Can J Anesth/J Can Anesth (2022)

ELECTRONIC SUPPLEMENTARY MATERIAL

Shemie SD *et al.*: A brain-based definition of death and criteria for its determination after arrest of circulation or neurologic function in Canada: a 2023 clinical practice guideline

Disclaimer: *Electronic Supplementary Material (ESM) is supplied by the authors for the benefit of readers. This feature is intended to provide additional information, context, and/or dimension to complement articles. Readers should be aware that unlike the main print manuscript, ESM may not undergo extensive peer review and typically is posted as supplied by the authors without editing, proofreading, accuracy checking, copyediting, or typesetting; it is published online only.*

TABLE OF CONTENTS

eAppendix 1 Guideline development panel

Steering Committee

Andrew J. Baker MD	Chief, Departments of Critical Care and Anesthesia, St. Michael's Hospital, Unity Health Toronto University of Toronto Toronto, Ontario
Cécile M. Bensimon PhD	Director, Ethics and Professional Affairs, Canadian Medical Association Ottawa, Ontario *Representing the Canadian Medical Association*
Jennifer A. Chandler LLM	Professor, Bertram Loeb Research Chair, Faculty of Law, University of Ottawa Ottawa, Ontario
Michaël Chassé MD PhD	Associate Professor, Department of Medicine, Université de Montréal Scientist, Centre de Recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Université de Montréal Montréal, Québec
Rosanne Dawson LLB	Managing Counsel, Health Law, Ethics, and Privacy Legal Services, Canadian Blood Services Ottawa, Ontario
Sonny Dhanani MD	Chief, Pediatric Critical Care, Children's Hospital of Eastern Ontario Associate Professor, University of Ottawa Ottawa, Ontario *Representing the Canadian Donation and Transplantation Research Program*
Laura Hornby MSc	Research and Clinical Practice Guideline Methodology Consultant Organ and Tissue Donation and Transplantation, Canadian Blood Services Montreal, Quebec
Owen T. Mooney MD	Assistant Professor, University of Manitoba Department of Internal Medicine/Critical Care Medical Director, Transplant Manitoba Gift of Life Medical Director, ICMS St. Boniface Hospital

	Representing the Canadian Critical Care Society
Bram Rochwerg MD MSc	Department of Medicine, Department of Health Research Methods, Evidence & Impact, McMaster University Knowledge Translation Chair, Canadian Critical Care Society Executive Member, Canadian Critical Care Trials Group Hamilton, Ontario
Aimee J. Sarti MD MEd	Intensivist, Department of Critical Care, The Ottawa Hospital Associate Professor, University of Ottawa Clinician Investigator, Ottawa Hospital Research Institute Ottawa, Ontario
Sam D. Shemie MD	Division of Critical Care Medicine, Montreal Children's Hospital, McGill University Health Centre Professor of Pediatrics, McGill University Associate Investigator, MUHC Research Institute Medical Advisor, System Development, Organ and Tissue Donation and Transplantation, Canadian Blood Services Montreal, Quebec
	Project Chair
Christy Simpson PhD	Associate Professor, Department of Bioethics, Dalhousie University Bioethics Consultant, Canadian Blood Services Halifax, Nova Scotia
Jeanne Teitelbaum MD	Montreal Neurological Institute, McGill University Health Centre McGill University Montreal, Quebec
	Representing the Canadian Neurological Sciences Federation
Sylvia Torrance BSc	Process Design and Project Management Consultant Ottawa, Ontario
Lindsay Wilson MHA	Sr. Advisor and Lead, System Development Organ and Tissue Donation and Transplantation, Canadian Blood Services Toronto, Ontario

Guideline Panel

Death Determination by Circulatory Criteria Working Group

Sonny Dhanani MD *Working Group Lead*	Chief, Pediatric Critical Care, Children's Hospital of Eastern Ontario Associate Professor, University of Ottawa Ottawa, Ontario *Representing the Canadian Donation and Transplantation Research Program*
Kirk J. Dawe NP MN	Critical Care Program, Eastern Health Discipline of Medicine, Faculty of Medicine, Memorial University of Newfoundland St. John's, Newfoundland and Labrador *Representing the Nurse Practitioners Association of Canada*
Christopher J. Doig MD MSc	Departments of Critical Care Medicine, Medicine, and Community Health Sciences, Cumming School of Medicine, University of Calgary Alberta Health Services Calgary, Alberta
Teneille E. Gofton MD MSc	Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, Western University| London, Ontario
Laura Hornby MSc	Research and Clinical Practice Guideline Methodology Consultant Organ and Tissue Donation and Transplantation, Canadian Blood Services Montreal, Quebec
Jennifer A. Klowak MD MSc	Department of Critical Care, Children's Hospital of Eastern Ontario Ottawa, Ontario
Joann Kawchuk MD	Departments of Adult Critical Care and Anesthesiology, Saskatchewan Health Authority Saskatoon, Saskatchewan
Shauna Matheson RN BScN	Organ and Tissue Donation Coordinator, Legacy of Life, Nova Scotia Health Halifax, Nova Scotia
Mypinder S. Sekhon MD PhD	Staff Intensivist, Vancouver General Hospital Clinical Associate Professor, Division of Critical Care Medicine, Department of Medicine, University of British Columbia Vancouver, British Columbia
Matthew J. Weiss MD	Transplant Québec CHU de Québec – Université Laval Research Center, Population

	Health and Optimal Health Practices Research Unit Trauma-Emergency-Critical Care Medicine, Université Laval Québec, Québec
Gurmeet Singh MD MSc	Associate Clinical Professor, Departments of Critical Care Medicine & Surgery, Division of Cardiac Surgery Medical Director, Adult ECLS Program Mazankowski Alberta Heart Institute and University of Alberta, Edmonton, Alberta *Representing the Canadian Cardiovascular Critical Care Society*
David J. Zorko MD MSc	Department of Critical Care Medicine, The Hospital for Sick Children University of Toronto Toronto, Ontario

Death Determination by Neurologic Criteria Working Group

Andrew J. Baker MD *Working Group Lead*	Chief, Departments of Critical Care and Anesthesia, St. Michael's Hospital, Unity Health Toronto University of Toronto Toronto, Ontario
Jeanne Teitelbaum MD *Working Group Lead*	Montreal Neurological Institute, McGill University Health Center, McGill University Montreal, Quebec *Representing the Canadian Neurological Sciences Federation*
Andrew Healey MD	Provincial Medical Director, Ontario Health (Trillium Gift of Life Network) Associate Clinical Professor, Department of Medicine, Divisions of Emergency and Critical Care Medicine, McMaster University Hamilton, Ontario Emergency and Critical Care Physician, William Osler Health System Brampton and Etobicoke, Ontario
Karen Hornby MSc	Research Consultant Montreal, Quebec
George Isac MD	Division of Critical Care Medicine, Department of Anesthesia, Faculty of Medicine, University of British Columbia Vancouver, British Columbia
Allana E. LeBlanc RN MScN	Vancouver Coastal Health University of British Columbia School of Nursing Vancouver, British Columbia

