cells that can be measured by laboratory means.
Asystole - electrical	A condition characterized by the absence of electrical, and hence mechanical, activity of the heart, resulting in the absence of contractions of the myocardium and cardiac output/anterograde blood flow.
Asystole - mechanical	The absence of effective contractions of the myocardium and no cardiac output/anterograde blood flow. May occur in the presence of an organized or disorganized electrocardiac rhythm, e.g. pulseless electrical activity.
Autoresuscitation	The *spontaneous* resumption of heart contractions causing anterograde circulation that is not induced by cardiopulmonary resuscitation or other external assistance.
Brain death	Diagnosis and confirmation of death based on the irreversible cessation of functioning of the entire brain, including the brainstem (this forum supports the movement away from this traditional and imprecise terminology in favour of the Cessation of Neurological Function).
Brainstem death	Diagnosis and confirmation of death based on the irreversible cessation of functioning of the brainstem, predominantly but not exclusively secondary to a supratentorial brain injury (this forum supports the movement away from this traditional and imprecise terminology in favour of the Cessation of Neurological Function).
Cardiac arrest	The abrupt cessation of circulation of the blood due to failure of the heart to contract effectively. Also known as cardiorespiratory arrest, cardiopulmonary arrest or circulatory arrest.
Catastrophic brain injury leading to death	Etiologies of high severity that are common causes of brain death, such as but not limited to, traumatic brain injury, cerebrovascular accidents and hypoxic-ischemic encephalopathy after resuscitated cardiac arrest. Other forms of catastrophic brain injury that have any degree of residual clinical brain or brainstem function are not under consideration and may include persistent vegetative states, permanent vegetative states, anencephaly or those conditions related to the historical concept of higher brain (cortical) death.

Term	Definition
Cerebral electrical activity	Electrical activity of the brain, as measured using an electroencephalogram (EEG).
Cessation	Stoppage, termination.
Circulation	Anterograde flow of blood through the aorta and arterial system.
Circulatory death determination	Diagnosis and confirmation of death based on circulatory criteria. Also known as death after cardiac arrest, or death after cardiocirculatory arrest, or death after circulatory-respiratory determination (this forum supports the movement away from this traditional and imprecise terminology in favour of the Cessation of Circulatory Function).
Clinical	Based on direct, measurable observation or examination of the patient.
Coma	Prolonged absence of wakefulness, awareness and the capacity for sensory perception or responsiveness to the external environment.
Confounding conditions	Circumstances during which a diagnostic test may become unreliable and require repetition over time or application of an alternative test.
Consciousness – loss of capacity for	Lack of current or any future potential for awareness, wakefulness, interaction and capacity for sensory perception of, or responsiveness to the external environment
Criteria - minimal	Refers to the least possible that can be done and is an absolute value.
Criteria - minimum	Refers to the lowest acceptable standard, which is a relative standard often pitched above the minimal. The standard recommended by this forum sets the minimum clinical criteria.
Dead donor rule	A principle governing deceased donation practices stating that vital organs should only be taken from dead patients and, correlatively, living patients must not be killed by organ retrieval. This rule does not apply to living donation of non-vital organs.
Death	The moment in time during the dying process when the individual passes from the state of being alive to that of being dead.
Death – concept of	An abstract, unprovable explanation of death, generally based on religious, spiritual or philosophical beliefs (this forum supports the movement away from this traditional terminology in favour of the Operational Definition of Human Death).
Death – declaration of	The point in time at which a health professional, having determined that an individual is dead, formally states this finding.
Death – operational definition of	Biomedical criteria that describe the state of human death.

Term	Definition
Death – determination of	Processes and tests required to diagnose death in accordance with established criteria.
Disintegration	Loss of intactness, solidness or cohesion. Such loss can apply to function or to matter (tissues, etc.).
Dying	The process of moving from the state of being alive to that of being dead.
ECMO	Extracorporeal membrane oxygenation / extracorporeal oxygenation and circulation of blood deployed for life threatening lung or heart-lung failure.
Electromechanical dissociation	A form of mechanical asystole. A rhythm frequently encountered during cardiac arrest, characterized by organized electrical activity without circulation, traditionally measured by the absence of a palpable pulse or pulsatile arterial blood pressure.
Fixed dilated pupils	Pupils in mid-position or greater and unreactive to light.
Function	In the context of organs, the primary and fundamental purpose of that organ that can be assessed by observation and examination and is necessary for sustained life.
Integration	Combined or coordinated separate elements that provide a harmonious, interrelated whole; organized or structured so that constituent units function cooperatively.
Irreversible	Pertaining to a situation or condition that will not or cannot return or resume. In the context of death determination, there are variable definitions including: 1. Loss of function or a condition that cannot be restored by anyone under any circumstances at a time now or in the future 2. Loss of function or a condition that cannot be restored by those present at the time 3. Loss of function or a condition that will not resume and will not be restored. Also referred to as permanent.
Neuroimaging	Diagnostic brain imaging techniques to identify structural brain injury, e.g., CT scan, MRI.
Neurological death determination	Diagnosis and confirmation of death based on neurological criteria.
No effective intervention	A therapeutic intervention that is not deployed because it is not effective, not medically indicated under those circumstances, not available or accessible.
Mechanical ventilation	Assisted ventilation including bag/mask ventilation, non-invasive support e.g. BiPAP (bilevel positive airway pressure), conventional mechanical ventilation via artificial airway
Refractory to treatment	Does not respond to intervention in a clinically meaningful manner.

Term	Definition
Permanent	Pertaining to a situation or condition that will not return to its previous state. In the context of death determination, refers to loss of function that will not resume spontaneously and will not be restored through intervention.
Preconditions	Patient related prerequisites that should be fulfilled prior to application of diagnostic tests.
Respiratory arrest	Cessation of breathing. In the context of death discussions, this may be primary and lead to a subsequent cardiac arrest, or it may be secondary to the loss of brainstem function.
Test	A procedure performed in diagnosis or detection.
Test - ancillary	A complementary test or an alternative test to one that otherwise, for any reason, cannot be conducted or is unreliable.
Test - clinical	A bedside test typically based on physical examination of the patient, but may include the use of a stethoscope and vital signs monitors.
Test - confirmatory	A test performed to confirm a previously conducted test.
Test - laboratory	A technical test requiring use of elaborate equipment and medical technologies, e.g., blood testing, diagnostic imaging.
Test - supplemental	A test performed in addition to an already conducted test.
Unity	The combination or arrangement of parts into a whole.
Ventricular fibrillation	A condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles that causes the cessation of circulation. Also referred to as V-fib or VF.
Vital function	Necessary for sustained life.

2.2 Death and the Brain

Supplemental Reference Document

Participants reviewed and revised the supplemental reference document provided on Death and the Brain. This document contained condensed information from the selected bibliography of scientific, peer-reviewed articles selected by the Planning Committee (Appendix A) to assist in deliberations and decision making. The document is presented below.

Illustrative Examples for Preconditions to Neurological Testing

1. Established etiology of brain injury that is capable of causing irreversible cessation of brain function
2. Absence of:
    - Hemodynamic shock
    - Clinically significant drug intoxication
    - Hypothermia
    - Clinically significant electrolyte or metabolic disturbances
3. Intact neuromuscular function including reversal of neuromuscular blockade

Tests of Neurological Function

1. **Clinical Tests**
    - loss of consciousness
    - absence of spontaneous movements (excluding spinal reflexes)
    - absence of motor responses in cranial distribution
    - loss of brainstem reflexes
        - absent pupillary light reflex-pupils mid-position or greater (‘fixed dilated pupils’)
        - corneal
        - gag/pharyngeal
        - cough/tracheal
        - vestibulo-ocular (‘cold caloric’)
        - oculo-cephalic (‘dolls eye’)
        - loss of capacity to breathe

2. **Laboratory Tests**
    - isoelectric EEG
    - absent brain blood flow
    - absence of brain perfusion
    - absence of cerebral metabolic activity
    - absent brainstem evoked potentials after wave 1
    - evidence of tonsillar herniation by neuro-imaging

- Other:
  - observation time
  - repetition of testing

3. Guidelines

- Areas of general consistency among country specific guidelines for brain death [5,8-11] include:
  - unresponsive coma with an established etiology
  - absence of reversible conditions
  - absence of cortical or brainstem mediated motor responses
  - absent brainstem reflexes
  - loss of the capacity to breathe

- Variability in practice[6,12,13] includes:
  - procedural aspects of apnea testing
  - impact of therapeutic medications that may depress central nervous system function
  - observation time
  - age-related criteria
  - required level of physician expertise
  - provisions for anoxic-ischemic brain death
  - effect of therapeutic hypothermia
  - confirmatory, supplemental or ancillary testing (EEG, brain blood flow testing)
  - time of death

4. Spinal Reflexes

- In a systematic review of movements in brain death[14] spinal-mediated reflexes included plantar flexion and triple flexion responses, muscle stretch reflexes, abdominal contractions, sitting up posturing and respiratory-like movements that may be present in as many as 40-50% of brain death cases.
- Complex, non-brain mediated motor and spontaneous movements and non-respiratory triggering of the ventilator may occur in patients who are brain dead[5].

5. Single vs Multiple Exams

- In a review of 1,229 adult and 82 pediatric patients pronounced brain dead, there were no cases of recovery of brainstem function upon repeat examination[15].
- Wijdicks et al[5] reported that there is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly.