	Representing the Canadian Association of Critical Care Nurses
Murdoch Leeies MD MSc	Assistant Professor, Department of Emergency Medicine, Section of Critical Care Medicine, Rady Faculty of Health Sciences, University of Manitoba Transplant Manitoba Gift of Life Program, Shared Health Manitoba Winnipeg, Manitoba Director of Equity, Diversity and Inclusion, Canadian Critical Care Society
	Representing the Canadian Association of Emergency Physicians
Laurie A. Lee NP MN	PICU Nurse Practitioner Director PICU Research Program, Alberta Children's Hospital Adjunct Clinical Associate, Faculty of Nursing,University of Calgary Adjunct Assistant Professor, Department of Paediatrics, Cumming School of Medicine, University of Calgary Calgary, Alberta
	Representing the Nurse Practitioners Association of Canada
Bram Rochwerg MD MSc	Department of Medicine, Department of Health Research Methods, Evidence & Impact, McMaster University Knowledge Translation Chair, Canadian Critical Care Society Executive Member, Canadian Critical Care Trials Group Hamilton, Ontario
Jeffrey Singh MD MSc	Department of Medicine and Interdepartmental Division of Critical Care Medicine, University of Toronto Krembil Brain Institute, University Health Network Regional Medical Lead, Ontario Health - Trillium Gift of Life Network Toronto, Ontario
Karim Soliman MD	Chief, Department of Critical Care, Lakeridge Health Assistant Professor, Department Critical Care, Queen's University Regional Medical Lead, Ontario Health - Trillium Gift of Life Network Toronto, Ontario

Ancillary Investigation Working Group

Michaël Chassé MD PhD *Working Group Lead*	Associate Professor, Department of Medicine, Université de Montréal Scientist, Centre de Recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Université de Montréal Montréal, Québec
John Basmaji MD	Western University London, Ontario
J. Gordon Boyd MD PhD	Departments of Medicine (Neurology) and Critical Care Medicine, Kingston General Hospital Associate Professor, Queen's University Kingston, Ontario
Andreas H. Kramer MD MSc	Clinical Professor Departments of Critical Care Medicine and Clinical Neurosciences, University of Calgary Medical Director, Southern Alberta Organ & Tissue Donation Program Calgary, Alberta
Julie Kromm MD	Departments of Critical Care Medicine and Clinical Neurosciences, University of Calgary Hotchkiss Brain Institute, Alberta Health Services Calgary, Alberta
Nicole K.A. McKinnon MD PhD	Department of Critical Care, Hospital for Sick Children University of Toronto Peter Gilgan Center for Research and Learning Toronto, Ontario
Owen T. Mooney MD	Assistant Professor, University of Manitoba Department of Internal Medicine/Critical Care Medical Director, Transplant Manitoba Gift of Life Medical Director, ICMS St. Boniface Hospital *Representing the Canadian Critical Care Society*
Joel Neves Briard MD MSc	Department of Neuroscience, Université de Montréal Centre de recherche du Centre hospitalier de l'Université de Montréal Montreal, Quebec
Jai J.S. Shankar MD DM MSc	Diagnostic and Interventional Neuroradiologist, Department of Radiology-Neuroradiology, University of Manitoba Winnipeg, Manitoba

Marat Slessarev MD PhD	Department of Medicine, Western University Trillium Gift of Life Network London, Ontario
Lionel S. Zuckier MD MBA	Attending Physician, Division of Nuclear Medicine The Ottawa Hospital Professor, Departments of Medicine and Radiology University of Ottawa, Faculty of Medicine Ottawa, Ontario

Legal Ethics Working Group

Jennifer A. Chandler LLM *Working Group Lead*	Professor, Bertram Loeb Research Chair, Faculty of Law, University of Ottawa Ottawa, Ontario
Christy Simpson PhD *Working Group Lead*	Associate Professor, Department of Bioethics, Dalhousie University Bioethics Consultant, Canadian Blood Services Halifax, Nova Scotia
Cécile M. Bensimon PhD	Director, Ethics and Professional Affairs, Canadian Medical Association Ottawa, Ontario *Representing the Canadian Medical Association*
Rosanne Dawson LLB	Managing Counsel, Health Law, Ethics, and Privacy Legal Services, Canadian Blood Services Ottawa, Ontario
Michael Hartwick MD MEd	Associate Professor, Department of Medicine, Divisions of Critical Care and Palliative Medicine, University of Ottawa Regional Medical Lead, Trillium Gift of Life Network Ottawa, Ontario
Aly Kanji MDCM MSc	Assistant Professor, Department of Medicine, Division of General Internal Medicine, McGill University Director, GIM consult service, McGill University Health Centre Montreal, Quebec
Katarina Lee-Ameduri JD MA	Clinical Ethicist, St. Boniface Hospital, Reseau Compassion Network Assistant Professor, University of Manitoba Winnipeg, Manitoba
Nicholas Murphy PhD	Postdoctoral Fellow, Departments of Medicine and Philosophy, Western University London, Ontario

Thaddeus Mason Pope PhD HEC-C	Professor, Mitchell Hamline School of Law Saint Paul, Minnesota 2021 Fulbright Canada Research Chair in Health Law, Policy and Ethics, University of Ottawa Ottawa, Ontario Adjunct Professor, Australian Centre for Health Law Research, Queensland University of Technology Brisbane, Australia Adjunct Associate Professor, Alden March Bioethics Institute, Albany Medical College Albany, New York Affiliate Faculty, University of Minnesota Center for Bioethics Minneapolis, Minnesota
Sylvia Torrance BSc	Process Design and Project Management Consultant Ottawa, Ontario
Randi Zlotnik Shaul LLM PhD	Director Bioethics Department, The Hospital for Sick Children Associate Professor, Department of Paediatrics, University of Toronto Toronto, Ontario

Stakeholder Engagement Working Group

Aimee J. Sarti MD MEd *Working Group Lead*	Intensivist, Department of Critical Care, The Ottawa Hospital Associate Professor, University of Ottawa Clinician Investigator, Ottawa Hospital Research Institute Ottawa, Ontario
Joanne Brennan RN	Patient/Family Partner The Ottawa Hospital-Vascular Surgery Research Ottawa, Ontario
Heather Brewster	Patient/Family Partner Pilot Mound, Manitoba
Robert Carignan	Patient/Family Partner Ponteix, Saskatchewan *Representing the Canadian Medical Association Patient Voice*
Kennedy Elliott-Pohl BSKin	Patient/Family Partner Lethbridge, Alberta
Kimia Honarmand MD MSc	Division of Critical Care, Department of Medicine, Western University

	London Health Sciences Centre London, Ontario
Laura Hornby MSc	Research and Clinical Practice Guideline Methodology Consultant Organ and Tissue Donation and Transplantation, Canadian Blood Services Montreal, Quebec
Andrew MacLeod HBA	Canadian Blood Services Toronto, Ontario
Stephanie Sutherland PhD	PhD Research Associate Department of Critical Care, The Ottawa Hospital Ottawa, Ontario
Lindsay Wilson MHA	Sr. Advisor and Lead, System Development Organ and Tissue Donation and Transplantation, Canadian Blood Services Toronto, Ontario

Definition of Death Working Group

Sam D. Shemie MD *Working Group Lead*	Division of Critical Care Medicine, Montreal Children's Hospital, McGill University Health Centre Professor of Pediatrics, McGill University Associate Investigator, MUHC Research Institute Medical Advisor, System Development, Organ and Tissue Donation and Transplantation, Canadian Blood Services Montreal, Quebec *Project Chair*
Joanne Brennan RN	Patient/Family Partner The Ottawa Hospital-Vascular Surgery Research Ottawa, Ontario
Robert Carignan	Patient/Family Partner Ponteix, Saskatchewan *Representing the Canadian Medical Association Patient Voice*
Jennifer A. Chandler LLM	Professor, Bertram Loeb Research Chair, Faculty of Law, University of Ottawa Ottawa, Ontario

Rosanne Dawson LLB	Managing Counsel, Health Law, Ethics, and Privacy Legal Services, Canadian Blood Services Ottawa, Ontario
Michael Hartwick MD MEd	Associate Professor, Department of Medicine, Divisions of Critical Care and Palliative Medicine, University of Ottawa Regional Medical Lead, Trillium Gift of Life Ottawa, Ontario
Laurie A. Lee NP MN	PICU Nurse Practitioner Director PICU Research Program, Alberta Children's Hospital Adjunct Clinical Associate, Faculty of Nursing,University of Calgary Adjunct Assistant Professor, Department of Paediatrics, Cumming School of Medicine, University of Calgary Calgary, Alberta *Representing the Nurse Practitioners Association of Canada*
Christy Simpson PhD	Associate Professor, Department of Bioethics, Dalhousie University Bioethics Consultant, Canadian Blood Services Halifax, Nova Scotia
Gurmeet Singh MD MSc	Associate Clinical Professor, Departments of Critical Care Medicine & Surgery, Division of Cardiac Surgery Medical Director, Adult ECLS Program Mazankowski Alberta Heart Institute and University of Alberta, Edmonton, Alberta *Representing the Canadian Cardiovascular Critical Care Society*
Marat Slessarev MD PhD	Department of Medicine, Western University Trillium Gift of Life Network London, Ontario
Sylvia Torrance BSc	Process Design and Project Management Consultant Ottawa, Ontario

Brainstem versus Whole Brain Death

Sam D. Shemie MD *Working Group Lead*	Division of Critical Care Medicine, Montreal Children's Hospital, McGill University Health Centre Professor of Pediatrics, McGill University Associate Investigator, MUHC Research Institute Medical Advisor, System Development, Organ and Tissue Donation and Transplantation, Canadian Blood Services Montreal, Quebec *Project Chair*

Michaël Chassé MD PhD	Associate Professor, Department of Medicine, Université de Montréal Scientist, Centre de Recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Université de Montréal Montréal, Québec
J. Gordon Boyd MD PhD	Departments of Medicine (Neurology) and Critical Care Medicine, Kingston General Hospital Associate Professor, Queen's University Kingston, Ontario
Teneille E. Gofton MD MSc	Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, Western University| London, Ontario
Priti Gros MD	Movement Disorders Fellow, MSc Student, Clin. Epi. & Health Care Research, Toronto Western Hospital Toronto, Ontario
Andreas H. Kramer MD MSc	Clinical Professor Departments of Critical Care Medicine and Clinical Neurosciences, University of Calgary Medical Director, Southern Alberta Organ & Tissue Donation Program Calgary, Alberta
Joel Neves Briard MD MSc	Department of Neuroscience, Université de Montréal Centre de recherche du Centre hospitalier de l'Université de Montréal Montreal, Quebec
Jeffrey Singh MD MSc	Department of Medicine and Interdepartmental Division of Critical Care Medicine, University of Toronto Krembil Brain Institute, University Health Network Regional Medical Lead, Ontario Health - Trillium Gift of Life Network Toronto, Ontario
Shaurya Taran MD	Clinical Associate, Department of Medicine and Interdepartmental Division of Critical Care Medicine, University of Toronto Toronto, Ontario

International Advisors

Ariane Lewis MD	Professor, Departments of Neurology and Neurosurgery NYU Langone Medical Center New York, New York
Alex Manara FRCP FFICM	Consultant Intensive Care Medicine, Southmead Hospital North Bristol NHS Trust Bristol, United Kingdom

eAppendix 2 Scoping review

Authors:

Karen Hornby (KH), Laura Hornby (LH)

Acknowledgements:

Robine Featherstone (RF)

Introduction

One of the initial steps in clinical practice guideline development is to perform a scoping review of literature in order to determine whether any previously published high quality (as assessed by the AGREE II tool[1]) guidelines already exist on the topic and if so, whether they can be updated and adapted to the relevant context. If no appropriate guideline exists, the scoping review can be used to: (1) summarize, synthesize and disseminate the findings of this topic; and (2) identify areas of variability; and (3) identify knowledge gaps.

The scoping review can also function to guide the determination of the scope of the guideline. It can be used by members of the guideline panel, with consultation from stakeholders, to define the following:

- The area of practice and policy to which the guideline applies
- Stakeholders affected by the recommendations
- The actions and interventions of interest and the outcomes that may result – both positive and negative.

Defining the scope as per above can also aid the guideline panel to identify and prioritize the most important clinical questions requiring recommendations and any good practice statements that should accompany these recommendations.

Objective

This scoping review aimed to collate and synthesize the available literature on medical guidelines for death determining by circulatory or neurologic criteria in adult or pediatric patients.

Methods

We performed a scoping review of guidelines for death determination by circulatory or neurologic criteria in adult or pediatric patients in accordance with Joanna Briggs Institute methodology[2]. The review was designed to answer the question "*What guidelines exist for determining death using circulatory or neurologic criteria and what is the level of quality of existing guidelines*?"

Search strategy

An information specialist (RF) was responsible for creating the search strategy (Appendix 1), with input from the coauthors (LH & KH), to identify published and unpublished material. A search of Ovid MEDLINE (1946 to November 22, 2019) was performed on November 23, 2019 using controlled vocabulary (MeSH) and text words for concepts: death (including neurological and circulatory death), definitions and guidelines. Additional searches were conducted of international guideline sources from CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters) and

Google (https://www.google.ca and https://www.google.fr). Results were limited to English and French records published since 2003. To ensure the most up to date coverage, the same information specialist (RF) conducted an updated search in Ovid MEDLINE (1946 to June 5, 2020) on June 6, 2020 using the same methodology as the original search. Results were managed using EndNote X9 (Clarivate Analytics).

Study selection

Citation titles and abstracts were scanned independently by two reviewers (KH & LH) to identify any relevant original or review articles. We excluded legal analysis of legislation governing the determination of death, institutional specific protocols, editorials, letters, narrative type reviews and animal studies. We only included articles pertaining to death determination by neurologic or circulatory criteria that were endorsed by at least one medical professional society/association or a national or international organization.