6. Ancillary and Supplemental Testing

- In many jurisdictions, brain death is a clinical determination and ancillary testing is reserved for cases when clinical criteria cannot be completed or confounding conditions cannot be resolved.
- In some jurisdictions, brain death requires the use of a supplementary or confirmatory test. The most commonly recommended supplemental tests are EEG, 4 vessel cerebral angiography or radionuclide testing.
- Newer tests – inconsistently recommended – include CT angiography, CT perfusion, MR angiography and transcranial Doppler.
- There is insufficient evidence to determine if newer ancillary tests accurately confirm the cessation of function of the entire brain[5].

7. Apnea test

- Wijdicks et al[5] reported that apneic oxygenation diffusion to determine apnea is safe, but there is insufficient evidence to determine the comparative safety of techniques used for apnea testing.
- Due to theoretical concerns about the effect of hypercarbia on cerebral blood flow in potential brain death, many guidelines recommend performance of the apnea test after all other clinical testing has been completed[8].

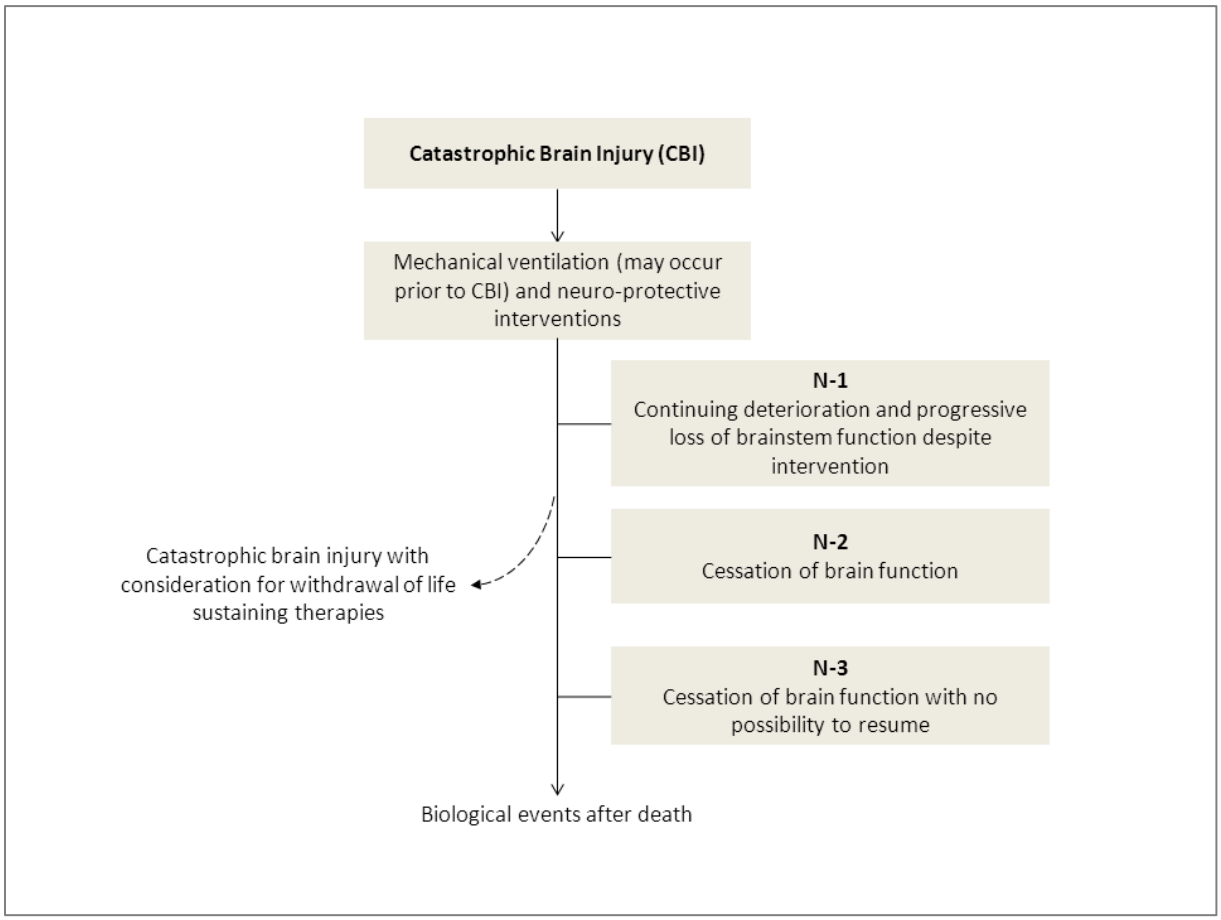
8. Reports of Reversibility

- There are no published reports of recovery of neurologic function after a diagnosis of brain death in adults using the criteria reviewed in the 1995 American Academy of Neurology practice parameters[5].
- ANZICS[8] states there is no documented case of a person who fulfils the preconditions and criteria for brain death ever subsequently developing any return of brain function.
- There are a number of subsequent case reports describing apparent recovery of neurological function after the diagnosis of brain death. It is controversial as to whether these reports represent errors in the application of diagnostic criteria, confounding conditions or cases of reversibility after properly applied testing.
- Recent cases[16,17] also emphasize the potential for the confounding impact of therapeutic hypothermia.

Neurological Sequence in the Dying Process

Participants came to consensus on the neurological sequence of the dying process. A summary of the sequence is provided below.

Figure 1: Neurological Sequence in the Dying Process



The following terminology was particularly relevant during discussions, and is repeated here to provide clarity in the description of the process:

Catastrophic Brain Injury: Etiologies of high severity that are common causes of brain death, such as but not limited to, traumatic brain injury, cerebrovascular accidents and hypoxic-ischemic encephalopathy after resuscitated cardiac arrest. Other forms of catastrophic brain injury that have any degree of residual clinical brain or brainstem function are not under consideration and may include persistent vegetative states, permanent vegetative states, anencephaly or those conditions related to the historical concept of higher brain (cortical) death.

Function: In the context of organs, the primary and fundamental purpose of that organ that can be assessed by observation and examination and is necessary for sustained life. Function should be distinguished from activities, as defined by physiologic properties of cells and groups of cells that can be measured by laboratory means. Examples of brain function such as the capacity for consciousness or ability for unassisted breathing as distinguished by examples of brain activity such as posterior pituitary antidiuretic hormone release or residual nests of neuronal electrical function.

Description of the Neurological Sequence of the Dying Process

This pathway illustrates the critical events that occur when a catastrophic brain injury leads to the death of the individual as determined using neurological criteria. Patients who have a catastrophic brain injury where death follows the withdrawal of life-sustaining therapies follow a different sequence of events (see Figure 2, A). Patients will have received mechanical ventilation, and various other neuro-protective interventions (such as hyperosmolar therapy, ventricular drainage, decompressive craniectomy) may have been initiated. At N-1, the patient continues to deteriorate in spite of intervention and there is recognition that the patient may evolve to brain death. At N-2, the deterioration has continued to a point that brain function has ceased. However, at this point, there may still be a possibility that brain function can be restored spontaneously or through intervention. If preconditions are met, confounding factors are absent and there is no effective treatment available, then by N-3, the brain has ceased functioning and there is no possibility to resume.

Because of the dynamic nature of events in this situation, precise time intervals between events will vary and cannot be determined. In fact, the events may overlap and occur at the same time. For example, if the conditions of N-1 and N-2 are met, i.e. the situation is refractory to intervention (N-1), no effective treatment is available and brain function has ceased (N-2), N-3 has occurred. The timeline also reflects the evaluation and testing sequence followed by the physician, recognizing that the determination of death after cessation of brain function is a process that identifies an event that has already occurred.

Minimum Acceptable Clinical Standard and Additional Tests for Cessation of Brain Function

After agreeing that death is first and foremost determined using clinical criteria, participants came to consensus on the minimum acceptable clinical standards to test for the cessation of brain function. There was also recognition that there are certain ancillary laboratory tests that may be useful in situations where clinical testing cannot be performed or in situations where confounding or special conditions are present. Table 1 presents the consensus points for both the clinical criteria and the laboratory tests.

Table 1: Minimum Acceptable Clinical Standard and Additional Tests for Cessation of Brain Function

	Description	Minimum Acceptable Clinical Standard	Beyond the Minimum Clinical Standard Additional Testing
N-1	Catastrophic brain injury: Continuing deterioration and progressive loss of brainstem function despite intervention	1. Established etiology and/or structural lesion capable of causing death by neurological criteria 2. Reduced consciousness (as measured by GCS 3-5 or 4-score) 3. Evidence for progressing loss of brainstem function	1. Neuroimaging that explains the severity of brain injury 2. Repetition of clinical exams with trends 3. Demonstration of elevated intracranial pressure(ICP) by monitoring
N-2	Cessation of brain function	1. Coma (excluding spinal cord mediated reflexes) 2. Absence of brainstem reflexes: • Pupils mid-position or greater and absent pupillary light reflex (fixed dilated pupils) • Corneal • Gag/pharyngeal • Cough/tracheal • Vestibulo-ocular ('cold caloric') • Loss of capacity to breathe NB: performance of apnea testing should be reserved as the last test of brainstem function	None: cessation of brain function is a clinical determination
N-3	Cessation of brain function with no possibility to resume	1. Preconditions fulfilled 2. Confounding conditions excluded or addressed 3. Refractory to all applied interventions 4. Intervention not available or indicated	1. Repetition of the minimum clinical standard examination 2. Ancillary laboratory tests e.g., • Demonstration of brain blood flow or perfusion to be absent • Refractory intracranial hypertension as measured by ICP monitoring • Transcranial Doppler consistent with absent net flow velocity • Electrodiagnostic testing (e.g., EEG, absent evoked potentials)