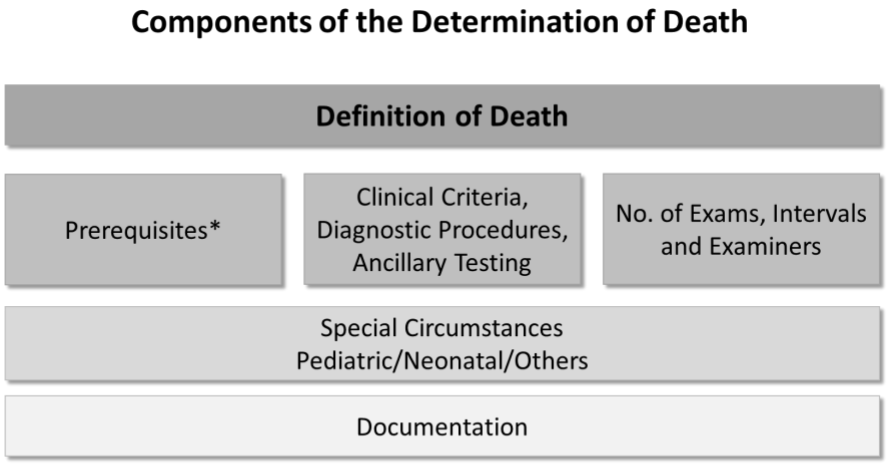
The full texts of retrieved articles were independently reviewed to assess study eligibility. In addition, the reference lists of these articles were independently examined to identify additional relevant articles. All disagreements were to be resolved by a third reviewer; however, none were identified. Studies that were excluded were tracked and reasons for their exclusion recorded.

Data extraction and synthesis

A framework (see Figure 1) was developed to identify and capture data elements from the articles included in this review. For each article, when available, we captured the definition of death, and any prerequisites (patient-related clinical, laboratory, or imaging requirements that should be fulfilled prior to starting the clinical evaluation)[3]. We also captured details on: the clinical criteria; diagnostic testing; ancillary investigation; the requirements for the number of exams; intervals before and between exams; the number of examiners and their level of expertise. Any special circumstances mentioned in the articles such as: death determination in pediatrics/neonates; patients on ECMO; and patients who had undergone targeted temperature management, were also captured. Finally, we collected information on, and examples of, documentation of the process to determine death.

Two data extraction spreadsheets (one to capture details from guidelines for determining death using circulatory criteria and the other for guidelines using neurologic criteria), based on the framework mentioned above, were designed and pilot-tested by the two reviewers. Data was independently extracted from each of the studies included in the final review, with disagreements resolved by consensus.

Figure 1: Components of the Determination of Death



*Patient-related clinical, laboratory, or imaging requirements that should be fulfilled prior to application of diagnostic tests or clinical evaluation

Search results

The original search conducted in November 2019 retrieved 509 records for primary (title and abstract) screening. No duplicates were retrieved by the search. Of these 509 records, 115 articles were identified for full text review. Eleven additional articles were identified for full test review from an examination of the reference lists of the 115 articles. To ensure the most up to date coverage, an updated search retrieved 506 records that were compared against results from the original search. Four hundred and fifty-five records were removed as previously screened, and 51 records were prepared for primary (title and abstract) screening. Only 1 article was identified for full text review from a screen of these 51 records. In summary, 571 unique records were retrieved for primary screening. Of these, we performed a full text review of 127 articles resulting in the identification of 21 articles. One article (*Academy of Medical Royal Colleges - Supplementary Guidance for the Diagnosis of Death using Neurological Criteria when the patient is supported with extracorporeal membrane oxygenation (ECMO) 2018)*[4]*,* was counted as a separate article in PRISMA flow diagram but merged with *A code of practice for the diagnosis and confirmation of death: Academy of Medical Royal Colleges; 2008*[5] resulting in 20 articles being used for the data extraction and analysis. Refer to Appendix 2 for the PRISMA summary for scoping reviews[6] of the search and review results.

Characteristics of included articles

A variety of terms were used by the authors to describe the articles that were retained for data extraction: code of practice, guidelines, national protocol, policy statement, practical guidance, report of a consensus meeting, (national) recommendations, and statement. We considered all the articles to be "guidelines" based on the broad definition of the term "guideline" that we applied as all articles focused on a condition (death) and included recommendations for appropriate "management" (how to determine death) of patients with this condition. All articles adhered to the majority of the domains AGREE II uses to assess guideline quality.

Source of article

Europe (45%), North America (30%), Other (15%), Multi-national (10%)

Language

English (90%), French (10%)

Year of "publication"

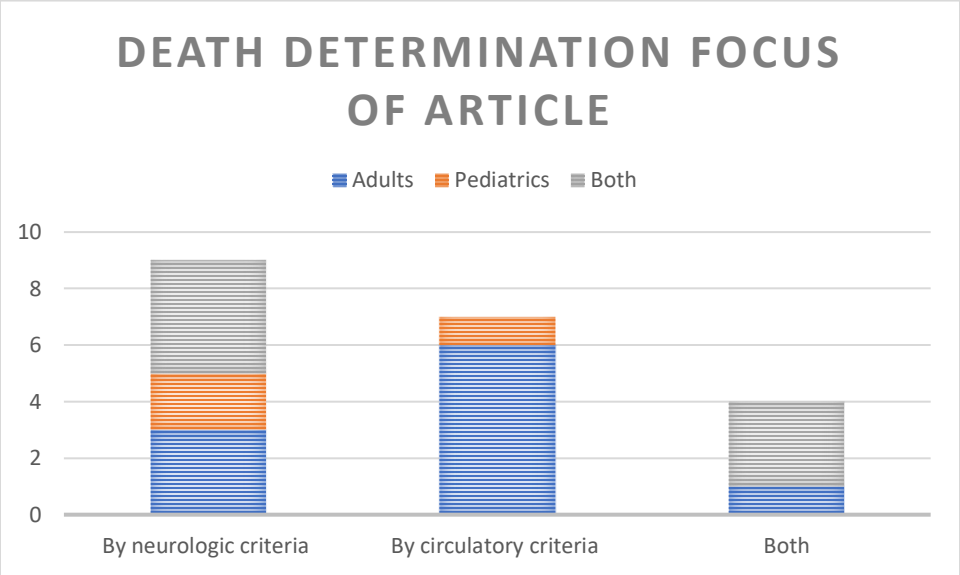
2015 to 2020 (45%), 2009 to 2014 (35%), 2003 to 2008 (20%)

Literature

Peer reviewed publications (60%), Grey literature (40%)

Focus

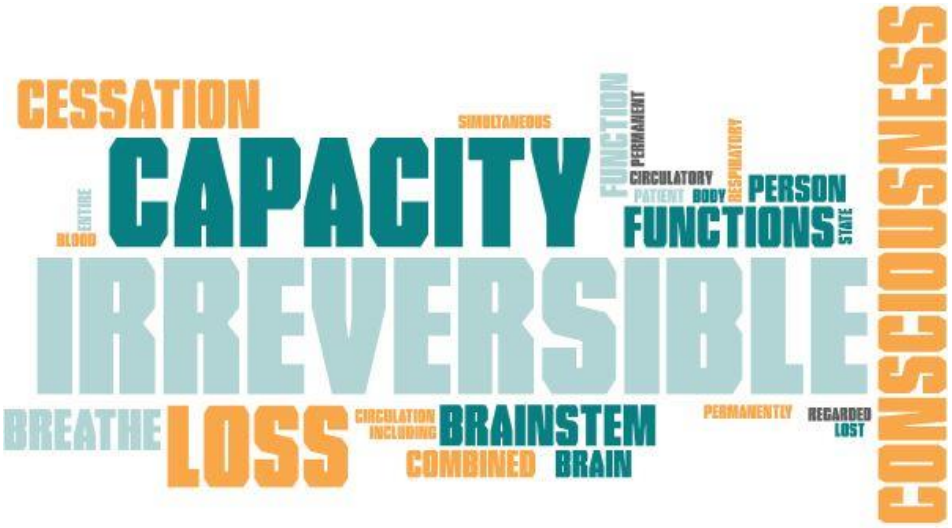
The following graph summarizes the death determination focus (neurologic/circulatory/both, adults/pediatric/both) of the included articles.



Definition of death

Only 15 of the 20 articles provided a definition of death. Of these definitions, seven defined "death",[5, 7-12] five defined "brain death/neurological death"[3, 13-16] and three defined "cardiac death/circulatory death"[17-19].

Contents of the definitions



The term "irreversible" was used in 11 of the 15 definitions provided[5, 7-10, 12-15, 17, 18].

Irreversible was defined in two articles:

1. Irreversible was defined as "may be taken to mean either that the relevant vital function is not able to be reversed or that no attempt will be made to reverse it"[8]
2. "irreversible" Pertaining to a situation or condition that cannot return or resume. In the context of BD/DNC, it is recognized that interventions to decrease intracranial pressure, such as hyperosmolar therapy, ventricular drainage, and decompressive craniectomy, should be applied when clinically indicated during neuroprotective phases of care. Ensuring irreversibility of a person's clinical state does not require performance of nontherapeutic interventions to decrease intracranial pressure that are not judged to be clinically indicated[3].

The term "permanent" was used in five of the 15 definitions[3, 9, 11, 18, 19], and mentioned in one of the articles but not included in its definition[8]. Three of these articles provided a (the same) definition of Permanent. Permanent was defined as "loss of function that cannot resume spontaneously and will not be restored through intervention"[3, 11, 19]

Death Determination by Circulatory Criteria

Prerequisites

Only 2 of the 11 articles on death determination by circulatory criteria mentioned any prerequisites to consider prior to determining death. One article described this as follows: *extensive attempts at reversal of any contributing cause to the cardiorespiratory arrest have been made...such factors, which include body temperature, endocrine, metabolic and biochemical abnormalities*[5]. The other mentioned induced hypothermia[20].

Clinical criteria and diagnostic procedures

Ten articles identified some diagnostic procedure/clinical criteria required for death determination by circulatory criteria[5, 8, 9, 11, 12, 18-22]. The remaining article did not mention specific clinical criteria and used

the term "according to accepted medical standards"[17]. The most common cardiorespiratory criteria were apnea, absent pulse, and absent heart sounds. Of note, four articles indicated that absent pulse by palpation was not recommended[9, 12, 18, 19] (one of these was an article specific to pediatrics[19]). Five articles did not require any neurologic criteria[9, 12, 17, 19, 22]. The most common neurologic criteria were: unresponsiveness/immobility/coma; absent pupillary responses to light; and absent corneal reflexes. The most common diagnostic procedure identified was intra-arterial pressure monitoring.

Clinical criteria and diagnostic procedures

	1	2	3	4	5	6*	7	8	9	10	PEDS 11
Apnea	x	x	x	x	x		x	x	x		
Cardiorespiratory											
Pulselessness	x	x	x	x	x		x	x		x	x
Absent heart sounds	x		x					x			
Absent cardiac output					x						
Asystole					x					x	
Neurological (absent)											
"Coma"	x	x	x		x			x	x		
Pupillary reflexes	x				x			x	x		
Corneal reflexes	x				x				x		
Vestibulo-ocular reflexes									x		
Tracheal reflexes									x		
Clinical signs of brain death		x									
Diagnostic procedures											
Arterial line	x	x	x	x	x		x			x	x
ECG	x		x	x	x			x		x	
Echo	x	x		x				x	x	x	x
Doppler								x			x

*According to accepted medical standards

Red colour indicates Canadian guideline

Clinical assessments (exams)/examiners/expertise/qualifications

Five of 11 articles mentioned information pertaining to clinical assessments (exams/examiners). For adults, four articles mentioned the requirement for one exam[8, 11, 18, 22] with two of these requiring two examiners[18, 22]. For pediatrics, one article[19] required one exam with two examiners. Nine articles mentioned examiners expertise/qualifications[5, 8, 11, 17-22].

Observation/Hands off/No touch period

All articles mentioned an "observation period", however, this terminology requires clarification (observation vs stand off vs no touch). As outlined below, there was a range of requirements for the length of this period with the most common being 5 minutes.

ADULTS

2 to 5 mins[11, 17]

3 min ≥ and ≤ 5 min[8]

5 mins[5, 9, 12, 18, 21, 22]

10 minutes? (death certified after 5 min, then 5 min stand down time)[20] (O'Rourke 2013)

PEDIATRICS

5 minutes hands-off (observation of arrest of circulation prior to determination of death)[19]

A few other concepts to consider pertaining to the "observation period" were mentioned in the articles included in this review. Some examples are:

When to start? *The starting point for the determination of cardio-respiratory death should be the absence of mechanical cardiac function..confirmed by the absence of pulsatile flow on a correctly functioning arterial line (or by using echocardiography if expertise exists)*[12]

What to do during? *During which the absence of palpable pulses, blood pressure and respiration are continuously observed by at least 1 physician*[22].

What triggers a restart of the clock? Any spontaneous return of cardiac or respiratory activity during this period of observation should prompt a further five minutes observation from the next point of cardiorespiratory arrest[5].

Is anything required at the end of the period? *After five minutes of continued cardiorespiratory arrest the absence of the pupillary responses to light, of the corneal reflexes, and of any motor response to supra-orbital pressure should be confirmed*[5].

Interventions to restore circulation

Six articles indicated that interventions to restore circulation (once circulatory arrest has occurred) are not permitted[5, 8, 9, 11, 12, 19]. Four of these specifically mentioned circulation to the brain[5, 9, 12, 19] (cerebral perfusion/circulation/brain blood flow/oxygenated brain blood flow).

Time of Death

Only 4 of 11 articles specifically mentioned the time of death. In adults this was defined as:

the time at which these criteria are fulfilled[5] *; the determination after a 5-minute observation period* [22] and *at the end of testing* [18]. In pediatrics this was defined as *at the end of this period (hands off)*[19].

Death determination in the situation of failed resuscitation following cardiac arrest

All of the articles that addressed death determination after circulatory arrest were in the situation of "controlled DCD". Only 3 articles mentioned information relevant to the determination of death in the context of "uncontrolled DCD"[5, 9, 18].

Documentation

Only three articles provided specific guidance on the documentation of the process. Two pertained to adults:

> "For the purposes of organ donation, circulatory determination of death should be documented using a specific form (see Appendix E) to demonstrate explicitly that all criteria set out in this Statement are met. The same criteria should be listed in local hospital forms"[8].