Preconditions Prior to Testing

Preconditions are prerequisites that must be fulfilled prior to application of diagnostic tests:

- Absence of hemodynamic shock
- Established etiology and absence of reversible etiologies to explain the coma
- Competency of the health care professional performing the clinical determination
- Competency of the health care professional performing and interpreting ancillary laboratory testing

Confounding Conditions for Testing

Confounding conditions are circumstances during which a diagnostic test may become unreliable and require repetition over time or application of an alternative test:

- Hypothermia
- The use of therapeutic hypothermia prior to determination
- The presence of central nervous system (CNS) depressing drugs that may explain or contribute to coma. Clinical judgment of the physician is required to determine at what level drugs play a role as confounders due to differences in drug tolerance and type of drug, inherent metabolism and hepato-renal function, as well as complicating effects between treatments, especially related to altered pharmacokinetics and pharmacodynamics associated with therapeutic hypothermia
- High cervical spine injury
- Evidence of acquired or iatrogenic neuromuscular paralysis, e.g., Guillain-Barré syndrome, residual neuromuscular blockade
- Severe acid-base, electrolyte, endocrine abnormality that may explain or contribute to coma
- Shock

Key Considerations

Key considerations describe points made by participants that identify important circumstances, data, reflections, and potential impacts that were taken into account during discussions:

- The clinical criteria and conditions listed here may not be applicable to neonatal patients (term $\geq$ 36 weeks, age $\leq$ 30 days).
- Ancillary tests to demonstrate the absence of brain blood flow or brain electrical function may be used in addition to, but not a substitute for, the clinical determination when unresolved confounding conditions exist, or when there is an inability to complete the clinical determination.
  - Depending on the jurisdiction, the determination of death may or may not involve complementary testing.
  - If neuroimaging does not demonstrate structural injury to explain the coma, great caution is advised in determining death using neurological criteria.

  - While EEG is still accepted as an ancillary test in some jurisdictions, practitioners must be aware of the limitations of its use, including the possibility of electrical artifacts and its measurements being restricted to cortical function with no ability to detect deep cerebrum or brainstem activity.
  - Evoked potentials are limited to the evaluation of specific anatomic brainstem tracts.
- In some situations, observation and repeat clinical testing over time may be an alternative to achieve a higher standard when laboratory testing is unavailable.
- There are legal, cultural, religious and socioeconomic factors that may warrant using differing approaches (e.g., legislated evaluation by a second physician when organ donation is being considered, requirements for laboratory technology and ancillary testing). These factors are respectfully acknowledged but out of scope for the purpose of these guidelines.
- The time of death is the time when the apnea test is completed (after all other clinical criteria are met).
- Time delay from injury to treatment: If there is a treatment change, reassessment may be needed to evaluate response to therapy.
- The decision whether intervention (e.g., decompressive craniectomy) is effective or medically indicated in a particular circumstance is a clinical decision that is out of the scope of this forum.

2.3 Death and Circulation

Supplemental Reference Document

Participants reviewed and revised the supplemental reference document provided on Death and Circulation. This document contained condensed information from the selected bibliography of scientific, peer-reviewed articles selected by the Planning Committee (Appendix A) to assist in deliberations and decision making. The document is presented below.

Tests of Circulatory Function

1. **Clinical Tests**
   - absence of palpable pulse
   - absence of heart sounds
   - absent breath sounds by auscultation
   - pulseless electrical activity (non-perfusing rhythm)
   - isoelectric EKG
   - absence of breathing
   - pupils fixed and dilated
   - no response to pain
   - loss of pulsatile arterial blood pressure (non-invasive)

2. **Laboratory Tests**
   - absent pulse by audible Doppler
   - loss of pulsatile arterial blood pressure (invasive intra-arterial line)
   - echocardiographic absence of aortic valve opening or anterograde circulation
   - absent pulse oximetry (no oxygen saturation and/or no plethysmography tracing)
   - other:
     - observation time
     - repetition of testing

3. **Guidelines**
   - An international literature review[18] demonstrated that significant variability exists in the guidelines and statements for the determination of death within selected countries that practice donation after cardiac death, particularly in regard to the criteria, diagnostic procedures and wait times. Where testing was specifically addressed, unresponsiveness, absent arterial pulse and apnea were most consistently recommended. Waiting periods ranged from 2 to 10 min, with a 5-minute interval the most frequent.

4. Autoresuscitation

- In a 2012 retrospective study[19] of 73 DCD patients (including 8 children), no patients exhibited autoresuscitation (AR) during the 5 min observation period following asystole.
- A systematic review of published studies[20] found no reported cases of spontaneous resumption of circulation after withdrawal of life support (absence of CPR). In 8 studies that reported continuing ECG monitoring and exact times, AR did not occur beyond 7 min after discontinued CPR.
- In comatose patients who die after withdrawal of life support, ECG activity can persist up to 10 min after terminal cardiac arrest without resumption of circulation[21].

5. Circulatory Arrest to Arrest of Brain Function

- Following cardiac arrest in humans, loss of consciousness occurs in 5-6 sec[22].
- In human studies of brief cardiac arrest, the EEG becomes isoelectric within 7-20 sec[23-25].
- Animal studies demonstrate isoelectric EEGs within 15-44 sec of cerebral ischemia[26-28].
- To our knowledge, there are no published studies evaluating brainstem electrical function after circulatory arrest.

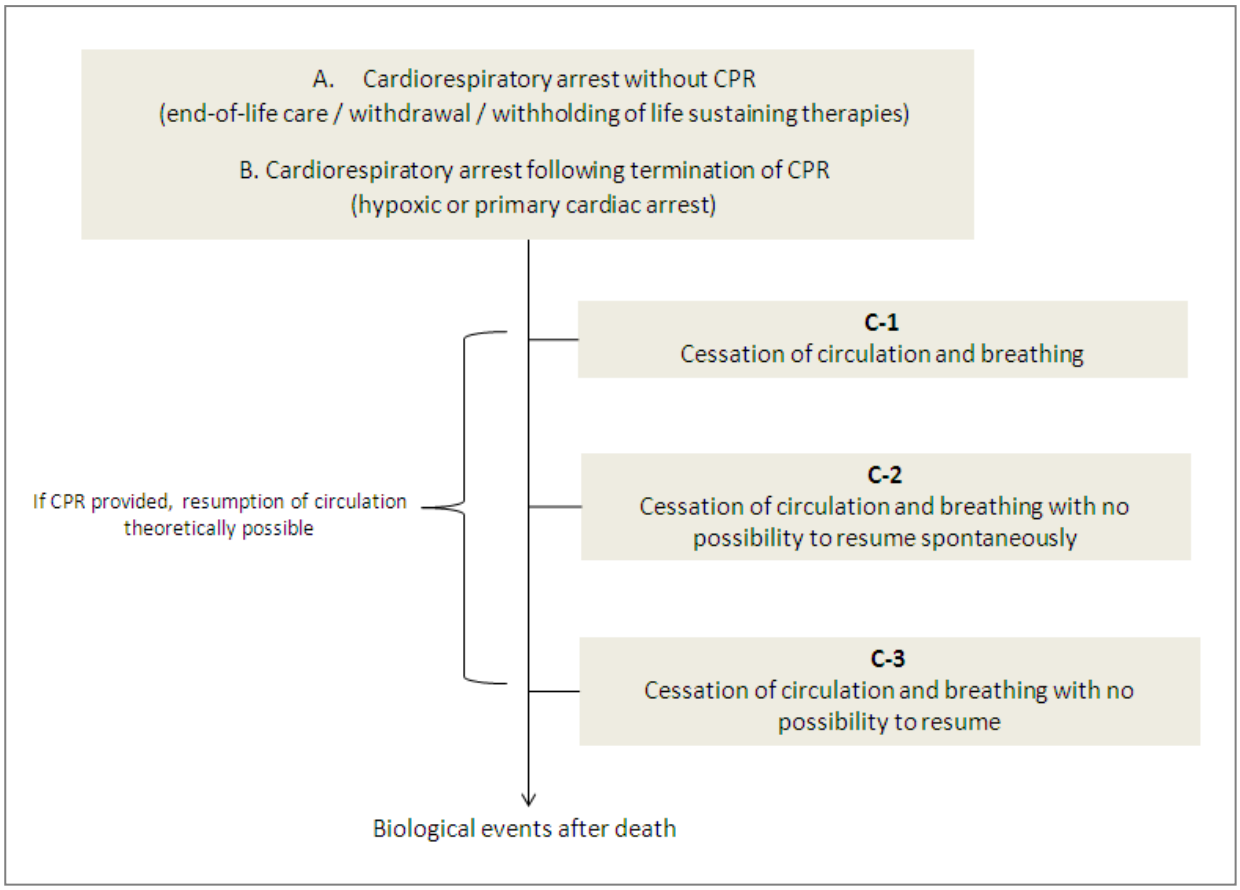
6. Cardiopulmonary Resuscitation/Extracorporeal Life Support

- CPR and/or Extracorporeal life support (ECLS) has been deployed as advanced resuscitation techniques for refractory cardiac arrest.
- The recommended duration of CPR prior to discontinuing resuscitation efforts remains unresolved and depends on a number of factors including the effectiveness of CPR, pre-existing disease, location, body temperature and age.
- CPR-ECLS has shown encouraging results in the resuscitation of in-hospital refractory cardiac arrest. However, the use of ECLS following out-of-hospital refractory cardiac arrest is associated with poor outcomes[29,30].
- *In situ* organ preservation techniques have been used to preserve organs in DCD protocols. These techniques are performed post mortem and therefore are beyond the scope of this forum. Existing research is insufficient to determine whether these techniques affect the validity of the determination of death.

Circulatory Sequence in the Dying Process

Participants came to consensus on the circulatory sequence of the dying process. A summary of the sequence is provided below.

Figure 2: Circulatory Sequence in the Dying Process



The following terminology was particularly relevant during discussions, and is repeated here to provide clarity in the description of the process:

Autoresuscitation: The *spontaneous* resumption of heart contractions causing anterograde circulation that is not induced by cardiopulmonary resuscitation or other external assistance. Examples of heart function such as effective contractions of the myocardium leading to anterograde flow of blood through the aorta and arterial system should be distinguished from examples of heart activity such as atrial natriuretic hormone release or residual pulseless electrical activity.

Permanent: Pertaining to a situation or condition that will not return to its previous state. In the context of death determination, refers to loss of function that will not resume spontaneously and will not be restored through intervention.

Description of the Circulatory Sequence of the Dying Process

The sequence illustrates the critical events that occur when circulatory arrest leads to the death of a patient.

In situation A, the patient has had a cardiac arrest and there is no CPR intervention, either because it is not medically indicated or it is against the wishes of the patient or surrogate decision makers. This would include patients who have terminal illness/end-of-life care that includes the limitation or withdrawal of life sustaining therapies.

At C-1, circulation and breathing stop. After a certain time period (between 2 and 5 min[31], based on expert consensus) there is no possibility that circulation and respiration will resume spontaneously (C-2). Because there is no intent to intervene to restore circulation, cessation of breathing and circulation is permanent and the patient is determined to be dead (C-2 and C-3 occur at the same time).

In situation B, there has been an attempt to restore circulation and respiration through CPR; however, CPR has been terminated because of lack of success in reviving the patient. The sequence is similar to situation A; however, because CPR has been attempted, existing evidence suggests that the time interval for the possibility of autoresuscitation (between C-1 and C-2) is longer - approximately 7 min[20]. As with situation A, once the time interval has passed, the patient is determined to be dead because there will be no additional interventions to attempt to revive the patient.

The above scenarios reflect situations where intervention has been deemed inappropriate or where CPR has been terminated. In situations where CPR is indicated for the patient (which may or may not be immediately available), the patient is not determined to be dead until there is no possibility of resuming circulation by any means (at C-3). The duration of time required after which there is no possibility of resuming the circulation is unresolved.

Minimum Acceptable Clinical Standard and Additional Tests for Circulatory Arrest Causing Death

There was agreement that death is first and foremost determined using clinical criteria and participants came to consensus on the minimum acceptable clinical standards for circulatory arrest causing death. There was also recognition that there are additional tests that may be useful in situations where clinical testing cannot be performed or in situations where confounding or special conditions are present. The table below presents the consensus points for both clinical criteria and ancillary tests.

Table 2: Clinical Standards and Ancillary Laboratory Tests for Circulatory Arrest Causing Death

	Description	Minimum Acceptable Clinical Standard	Beyond the Minimum Clinical Standard Additional Testing
C-1	Cessation of circulation and breathing	1. Absent palpable pulse 2. Absent breath sounds 3. Absent heart sounds 4. Absent respiratory effort or chest wall motion 5. Loss of pulsatile arterial blood pressure by non-invasive measurement 6. Coma and fixed dilated pupils 7. Electrical asystole is *not* required (pulseless electrical activity is acceptable).	1. Loss of pulsatile arterial blood pressure by arterial line monitoring 2. Absence of anterograde blood flow through the aortic valve on echocardiography, 3. Isoelectric ECG, 4. Absence of pulse by Doppler NB: oxygen saturation pulse oximetry is an unreliable indicator of absence of pulsatile circulation.
C-2	Cessation of circulation and breathing with no possibility to resume spontaneously	1. The persistence of C-1 criteria over a period of time as confirmed by continuous observation and intermittent confirmation including repetition of this evaluation at the end of the period. The time period required is 2-5 min. 2. When breathing and circulation ceases following terminated CPR, the time period to reach the point of "no possibility to resume spontaneously" increases to 7 min.	1. Use of the same tests for a higher clinical/laboratory standard for C-1 applied after the time interval required to progress from C-1 to C-2 (2-5 min or 7 min following termination of CPR).
C-3	Cessation of circulation and breathing with no possibility to resume	1. When CPR will not be provided, (patient fulfills criteria for not providing CPR) C-3 occurs at the moment of C-2. 2. Following termination of CPR, including a decision not to reinstitute CPR, C-3 and C-2 occur at the same time.	1. Nothing in addition to those tests required for C-2.

Preconditions Prior to Testing

Preconditions are prerequisites that must be fulfilled prior to application of diagnostic tests:

- The absence of, or decision not to deploy, a functioning mechanical circulatory assist device including ECMO, VAD (ventricular assist device), CPB (cardiopulmonary bypass) and IABP (Intra-aortic balloon pump) as life-saving interventions.

Confounding Conditions for Testing

Confounding conditions are circumstances during which a diagnostic test may become unreliable and require repetition over time or application of an alternative test. These apply principally but not exclusively to the termination of CPR.

- Accidental hypothermia
- Drug intoxication (may change timelines for the rational decision to discontinue CPR)
- Tension pneumothorax
- Cardiac tamponade
- AutoPEEP, dynamic hyperinflation
- Massive pulmonary embolus
- Ongoing mechanical ventilation (potential for autoPEEP)
- The presence of a functioning pacemaker (may promote the resumption of circulation)

Key Considerations

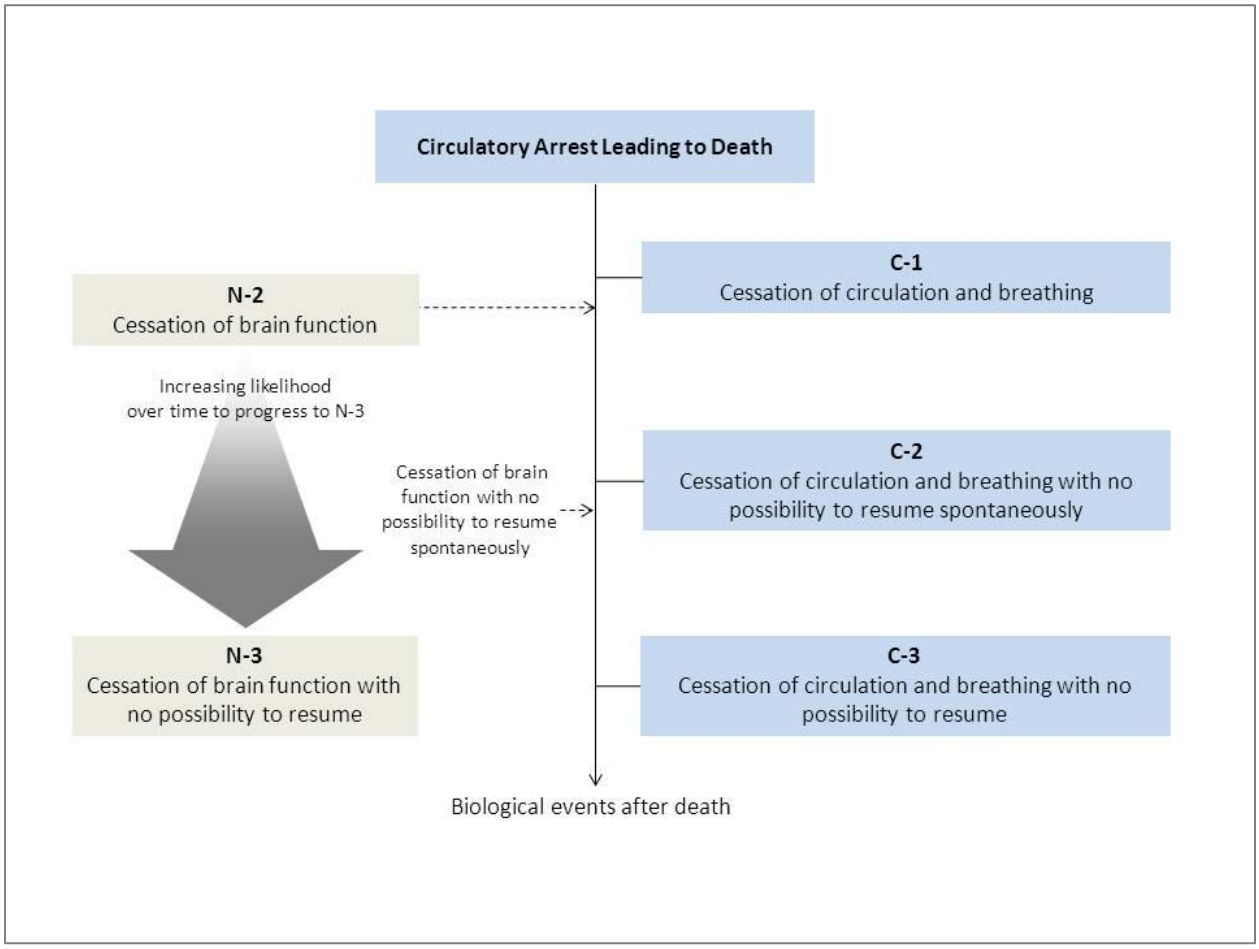
Key considerations describe points made by participants that identify important circumstances, data, reflections, and potential impacts that were taken into account during discussions:

- The clinical criteria and conditions listed here may not be applicable to neonatal patients (term $\geq$ 36 weeks, age $\leq$ 30 days). Further research is required in the neonatal population.
- Determination of death after cessation of circulation should be the same with or without organ donation.
- In the presence of mechanical ventilation and cardiac arrest, end tidal carbon dioxide monitoring can be an additional marker of circulation and may assist in the detection of the resumption of spontaneous breathing and circulation.
- Transthoracic echocardiography may be helpful to document the absence of effective contractile function.
- The decision whether intervention (e.g., CPR, ECMO) is effective or medically indicated in a particular circumstance is a clinical decision that is out of the scope of this forum, as is the decision of duration of intervention before being terminated. While out of scope for this forum, it is recognized that the establishment of guidelines by the cardiopulmonary resuscitation community, including when CPR should be terminated and the indications and limits of emergency deployment of life saving ECMO, would benefit practitioners and would contribute to the work of this forum.