> "Clinical findings, additional tests performed, discussions concerning organ donation and preparatory medical measures, and consent are to be documented. For this purpose, protocol templates are available in Appendix G; these may be adapted and expanded by the hospital authorities responsible"[18].

One pertained to pediatrics:

> "Although we do not provide specific recommendation for documentation, inherent in the quality assurance component of recommendation 54 is the assumption that the process of pDCD be well documented. We encourage teams developing pDCD practices to visit the Canadian Blood Services website link listed below to see sample clinical and administrative checklists as well as documentation tools" [19].

Death determination by neurological criteria

Prerequisites

Eight of the 13 articles pertaining to the determination of death using neurological criteria indicated the need for an interval prior to testing for certain conditions[3, 7, 8, 10, 13, 15, 16, 23] (see next section).

All articles indicated the need to establish a known cause of the brain injury and some indicated the need for imaging to support this[3, 8, 15, 16, 18, 23].

The following is a list of general categories of situations to consider prior to starting a clinical exam. All articles mentioned most of these categories.

- Hypothermia
- Sedatives/CNS depressant medications
- Circulatory disturbances
- Endocrine disturbances
- Acid-base disturbances
- Metabolic disturbances
- Electrolyte disturbances
- Neuromuscular blockade
- Peripheral nerve or muscle dysfunction

Interval prior to testing

Two articles indicated the need for an interval prior to testing in all cases of the determination of death using neurological criteria in adults. ANZICS 2019[8] requires a minimum 4-hour observation (and mechanical ventilation) period. Dubai Health Authority 2020[13] requires an interval of at least six hours. Four articles indicated the need for waiting period of (at least) 24 hours prior to testing of the determination of death using neurological criteria in adults in situations of acute hypoxic ischemia in adults[3, 8, 23, 24]. One article indicated the need for a waiting period of 24 hours in situations of hypothermia of duration greater than 6 hours in adults[8].

Two articles indicated the need for an interval prior to testing of the determination of death using neurological criteria in pediatrics. Nakagawa, et al[10]. indicate that:

immediately following cardiopulmonary resuscitation or other severe acute brain injuries evaluation for brain death should be deferred for 24 to 48 hours or longer if there are concerns or inconsistencies in the examination.

The Royal College of Paediatric and Child Health[7] indicate that:

in post-asphyxiated infants, or…after resuscitation, whether or not they have undergone therapeutic hypothermia, there should be a period of at least 24 hours of observation during which the preconditions necessary for assessment for death by neurological criteria should be present before clinical testing. If there are concerns about residual drug-induced sedation, then this period of observation may need to be extended.

Clinical criteria

The requirement to perform an apnea test was indicated in all articles included in this review. The following clinical criteria were found in almost every article included in the review: the absence of:

- Responsiveness (coma)
- Motor responses (response to pain, excluding spinal reflexes)
- Pupillary reflexes
- Corneal reflexes
- Gag reflex
- Cough/Tracheal reflexes
- Vestibulo-ocular reflexes
- Oculocephalic reflexes
- Sucking & rooting (neonates)

Exams/examiners/expertise/qualifications

Adults

Six articles indicated the need to perform two exams to determine death using neurological criteria in adults[5, 8, 13, 15, 18, 23]. Three articles [3, 11, 16] only required one exam to be performed for adults. Six articles indicated the need for two examiners to determine death using neurological criteria in adults.[3, 5, 8, 15, 18, 23, 25] One article[13] indicated the need for a minimum of 3 examiners for adults.

Pediatrics

All nine articles with information pertaining to pediatrics require two clinical assessments[3, 5, 7, 8, 10, 13-15, 18]. The two articles that only addressed the death determination by neurologic criteria in pediatrics provided further details such as:

The testing is to "*be undertaken by the (two) paediatricians together and must always be performed completely and successfully on two occasions in total*"[7]

And

"The examinations should be performed by different attending physicians involved in the care of the child. The apnea test may be performed by the same physician, preferably the attending physician who is managing ventilator care of the child[10]

Interval between tests

Requirements for an interval between exams for death determination by neurologic criteria in adults included: "an intervening time period is unnecessary"[3]; "conducted jointly"[18]; "no fixed interval"[8, 24]; "need not be a lengthy delay"[5]; "a 'reasonable' period of time"[23]; "4 hour interval between EEGs"[14]; and "6 hours"[13].

Six articles indicated requirements for an interval between exams to determine death using neurological criteria in pediatrics[7, 8, 10, 13-15]. Not surprisingly, these were quite detailed and heterogeneous:

- "In term neonates between 24 hours and 30 days old…a 24-hour interval before the second clinical examination"[8]
- "Age 7 days to 2 months: 48 hours…Age 2 months to 1 year: 24 hours (longer for anoxia), Age > 1 year: same as adults[14]
- "Age (7 to 60 days): 48 hours…Age (61 days to 1 year): 24 hours…Age (>1 – 18 years): 12 hrs"[13]
- "24 hours for neonates (37 weeks gestation to term infants 30 days of age), 12 hours for infants and children (30 days to 18 years)"[10]
- "The interval between tests need not be prolonged"[7]
- "Term newborns aged < 30 days... a minimum interval of 24 hours between examinations"[15]

Time of Death

Only 8 articles [3, 5, 8, 13, 15, 16, 18, 23] provided information on time of death in adults. Three indicated it was after the first exam[5, 15, 16] and three indicated it was after the second exam[8, 18, 23]. Greer et al.[3] indicated that the "*time of death be noted in accordance with regional legislation"* and provided detailed recommendations if no legislation exists. Dubai Health Authority[13] indicated:

> *If the patient is not a registered organ donor, a grace period of 24hrs shall be given to the family to respond about decision on organ donation. After the grace period, that patient is declared dead.*

Only one article provided information on time of death in pediatrics, indicating that "death is declared after confirmation and completion of the second clinical examination and apnea test"[10]

Ancillary/Confirmatory testing

Adult and pediatric systematic reviews of ancillary investigation for DNC was performed by the Ancillary Investigation Working Group and therefore not included as part of this review.

Documentation

Almost all articles (10/13) provided a sample of the form required for the documentation a death determination by neurologic criteria[3, 5, 7, 8, 10, 13, 15, 16, 18, 23].

In general, these forms included all phases of the determination:

- Etiology of the coma
- Absence of confounders
- Details of clinical testing including apnea testing & laboratory values
- Neuroimaging results & timing in relation to clinical testing
- Reason for & type of ancillary investigation performed & results

- Time of death
- Identity of practitioner performing the evaluation

Consensus

For the information pertaining to the death determination by neurological criteria, we found consensus (with minor differences) on what to consider as potential confounders prior to proceeding with a determination, as well as the clinical criteria to be used for a determination, including the use of apnea testing.

Variability

For the information pertaining to the death determination by circulatory criteria, we found variability in how death was defined; the criteria and procedures recommended to determine death (particularly whether or not there was a need for neurological criteria); and the number of exams & examiners required to determine death.

For the information pertaining to death determination by neurological criteria, we found variability in: how death was defined; what interval of time (if any) is required prior to a determination and between determinations; how many exams are required, including how many apnea tests, and examiners; and the point at which the actual time of death occurred.