2.4 Integrated Neurological and Circulatory Sequences

The following illustrates the integration of the neurological and circulatory sequences.

Figure 3: Integrated Neurological and Circulatory Sequences in the Dying Process



Description

Because of the inextricable link between circulation and brain function, the neurological and circulatory sequences integrate at several points in the dying process. Once circulation and breathing cease (C-1), there is a short time period between C1 and N2 (less than 20 sec)[23,24] during which brain function ceases (N-2). The longer the time period without oxygenated circulation to the brain (N-2 to N-3) the progressively higher likelihood that the cessation of brain function is irreversible, even if oxygenated circulation can be re-established (either spontaneously or through intervention). The precise time period for the complete cessation of brain function to be non-resuscitatable (through intervention) after circulatory arrest (N-2 to N-3) is unresolved but may vary depending on factors such as baseline neurological function, duration of anoxia, temperature and the effectiveness of restoring oxygenated

circulation to the brain if attempted. If circulation will not resume spontaneously (C-2) and will not be restored by intervention, brain function cannot resume and the final end point reached is the permanent cessation of brain function (N-3=C-2). If circulation cannot be restored through an intervention (e.g. CPR, ECMO) that may be intended (C-1 to C-3), then the the cessation of brain function without any possibility to resume occurs at N-3 $\geq$ C-3.

2.5 Operational Definition of Human Death

Supplemental Reference Document

Participants reviewed and revised the supplemental reference document provided on Operational Definition of Human Death. This document contained condensed information from a literature review on the topic, to assist in deliberations and decision making. The reference document is presented below.

Medical Definitions of Death
The definitions of death proposed in the literature over the last several decades can be grouped into 3 main categories as follows.

1. Irreversible loss of functioning of the organism as a whole (not the whole organism). Often cited as whole brain definitions. Examples:
    - irreversible cessation of the integrated functioning of an organism as a whole[32]
    - the permanent cessation of the *critical* functions of the organism as a whole[33]

2. Irreversible loss of the capacity for consciousness. Often cited as higher brain definitions. Examples:
    - loss of that which is considered to be essentially significant to the nature of man where consciousness is the essential characteristic of human beings[34]
    - the irreversible loss of embodied capacity for social interaction[35]
    - total and irreversible extinction of consciousness and sensation, including discontinuation of actual survival of the individual personality[36]
    - irreversible loss of awareness alone represents the loss of the person and signals human death[37]

3. A combination of #1 and #2. Examples:
    - a person is dead when he/she has suffered an irreversible loss of all capacity of integrating and of coordinating the physical and mental functions of the body[38]
    - irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe[39]
    - irreversible loss of the capacity for integrating the main human attributes with an integrative functioning of the body[40]
    - the loss of ability of the organism to work as expressed in its commerce with the surrounding world through receptivity to stimuli and signals, the drive to act and the ability to act[41]

4. Another perspective says that it is not possible to provide a definition of death. Examples:
    - should rest on the currently applied criterion of irreversible (however defined) asystole, with the open admission that it does not define “death” but only a moment in the process of dying where organ retrieval can be allowed[42]

- abandon the search for a definition of death and focus on a pragmatic definition of "explantability window" which allows us to discuss when explanation can be realized without committing ourselves with strong metaphysical and/or religious beliefs[43]
- The protocol has chosen not to define death but to request that death should be properly established[44]

Operational Definition of Human Death

After reviewing the historical taxonomy and definitions of death, and the neurological and circulatory dying sequences that had been previously discussed and created, participants came to consensus on an operational definition of human death. The term 'operational definition of human death' refers to a practical and concrete definition that describes the state of human death based on measureable and observable biomedical standards. Consistent with the aforementioned scope of the meeting, this definition does not attempt to explain death in religious, spiritual, philosophical or abstract terms.

The following terminology was particularly relevant during discussions, and is repeated here to provide clarity:

Loss of Capacity for Consciousness:	Lack of current or any future potential for awareness, wakefulness, interaction and capacity for sensory perception of, or responsiveness to the external environment.
Function:	In the context of organs, the primary and fundamental purpose of that organ that can be assessed by observation and examination and is necessary for sustained life. Function should be distinguished from activities, as defined by physiologic properties of cells and groups of cells that can be measured by laboratory means.
Permanent:	Pertaining to a situation or condition that will not return to its previous state. In the context of death determination, refers to loss of function that will not resume spontaneously and will not be restored through intervention.

Death occurs when there is permanent loss of capacity for consciousness and loss of all brainstem functions. This may result from permanent cessation of circulation and/or after catastrophic brain injury.

In the context of death determination, 'permanent' refers to loss of function that cannot resume spontaneously and will not be restored through intervention.

Key Considerations

Key considerations describe points made by participants that identify important circumstances, data, reflections, and potential impacts that were taken into account during discussions:

- Participants supported the movement away from anatomically based terms such as brain death or cardiac death that erroneously imply the death of that organ. Human death is based on the cessation of function rather than activities.
- Emphasis was placed on the predominance of brain function for determination of death. Death is a single phenomenon based on cessation of brain function (loss of capacity for consciousness and brainstem reflexes) with two mechanisms to reach that point: (i) permanent absence of circulation or (ii) subsequent to a catastrophic brain injury - two entrances, one exit.
- It is understood that the overwhelming majority of deaths in the world occurs after cessation of circulation and may also occur external to health care settings.
- There are a number of regions where deceased donation practices may include re-establishing circulation (e.g. cardiac compressions, extracorporeal organ support) post-mortem for the preservation of organs. There were differences in opinion on the biological consistency of this practice and whether this was within the scope of these discussions. There is a requirement for future discussions and elaboration on this issue and clarity on what constitutes re-establishing circulation, what is physiologically meaningful circulation, circulation versus oxygenation and distinctions between organ targeted, regional and whole body circulation.
- A global medical consensus on an operational definition of human death would support the public confidence required for the necessary implementation in various jurisdictions.
- Simplifying the concepts involved, and making the definitions accessible and comprehensible to the lay and professional public is a core responsibility of this process.

2.6 Building Global Agreement Around Complex Practices

Facilitator Dorothy Strachan reminded participants that the forum was an initial step in a longer and more comprehensive process. While this meeting created the architecture to support the development of a global consensus for the determination of death, pursuant phases must be rigorous with respect to the highest available levels of evidence to support conclusions and recommendations.

Next steps would involve moving forward the conclusions from this event to reaching agreement on shared practices at a global level. Dorothy urged participants to think creatively about how to advance this work in multiple ways, e.g., through research on gaps identified at this forum, regional consultations, information dissemination, guidelines development, expert presentations, face-to-face or virtual scientific workshops, global or regional forums, etc. Participants provided the following suggestions for moving forward with next steps.

Stakeholders:

- Engage up front those who have a stake in implementation so that they buy into dissemination and implementation. Move beyond physicians and involve nurses and forensic pathologists. Get non-medical people involved – these are the main stakeholders – and listen carefully to them.
- Engage a broader range of professional societies in future discussions, e.g., the World Heart Federation, Inter-American Heart Foundation, International Council for Respiratory Care, the Asia Pacific Association of Critical Care Medicine, the World Medical Association, and the International Academy of Pathology.
- Be prepared to move forward even if representatives from all world regions are not immediately available.
- Prospectively involve as many stakeholders as possible - make stakeholders part of the process from the beginning.

Process:

- Establish an external review group to comment on guidelines development and provide advice on the process.
- Consider setting up parallel pathways, i.e., WHO process, publishing in journals, to ensure that guidelines are completed and disseminated in a timely manner.
- Define the key issues upfront, especially controversial ones. Develop a process for developing consensus on how to address these issues.
- Develop a process for the communication and dissemination of literature.
- Develop protocols and standard operating procedures where there is consensus.
- The lack of evidence provides a clear message about the importance of a comprehensive research agenda to support future decision making.

Implementation:

- Create a simplified version of the terminology and guidelines for dissemination to the public.
- Consider developing a way to monitor and evaluate the impact of guideline implementation.
- Be sensitive to cultural and religious differences when considering implementation.

2.7 Research Agenda

The following Research Agenda was created by participants at the meeting. Along with topics for study, suggestions on how to proceed with new studies were provided, including: ensuring that studies were planned with evaluation and outcome data to measure impact of the work, through the use of baseline comparative analysis; and using global networks (such as the Intensive Care Outcome Network study (ICON)) to initiate international point prevalence studies.

Relevant Research Currently in Progress or Planning and Known to Participants

- **Determination of Death Practices in Intensive Care Units (DDePICt) Research Program:** This is a program of research with the purpose of examining death determination practices in the ICU. Work to date includes a systematic review on autoresusciation[20], a narrative review of guidelines and statements for the determination of death after cardiac arrest[18], a survey of ICU physician practice for the determination of death after cardiac arrest[45] and a pilot feasibility study; "Pilot Study for the Determination of Death after Cardiac Arrest"(in preparation). The purpose of this pilot study is to determine the feasibility of systematically recording physiological information just before and for 30 min following a determination of death after cardiac arrest.Forty-one patients were enrolled in this study and the data from it is currently being analyzed and will be used to plan a multi-centre, international, observational study of the determinants of death after cardiac arrest with the following objectives: The primary objective is to collect invasive and non-invasive monitoring data just prior to and throughout withdrawal of life sustaining treatment (WLST) and the dying process to better address the question of autoresuscitation, inform future policy and further studies and to improve DCD implementation. The secondary objective is to collect data on variables that may influence timing of death (co-morbidities, interventions, etc.) following WLST. These data will be used to develop a novel prediction model to determine the likelihood of death within acceptable timelines to permit successful donation; and to assess the ethical and legal implications of the study with regards to the medical personnel and family members involved.
- In Toronto, a rodent model is being used to study anoxic death by measuring spontaneous and stimulated neuronal activity of deep structures of the brain.

Synthesis of Potentially Available Information

- A systematic review and grading of existing evidence related to both the neurological and cardiocirculatory determination of death is required.
- There needs to be a review of observational studies of clinical events following brain death, including those that look at the stability of diagnosis and the absence of the need for a second determination.
- In order to address issues regarding the competency of professionals determining death by cardiac and neurologic criteria, there should be a review of the documentation of qualifications for personnel, for both clinical and ancillary testing. There should also be an evaluation of

educational strategies (including continuing education and maintenance of competence) for death determination.

- The existing literature on the utility and receiver operating characteristics (ROC) curves used to evaluate the performance of the proposed ancillary laboratory tests should be reviewed and gaps identified.
- A point prevalence study of the worldwide incidence of brain death.

New Biological and Clinical Information Required

Studies initiated in the following areas would be useful in informing practice and policy decisions:

- Natural history of cessation of brainstem-evoked potentials during circulatory arrest
- Natural history of cessation of circulatory and neurological variables comparing patients in three categories: DCD (donation after cardiocirculatory death), terminated CPR (cardiopulmonary resuscitation), and WLST (withdrawal of life sustaining treatment),
- Collaboration with the acute resuscitation communities to establish guidelines on best practices regarding:
  - duration of life-saving CPR beyond which resumption of brain function is not reasonably possible
  - the indications and limits for the urgent deployment of ECMO during refractory cardiac arrest
- Evaluation of autoresuscitation times in categories mentioned above and better define what is physiologically meaningful circulation to further inform definitions of autoresuscitation
- Clarity and impact on what constitutes re-establishing circulation, circulation versus oxygenation and distinctions between organ targeted, regional and whole body circulation.
- Research specific to pediatric and neonatal populations.

References

1. Naffine N, Richards B, Rogers W. Scaring us all to death: the need for responsible legal scholarship on post-mortem organ donation. Journal of law and medicine 2009;16:696-707.
2. Steering Committee of the Istanbul Summit. Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul. Lancet 2008;372:5-6.
3. The Madrid resolution on organ donation and transplantation: national responsibility in meeting the needs of patients, guided by the WHO principles. Transplantation 2011;91 Suppl 11:S29-31.
4. World Health Assembly. 63rd WHA Resolutions and Decisions: WHA 63:22 Human organ and tissue transplantation; 2010.
5. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:1911-8.
6. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 2002;58:20-5.
7. Sprung CL, Woodcock T, Sjokvist P, et al. Reasons, considerations, difficulties and documentation of end-of-life decisions in European intensive care units: the ETHICUS Study. Intensive Care Med 2008;34:271-7.
8. THE ANZICS STATEMENTON DEATH AND ORGAN DONATION. 2008. (Accessed February, 2012, at http://www.anzics.com.au/uploads/ANZICSstatementfinal26sept08.pdf.)
9. Shemie SD, Doig C, Dickens B, et al. Severe brain injury to neurological determination of death: Canadian forum recommendations. CMAJ 2006;174:S1-13.
10. Nakagawa TA, Ashwal S, Mathur M, Mysore M. Clinical report-Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. Pediatrics 2011;128:e720-40.
11. Wijdicks EF, Pfeifer EA. Neuropathology of brain death in the modern transplant era. Neurology 2008;70:1234-7.
12. Hornby K, Shemie SD, Teitelbaum J, Doig C. Variability in hospital-based brain death guidelines in Canada. Canadian Journal of Anaesthesia 2006;53:613-9.
13. Powner DJ, Hernandez M, Rives TE. Variability among hospital policies for determining brain death in adults. Crit Care Med 2004;32:1284-8.
14. Saposnik G, Basile VS, Young GB. Movements in brain death: a systematic review. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 2009;36:154-60.
15. Lustbader D, O'Hara D, Wijdicks EF, et al. Second brain death examination may negatively affect organ donation. Neurology 2011;76:119-24.

16. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. Crit Care Med 2011;39:1538-42.
17. Joffe AR, Kolski H, Duff J, deCaen AR. A 10-month-old infant with reversible findings of brain death. Pediatr Neurol 2009;41:378-82.
18. Dhanani S, Hornby L, Ward R, Shemie S. Variability in the determination of death after cardiac arrest: a review of guidelines and statements. J Intensive Care Med 2012;27:238-52.
19. Sheth KN, Nutter T, Stein DM, Scalea TM, Bernat JL. Autoresuscitation after asystole in patients being considered for organ donation. Crit Care Med 2012;40:158-61.
20. Hornby K, Hornby L, Shemie SD. A systematic review of autoresuscitation after cardiac arrest. Crit Care Med 2010;38:1246-53.
21. Wijdicks EF, Diringer MN. Electrocardiographic activity after terminal cardiac arrest in neurocatastrophes. Neurology 2004;62:673-4.
22. Rossen R. Acute arrest of cerebral circulation. Arch Neurol Psychiatry 1943;50:510-28.
23. Clute HL, Levy WJ. Electroencephalographic changes during brief cardiac arrest in humans. Anesthesiology 1990;73:821-5.
24. Losasso TJ, Muzzi DA, Meyer FB, Sharbrough FW. Electroencephalographic monitoring of cerebral function during asystole and successful cardiopulmonary resuscitation. Anesthesia and Analgesia 1992;75:1021-4.
25. Moss J, Rockoff M. EEG monitoring during cardiac arrest and resuscitation. JAMA 1980;244:2750-1.
26. Bircher N, Safar P, Eshel G, Stezoski W. Cerebral and hemodynamic variables during cough-induced CPR in dogs. Crit Care Med 1982;10:104-7.
27. Hossmann KA, Kleihues P. Reversibility of ischemic brain damage. Archives of Neurology 1973;29:375-84.
28. Steen PA, Gisvold SE, Milde JH, et al. Nimodipine improves outcome when given after complete cerebral ischemia in primates. Anesthesiology 1985;62:406-14.
29. Le Guen M, Nicolas-Robin A, Carreira S, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. Crit Care 2011;15:R29.
30. Agostinucci JM, Catineau J, Jabre P, et al. Impact of the use of an automated chest-compression device on airway management during out-of-hospital cardiopulmonary resuscitation: the PLAINT study. Resuscitation 2011;82:1328-31.
31. Recommendations for nonheartbeating organ donation. A position paper by the Ethics Committee, American College of Critical Care Medicine, Society of Critical Care Medicine. Crit Care Med 2001;29:1826-31.
32. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Defining death: A report on the medical, legal and ethical issues in the

determination of death. 1981. (Accessed February 16, 2012, at http://bioethics.georgetown.edu/pcbe/reports/past_commissions/defining_death.pdf.)

33. Bernat JL. A defense of the whole-brain concept of death. Hastings Cent Rep 1998;28:14-23.
34. Veatch R. Death, dying and the biological revolution: our last quest for responsibility: New Haven: Yale University Press; 1976.
35. Veatch RM. Defining death: the role of brain function. JAMA 1979;242:2001-2.
36. Walton DN. On Defining Death. An Analytical Study of the Concept of Death in Philosophy and Medical Ethics: Montreal: McGill-Queens University Press; 1979.
37. Green MB, Wikler D. Brain death and personal identity. Philos Public Aff 1980;9:105-33.
38. Papieska Akademia Nauk. Deklaracja o sztucznym przedłu˙zaniu ˙zycia i dokładnym ustaleniu momentu s´mierci z dnia 21.10. ; 1985.
39. Pallis C. Brainstem death. In: Braakman R, ed. Handbook of Clinical Neurology: Head Injury.: Amsterdam:Elsevier Science Publisher BV; 13 (57) pp 441-496; 1990
40. Machado C. Consciousness as a definition of death: its appeal and complexity. Clin Electroencephalogr 1999;30:156-64.
41. Controversies in the Determination of Death: A White Paper by the President's Council on Bioethics. 2008. (Accessed February, 2012, at http://www.bioethics.gov:80/reports/death/index.html.)
42. Zamperetti N BRRC. Defining death in non-heart beating organ donors. J Med Ethics 2003;29:185.
43. Boniolo G. Death and transplantation: let's try to get things methodologically straight. Bioethics 2007;21:32-40.
44. Byk C. The European protocol on organ transplant: key issues. J Int Bioethique 2009;20:119-33, 53.
45. Dhanani S, Ward R, Hornby L, Barrowman NJ, Hornby K, Shemie SD. Survey of determination of death after cardiac arrest by intensive care physicians. Crit Care Med 2012;40:1449-55.