Lack of clarity

For the information pertaining to death determination by circulatory criteria, there was a lack of clarity around the concept of a "stand off period/wait time", particularly, when to start it, what to do during it and how long it should be. The point at which the actual time of death occurred was also not very clear.

For the information pertaining to death determination by neurological criteria, there was a lack of clarity pertaining to whether or not imaging was required to support the known cause of the brain injury.

Limited information

For the information pertaining to death determination by circulatory criteria, there was a limited amount of information on: what to consider as potential confounders prior to proceeding with a determination; what interval of time (if any) is required prior to a determination; and what interventions (if any) are permitted to restore circulation after the determination. There was also very limited information on determining death following failed resuscitation.

For both types of determinations, there is less information pertaining to pediatrics/neonates compared to adults.

Discussion

Previously published high quality guidelines for consideration

The primary reason for undertaking a scoping review as one of the first steps of of clinical practice guideline development is to determine whether any previously published high quality guidelines already exist on the topic and if so, whether they can be updated and adapted to the relevant context. Based on a review of the guidelines retrieved by this scoping review, all articles adhered to the majority of the

domains the AGREE II tool[1] uses to assess guideline quality. Some of the newer ones (especially[9, 10, 12, 16, 17]) used a multidisciplinary group of stakeholders for guideline development with reviews of the literature (occasionally scoping reviews but more often "evidence reviews"). The UK guideline[12] often included patients and the public, some guidelines indicated that GRADE methodology was used, but in general it was applied incorrectly.

We identified two guidelines that, in addition to adhering to the majority of domains, ranked highly in the third domain (rigour of development) of the AGREE II tool and thus were identified to be of high quality. Interestingly, both were pediatric guidelines. In the setting of death determination by circulatory criteria, we identified one guideline for consideration. This was the Canadian pediatric guideline by Weiss et al[19] published in 2017 in pediatric critical care medicine. It used the GRADE guideline development methodology[26]. In the setting of death determination by neurologic criteria we identified one guideline for consideration. This was the pediatric guideline from the Royal College of Paediatrics & Child Health compiled in 2015[7]. It used a procedure similar to GRADE for linking the strength of their recommendations to the quality of the evidence for them.

The most recent guideline for determination of death by neurologic criteria was published in 2020 by the Word Brain Death Project[3]. The recommendations have been endorsed by 5 world federations [World Federation of Critical Care Nurses, World Federation of Intensive and Critical Care, World Federation of Neurology, World Federation of Neurosurgical Societies, World Federation of Pediatric Intensive and Critical Care Societies], 27 medical societies from across the globe., and Canadian Neurological Sciences Federation, which represents the Canadian Neurological Society, Canadian Neurosurgical Society, Canadian Society of Clinical Neurophysiologists, Canadian Association of Child Neurology and the Canadian Society of Neuroradiology. However, the process by which this guideline was produced lacked transparency and did not include patient or public representation. Although the guideline was evidence based, the process for reviewing the literature and the method used to link the strength of the recommendations to the quality of the evidence was not one that is recognized by the Canadian Critical Care Society.

Limitations

Our methods resulted in several limitations. We limited the articles included in this review to those published in French or English and therefore may have missed guidelines published in other languages from countries such as Spain and The Netherlands who are world leaders in this domain. Our final search was performed in June 2020, and therefore we will have missed anything published after this. Also, lack of clarity in how some of the information was written in the articles could have led to a misinterpretation of the articles' recommendations.

Conclusion

In conclusion, we performed a scoping review of guidelines for death determination by circulatory or neurologic criteria in adult or pediatric patients. The review was designed to answer the question "*What guidelines exist for determining death using circulatory or neurologic criteria and what is the level of quality of existing guidelines*?" Our search strategy identified 571 unique records resulting in the identification of 20 articles inlcuded in this analysis. Although all articles adhered to the majority of the AGREE II domains, only two guidelines were identified to be of high quality. These were the Canadian pediatric guideline by Weiss et al[19] published in 2017, and the pediatric guideline from the Royal College

of Paediatrics & Child Health compiled in 2015[7]. The synthesis of the results of this scoping review will be used by the guideline development panel to: (1) identify areas of variability; (3) identify knowledge gaps; and (3) identify and prioritize the most important clinical questions requiring recommendations and any good practice statements that should accompany these recommendations.

References

1. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42.
2. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015;13(3):141-6.
3. Greer DM, Shemie SD, Lewis A, Torrance S, Varelas P, Goldenberg FD, et al. Determination of Brain Death/Death by Neurologic Criteria: The World Brain Death Project. Jama. 2020;324(11):1078-97.
4. Academy of Medical Royal Colleges. Supplementary Guidance for the Diagnosis of Death using Neurological Criteria when the patient is supported with extracorporeal membrane oxygenation (ECMO 2018 [cited 2021 September]. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/11683/supplementary-guidance-for-the-diagnosis-of-death-using-neurological-cri.pdf.
5. Academy of Medical Royal C. A code of practice for the diagnosis and confirmation of death. Academy of Medical Royal Colleges; 2008.
6. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169(7):467-73.
7. Royal College of P, Child H. The diagnosis of death by neurological criteria in infants less than two months old. Royal College of Paediatrics and Child Health; 2015.
8. Australian New Zealand Intensive Care Society. The ANZICS Statement on Death and Organ Donation: Australian and New Zealand Intensive Care Society;. Australian and New Zealand Intensive Care Society; 2019, 4th edition.
9. British Transplantation Society. Transplantation from deceased donors after circulatory death 2013 [Available from: https://bts.org.uk/wp-content/uploads/2016/09/15_BTS_Donors_DCD-1.pdf.
10. Nakagawa TA, Ashwal S, Mathur M, Mysore M, Society of Critical Care Medicine SoCC, Section on Neurology of American Academy of P, et al. Clinical report-Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. Pediatrics. 2011;128(3):e720-40.
11. Shemie SD, Hornby L, Baker A, Teitelbaum J, Torrance S, Young K, et al. International guideline development for the determination of death. Intensive Care Med. 2014;40(6):788-97.
12. British Transplant Society and Intensive Care Society. Donation after Circulatory Death - report on a consensus meeting 2010 [cited 2015 September]. Available from: https://http://www.bts.org.uk/Documents/Guidelines/Active/DCD for BTS and ICS FINAL.pdf.
13. Government of Dubai, Health Regularion Sector, Dubai Health Authority. Brain Death Determination. 2020.

14. Boulard G, P. Guiot, T. Pottecher, A. Tenaillon. Prise en charge des sujets en état de mort encéphalique dans l'optique d'un prélèvement d'organes. Annales Françaises d'Anesthésie et de Réanimation. 2005;24(7):836-43.

15. Shemie SD, Doig C, Dickens B, Byrne P, Wheelock B, Rocker G, et al. Severe brain injury to neurological determination of death: Canadian forum recommendations. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006;174(6):S1-13.

16. Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM, American Academy of N. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74(23):1911-8.

17. Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MMI, D'Alessandro A, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(9):2004-11.

18. Swiss Academy Of Medical S. Medical-ethical guidelines: Determination of death with regard to organ transplantation and preparations for organ removal. Swiss medical weekly. 2018;148:w14524.