Appendix A: Selected Bibliography

A selected bibliography was developed as a background document for the meeting, to help familiarize participants with current thinking and developments in the field. While not an exhaustive list, the documents listed were deemed to be significant and relevant by the Planning and Advisory Committee.

Table of Contents

Jefferson R, Young K, Teitelbaum J; Pediatric Reference Group; Neonatal Reference Group. CMAJ. 2006 Mar 14; 174(6):S1-13. English, French.

Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. Nakagawa TA, Ashwal S, Mathur M, Mysore MR, Bruce D, Conway EE Jr, Duthie SE, Hamrick S, Harrison R, Kline AM, Lebovitz DJ, Madden MA, Montgomery VL, Perlman JM, Rollins N, Shemie SD, Vohra A, Williams-Phillips JA; Society of Critical Care Medicine; Section on Critical Care and Section on Neurology of the American Academy of Pediatrics; Child Neurology Society. Crit Care Med. 2011 Sep; 39(9):2139-55.

A Code of Practice for the Diagnosis and Confirmation of Death. Academy of Medical Royal Colleges (UK) 2008

International perspective on the diagnosis of death. Gardiner D, Shemie S, Manara A, Opdam H. Br J Anaesth. 2012 Jan; 108 Suppl 1:i14-28.

A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, JAMA. 1968 Aug 5;205(6):337-40.

Apnea Test

Pronouncing brain death: Contemporary practice and safety of the apnea test. Wijdicks EF, Rabinstein AA, Manno EM, Atkinson JD. Neurology. 2008 Oct 14; 71(16):1240-4.

Brain Death Spinal Reflexes

Movements in brain death: a systematic review. Saposnik G, Basile VS, Young GB. Can J Neurol Sci. 2009 Mar; 36(2):154-60. Review.

Brain Death - Single vs. Multiple exams

Second brain death examination may negatively affect organ donation. Lustbader D, O'Hara D, Wijdicks EF, MacLean L, Tajik W, Ying A, Berg E, Goldstein M. Neurology. 2011 Jan 11; 76(2):119-24. Epub 2010 Dec 15.

Single brain death examination is equivalent to dual brain death examinations. Varelas PN, Rehman M, Abdelhak T, Patel A, Rai V, Barber A, Sommer S, Corry JJ, Venkatasubba Rao CP. Neurocrit Care. 2011 Dec; 15(3):547-53.

Circulatory Arrest To Arrest of Brain Function

Decapitation in rats: latency to unconsciousness and the 'wave of death'. van Rijn CM, Krijnen H, Menting-Hermeling S, Coenen AM. PLoS One. 2011 Jan 27; 6(1):e16514.

Surges of electroencephalogram activity at the time of death: a case series. Chawla LS, Akst S, Junker C, Jacobs B, Seneff MG. J Palliat Med. 2009 Dec; 12(12):1095-100.

EEG monitoring during cardiac arrest and resuscitation. Moss J, Rockoff M. JAMA. 1980 Dec 19; 244(24):2750-1.

Electroencephalographic changes during brief cardiac arrest in humans. Clute HL, Levy WJ. Anesthesiology. 1990 Nov; 73(5):821-5.

Electroencephalographic monitoring of cerebral function during asystole and successful cardiopulmonary resuscitation. Losasso TJ, Muzzi DA, Meyer FB, Sharbrough FW. Anesth Analg. 1992 Dec; 75(6):1021-4.

Nimodipine improves outcome when given after complete cerebral ischemia in primates. Steen PA, Gisvold SE, Milde JH, Newberg LA, Scheithauer BW, Lanier WL, Michenfelder JD. Anesthesiology. 1985 Apr; 62(4):406-14.

Processed electroencephalogram during donation after cardiac death. Auyong DB, Klein SM, Gan TJ, Roche AM, Olson D, Habib AS. Anesth Analg. 2010 May 1; 110(5):1428-32. Epub 2010 Mar 17.

Reversibility of ischemic brain damage. Hossmann KA, Kleihues P. Arch Neurol. 1973 Dec; 29(6):375-84.

Electrocerebral accompaniments of syncope associated with malignant ventricular arrhythmias. Aminoff MJ, Scheinman MM, Griffin JC, Herre JM. Ann Intern Med. 1988 Jun;108(6):791-6.

Cardiac/Circulatory Death

The circulatory-respiratory determination of death in organ donation. Bernat JL, Capron AM, Bleck TP, Blosser S, Bratton SL, Childress JF, DeVita MA, Fulda GJ, Gries CJ, Mathur M, Nakagawa TA, Rushton CH, Shemie SD, White DB. Crit Care Med. 2010 Mar; 38(3):963-70.

Variability in the determination of death after cardiac arrest: A review of guidelines and statements. Dhanani S, Hornby L, Ward R, Shemie S. J Intensive Care Med. 2011 Aug 12. [Epub ahead of print]

How the distinction between "irreversible" and "permanent" illuminates circulatory-respiratory death determination. Bernat JL. J Med Philos. 2010 Jun; 35(3):242-55. Epub 2010 May 3. Review.

ASTS recommended practice guidelines for controlled donation after cardiac death organ procure mentand transplantation. Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MM, D'Alessandro A, Pomfret EA, Freeman RB, Markmann JF, Hanto DW, Matas AJ, Roberts JP, Merion RM, Klintmalm GB; ASTS Standards on Organ Transplantation Committee. Am J Transplant. 2009 Sep; 9(9):2004-11. Epub 2009 Jul 16.

Non-heart-beating organ transplantation: practice and protocol. Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols, Division of Health Care Services, Institute of Medicine. ISBN: 0-309-55805-0 (2000)

Recommendations for nonheartbeating organ donation. A Position Paper by the Ethics Committee, American College of Critical Care Medicine, Society of Critical Care Medicine. Crit Care Med 2001 Vol. 29, No.9, 1826-1831

Cardiopulmonary Resuscitation / ExtraCorporeal Support

Out-of-hospital use of an automated chest compression device: facilitating access to extracorporeal life support or non-heart-beating organ procurement. Agostinucci JM, Ruscev M, Galinski M, Gravelo S, Petrovic T, Carmeaux C, Haouache H, Roussin F, Adnet F, Lapostolle F. Am J Emerg Med. 2011 Nov;29(9):1169-72. Epub 2010 Oct 15.

Extracorporeal life support following out-of-hospital refractory cardiac arrest. Le Guen M, Nicolas-Robin A, Carreira S, Raux M, Leprince P, Riou B, Langeron O. Crit Care. 2011;15(1):R29. Epub 2011 Jan 18.

Risen from the dead: A case of the Lazarus phenomenon—With considerations on the termination of treatment following cardiac arrest in a prehospital setting. Niels Henrik Krarup et. Al. Letter to the Editor, Resuscitation 81 (2010) 1598–1599

Definitions of Death

Controversies in the determination of death. A White Paper of the President's Council on Bioethics. Washington, DC December 2008

Are the Patients Who Become Organ Donors under the Pittsburgh Protocol for "Non-Heart-Beating Donors" Really Dead? Joanne Lynn, Kennedy Institute of Ethics Journal Vol. 3, No. 2, 167-178 1993

Defining death - A report on the medical, legal and ethical issues in the determination of death. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, July 1981

Constructing the death elephant: A synthetic paradigm shift for the definition, criteria, and tests for death. D. Alan Shewmon. Journal of Medicine and Philosophy, 35: 256–298, 2010, doi:10.1093/jmp/jhq022, Advance Access publication on May 3, 2010

The ethics of creating and responding to doubts about death criteria. James M. Dubois. Journal of Medicine and Philosophy, 0: 1–16, 2010

The Canadian Law Reform Commission's definition of death. 1979. www.bccla.org/positions/patients/79death.html

Eligibility for organ donation: a medico-legal perspective on defining and determining death. Jocelyn Downie, SJD,Matthew Kutcher, MSc, Chantelle Rajotte, LLB, Alison Shea, LL. Can J Anesth/J Can Anesth (2009) 56:851–86

2. RELATED RESOURCES

Commercial Organ Trade

Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul. Steering Committee of the Istanbul Summit. Lancet. 2008 Jul 5; 372(9632):5-6.

"Gratuities" for donated organs: ethically indefensible. Biller-Andorno N, Capron AM. Lancet. 2011 Apr 23; 377(9775):1390-1.

Organ trafficking and transplant tourism: a commentary on the global realities. Budiani-Saberi DA, Delmonico FL. Am J Transplant. 2008 May; 8(5):925-9.

The state of the international organ trade: a provisional picture based on integration of available information. Shimazono Y. Bull World Health Organ. 2007 Dec;85(12):955-62. Review.

The declaration of Istanbul on organ trafficking and transplant tourism. Participants in the International Summit on Transplant Tourism and Organ Trafficking convened by The Transplantation

Society and International Society of Nephrology in Istanbul, Turkey, April 30–May 2, 2008. Asian Bioethics Review March 2009 Volume 1, Issue 1 73–7

Global Guidelines

Brain death: time for an international consensus. Smith M. Br J Anaesth. 2012 Jan;108 Suppl 1:i6-9.

Are global guidelines desirable, feasible and necessary? Fried M, Quigley EM, Hunt RH, Guyatt G, Anderson BO, Bjorkman DJ, Farthing MJ, Fedail SS, Green-Thompson R, Hampton J, Krabshuis J, Laine L, Horton R. Nat Clin Pract Gastroenterol Hepatol. 2008 Jan;5(1):2-3. Epub 2007 Nov 13.

WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation.
http://www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf

Self Sufficiency in Donation and Transplantation

A call for government accountability to achieve national self-sufficiency in organ donation and transplantation. Delmonico FL, Domínguez-Gil B, Matesanz R, Noel L. Lancet. 2011 Oct 15;378(9800):1414-8.

The Madrid resolution on organ donation and transplantation: national responsibility in meeting t he needs of patients, guided by the WHO principles. Transplantation. 2011 Jun 15;91 Suppl 11:S29-31.

Appendix B: Funding Disclosure

Funding for this meeting has been provided by Canadian Blood Services. Canadian Blood Services is a national, not-for-profit charitable organization that manages the supply of blood and blood products in all provinces and territories in Canada (with the exception of Quebec) and oversees the OneMatch Stem Cell and Marrow Network. Canadian Blood Services operates 43 permanent collection sites and more than 20,000 donor clinics annually.

Canadian Blood Services also received a mandate in 2008 for national activities related to organ and tissue donation and transplantation (OTDT), which includes: development of leading practices, public awareness and education, system performance measurement, and establishing patient registries. Canadian Blood Services was also given responsibility to develop a national strategic plan in collaboration with the OTDT communities for an integrated OTDT system that would improve donation and transplantation performance in Canada.

Canadian Blood Services is not responsible for the management or funding of any Canadian Organ Procurement Organizations (OPOs) or Transplant Programs. Canadian Blood Services receives its funding from the provincial and territorial Ministries of Health. The federal government, through Health Canada, also contributes to the Canadian Blood Services OTDT mandate.

The following organizations kindly provided traveling expenses for their representatives to attend this meeting:

- Australia and New Zealand Intensive Care Society
- European Society of Intensive Care Medicine
- International Federation of Emergency Medicine
- International Pan Arab Critical Care Medicine Society and Sheikh Khalifa Medical City, United Arab Emirates
- Neurocritical Care Society
- Society of Critical Care Medicine
- World Federation of Neurology
- World Federation of Neurosurgical Societies
- World Federation of Pediatric Intensive and Critical Care Societies
- World Federation of Societies of Intensive and Critical Care Medicine

Role of Transplantation in this Meeting

Given concerns about potential conflict of interest, there has been a deliberate effort to exclude the involvement of transplant programs in this process. In support of the overall planning process, the following groups have been involved in their respective roles:

- The International Society for Organ Donation and Procurement (ISODP): The mission of ISODP includes promotion of high ethical standards in transplantation, as both donor and recipient are members of a community where equity and justice are equally important to success. The development of international guidelines for determination of death supports this goal. ISODP provided travel funds for its representative. No other funding for the meeting has been received from ISODP.

- The Transplantation Society (TTS), together with the WHO, has played a role in moving the international dialogue on transplant tourism forward. They have been active in the development of the Istanbul and Madrid accords and as a result have a breadth and depth of knowledge of practices across the globe. Francis Delmonico, their president-elect, has provided counsel as part of the international advisory committee but was not a participant at the meeting. No funding for the meeting has been received from TTS.

Appendix C: Forum Participants

Dr. Sam Shemie	Planning Committee (Chair) Canadian Blood Services	Professor of Pediatrics, McGill University Division of Critical Care, Montreal Children's Hospital Loeb Chair and Research Consortium in Organ and Tissue Donation, University of Ottawa CANADA
Dr. Andrew Baker	Planning Committee Canadian Critical Care Society	Chief, Department of Critical Care, Department of Anesthesia, St. Michael's Hospital Professor of Anesthesia and Critical Care, University of Toronto CANADA
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Ms. Dorothy Strachan	Planning Committee	Process Consultant, Strachan-Tomlinson Inc. CANADA
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Ms. Sylvia Torrance	Planning Committee Canadian Blood Services	Director, Strategic Planning , Organ Donation and Transplantation, Canadian Blood Services CANADA
Ms. Kimberly Young	Planning Committee Canadian Blood Services	Executive Director, Organs and Tissues, Canadian Blood Services CANADA
Dr. James Bernat	Advisory Committee	Louis and Frank Professor of Medicine , Dartmouth Medical School, New Hampshire Director, Clinical Ethics Program, Dartmouth-Hitchcock Medical Center, Department of Neurology, Dartmouth-Hitchcock Medical Center USA
Prof. Alexander Capron	Advisory Committee	Vice Dean, Faculty and Academic Affairs, USC Scott H. Bice Chair, Healthcare Law, Policy and Ethics Professor of Law and Medicine, Keck School of Medicine, USC Co-Director, Pacific Center for Health Policy and Ethics, USC Gould School of Law USA
Dr. Luc Noel	Advisory Committee	Coordinator, Clinical Procedures CPR/HPW/HSS, Department for Health Systems Policies and Workforce, World Health Organization-HQ SWITZERLAND

Dr. Tamer Abdelhak	International Pan Arab Critical Care Medicine Society	Vice President of the IPACCMS Neuro ICU Senior Staff, Neuro Critical Care Fellowship Program Director, Departments of Neurology and Neurosurgery, Henry Ford Hospital, Wayne State University School of Medicine USA
Dr. Mohammed Salah Ben Ammar	International Expert, WHO Member State Delegate	Chef du Service d'Anesthesie-Reanimation, CHU Mongi Slim TUNISIA
Dr. Sadek Beloucif	International Expert, WHO Member State Delegate	Dept. of Anesthesiology & Critical Care Medicine, Avicenne University Hospital FRANCE
Dr. Peter Black	World Federation of Neurosurgical Societies	President, World Federation of Neurosurgical Societies Franc D. Ingraham Professor of Neurosurgery emeritus, Harvard Medical School, Boston, USA
Dr. Thomas Bleck	Society of Critical Care Medicine	Professor of Neurological Sciences, Neurosurgery, Medicine, and Anesthesiology, Rush Medical College Associate Chief Medical Officer (Critical Care), Rush University Medical Center Founding Past President, The Neurocritical Care Society USA
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Dr. Giuseppe Citerio	European Society of Intensive Care Medicine	Chair Division of Scientific Affairs – European Society of Intensive Care Medicine Associate Editor, Intensive Care Medicine Neuroanestesia e Neurorianimazione, Dipartimento di Medicina Perioperatoria e Terapie Intensive, H San Gerardo - Monza ITALY
Prof. Geoff Dobb	Australia and New Zealand Intensive Care Society	Director, Critical Care, Royal Perth Hospital Clinical Professor, School of Medicine and Pharmacology, University of Western Australia AUSTRALIA
Dr. Waleed Jasim	International Pan Arab Critical Care Medicine Society	Sheikh Khalifa Medical City, Abu Dhabi UNITED ARAB EMIRATES
Dr. Edgar Jimenez	World Federation of Societies of Intensive and Critical Care Medicine	President, World Federation of Societies of Intensive and Critical Care Medicine Head, Division of Critical Care Medicine, Orlando Health Physicians Group Professor of Medicine, University of Central Florida Clinical Associate Professor of Medicine, University of Florida and Florida State University USA

Dr. Günter Kirste	International Society for Organ Donation and Procurement	Past-President, ISODP Medical Director, Deutsche Stiftung Organtransplantation Vorstand GERMANY
Dr. Niranjan Kissoon	World Federation of Pediatric Intensive and Critical Care Societies	President, WFPICCS VP Medical Affairs, BC Children's Hospital and Sunny Hill Health Centre for Children UBC & BC Children's Hospital Professor in Acute and Critical Care – Global Child Health Professor, Department of Pediatrics and Emergency Surgery, UBC CANADA
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Dr. Mikhail Sinkin	International Expert	Head of Neurodiagnostic Department of Moscow Municipal Hospital Consultant, Moscow Neurodiagnostical Group Consultant Neurologist, Federal Endocrinology Scientific Centre RUSSIA
Prof. Charles Sprung	International Expert	Director, General Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center ISRAEL
Dr. Gene Sung	Neurocritical Care Society	President, NCS Director, Neurocritical Care and Stroke Division, USC USA
Dr. John Tallon	International Federation of Emergency Medicine	Director, Nova Scotia Trauma Program and Queen Elizabeth II Health Sciences Centre Trauma Program Associate Professor, Departments of Emergency Medicine and Surgery, Dalhousie University, Halifax CANADA
Dr. Eelco Wijdicks	International Expert	Professor of Neurology, Mayo Clinic College of Medicine, Chair of the Division of Critical Care Neurology, Consultant in the Neurological Neurosurgical Intensive Care Unit, Saint Mary's Hospital, Mayo Clinic Founding editor-in-chief of Neurocritical Care USA
Dr. G. Bryan Young	World Federation of Neurology	Professor of Neurology and Critical Care, University of Western Ontario Department of Clinical Neurological Sciences, London Health Sciences Centre CANADA

Ms. Jennifer Chandler	Observer	Researcher, Loeb Chair and Research Consortium in Organ and Tissue Donation, University of Ottawa Associate Professor of Law, Faculty of Law, University of Ottawa
Dr. Margaret Harris	Observer	Guidelines Review Committee (GRC) Secretariat, WHO
Ms. Paulina Mirsky	Observer	Loeb Chair and Research Consortium in Organ and Tissue Donation, University of Ottawa
Ms. Karine Morin	Observer	Researcher, Loeb Chair and Research Consortium in Organ and Tissue Donation, University of Ottawa Director, National GE3LS Program, Genome Canada