19. Weiss MJ, Hornby L, Rochwerg B, van Manen M, Dhanani S, Sivarajan VB, et al. Canadian Guidelines for Controlled Pediatric Donation After Circulatory Determination of Death-Summary Report. Pediatr Crit Care Med. 2017;18(11):1035-46.

20. O'Rourke J. Non heart beating organ donation in adults: a clinical practice guideline. Irish medical journal. 2013;106(6):186-8.

21. Biomedecine Adl. Conditions a Respecter Pour Realiser des Prelevements d'Organes sur des Donneurs Decedes Apres Arret Circulatoire de la Categorie de Maastricht dans un Etablissement de Sante 2019 [Available from: https://www.agence-biomedecine.

22. Shemie SD, Baker AJ, Knoll G, Wall W, Rocker G, Howes D, et al. National recommendations for donation after cardiocirculatory death in Canada: Donation after cardiocirculatory death in Canada. CMAJ. 2006;175(8):S1.

23. Dwyer R, Motherway C, Phelan D, Intensive Care Society of I. Diagnosis of Brain Death in adults; Guidelines. Intensive Care Society of Ireland; 2018.

24. Shemie SD, Doig C, Dickens B, Byrne P, Wheelock B, Rocker G, et al. Severe brain injury to neurological determination of death: Canadian forum recommendations. CMAJ. 2006;174(6):S1-13.

25. Brain Injury Evaluation Quality Control Center of National Health C, Neurocritical Care Committe of the Chinese Society of N, Neurocritical Care Committe of China Neurologist A. Criteria and practical guidance for determination of brain death in adults (2nd edition). Chinese medical journal. 2019;132(3):329-35.

26. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

Appendix 1 – Search Strategy

Original search date: 20 Nov 2019 | Update date: 06 Jun 2020

Search Summary

Databases

Database Name	Platform	Database Coverage Dates	Search Date MM/DD/YYYY	Results (w/ duplicates)	Results (duplicates removed)*
MEDLINE	Ovid	1946 – 05 Jun 2019	06/06/2020	490	35
			Total Database Search Results:	**490**	**35**

*Removed duplicates compared against Nov 2019 results

Other Sources

Source Name	Search Date MM/DD/YYYY	Results (w/ duplicates)	Results (duplicates removed)
CADTH Grey Matters International Guidelines			
Aetna – Clinical Policy Bulletins (Medical)	06/06/2020	0	0
American Association for Clinical Chemistry	06/06/2020	0	0
Best Practice Advocacy Centre New Zealand	06/06/2020	0	0
CDC Guidelines Database	06/06/2020	0	0
The Regulation and Quality Improvement Authority (UK)	06/06/2020	0	0
French National Authority for Health Practice guidelines	06/06/2020	1	1
Institute for Clinical Systems Improvement guidelines (UK)	06/06/2020	1	1
ECRI Guidelines Trust	06/06/2020	0	0
National Health and Medical Research Council – CPG portal (Australia)	06/06/2020	0	0
NICE Guidelines (UK)	06/06/2020	0	0
SIGN Guidelines (UK)	06/06/2020	0	0
Search engines			
Google.ca	06/06/2020	14	14
	Total Other Search Results:	**16**	**16**
	Total Search Results:	**506**	**51**

Search methods:

An information specialist (RF) conducted an update search in Ovid MEDLINE (1946 to June 5, 2020) on June 6, 2020 using controlled vocabulary (MeSH) and text words for concepts: death (including neurological and circulatory death), definitions and guidelines. Additional searches were conducted of international guideline sources from CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters) and Google (https://www.google.ca and https://www.google.fr). Results were limited to English and French records published since 2003. See appendix for full search strategies.

Search results:

The search retrieved 506 records that were compared against results from the same search conducted in November 2019. 455 records were removed as previously screened and 51 records were prepared for primary (title and abstract) screening. Results were managed using EndNote X9 (Clarivate Analytics).

Appendix search strategies

Database: Ovid MEDLINE(R) ALL 1946 to June 05, 2020

Date of Search: 06 Jun 2020

Strategy:

1 *Brain Death/di, lj (1441)
2 Death/di (4)
3 1 or 2 [Coordinated concept for death determination] (1445)
4 *Brain Death/ (5197)
5 *Death/ (12070)
6 "BD/DNC".tw,kf. (1)
7 coma depass*.tw,kf. (19)
8 death$1.ti. (128591)
9 dead.ti. (7723)
10 dying.ti. (8231)
11 irreversible coma.ti. (61)
12 or/4-11 [Combined MeSH & text words for death] (147217)
13 Terminology as Topic/ (55074)
14 criteri*.tw,kf. (643683)
15 declar*.tw,kf. (28283)
16 diagnos*.ti. (589782)
17 diagnos*.ab. /freq=2 (848761)
18 determin*.ti. (351617)
19 determin*.ab. /freq=2 (652637)
20 defin*.ti. (69543)
21 defin*.ab. /freq=2 (192223)
22 provision$1.tw,kf. (83345)
23 or/13-22 [Combined MeSH & text words for determination] (2950087)
24 12 and 23 [Combined concepts for death & determination] (13666)
25 3 or 24 [Death determination] (14262)
26 Guidelines as Topic/ (39632)
27 *Organizational Policy/ (4091)
28 Practice Guidelines as Topic/ (117248)
29 consensus development conference.pt. (11661)
30 consensus development conference, NIH.pt. (788)
31 guideline.pt. (16249)
32 practice guideline.pt. (27059)
33 (academies or academy).ti. (12041)
34 association.ti. (234271)
35 best practice$1.ti. (4841)
36 ((bulletin$1 or paramet*) adj1 practice).ti. (1004)
37 (care and (path$1 or pathway$1 or map$1 or plan$1 or standard$1)).ti. (13155)
38 (committee or subcommittee).ti. (24046)
39 consensus*.ti. (24624)
40 ((critical or clinical or practice) and (path$1 or paramet* or pathway$1 or protocol*)).ti. (15560)
41 (CPG or CPGs).ti. (5724)
42 endorse*.ti. (1570)
43 guideline$1.ti. (76561)
44 guideline$1.ab. /freq=2 (78339)
45 ((paper or statement) adj1 (policy or position)).ti. (6035)
46 recommend*.ti. (46522)

47 standard$1.ti. (66859)
48 working group.ti. (5321)
49 or/26-48 [Guidelines filter] (654870)
50 25 and 49 [Guidelines filter applied to death determination] (763)
51 exp Animals/ not Humans/ (4705042)
52 (animal* or bovine* or calves or camel* or canine* or cat or cats or chimp* or dog or dogs or equine* or feline* or goat* or hamster* or horse* or llama* or mice* or monkey* or mouse* or pig or piglet* or pigs or porcine* or primate* or rabbit* or rat or rats or rodent* or sheep* or simian* or swine*).ti. (2281531)
53 50 not (51 or 52) [Exclude animal studies] (756)
54 ((editorial or comment or letter or newspaper article) not (comment and guideline)).pt. (1869204)
55 53 not 54 [Exclude opinion pieces] (680)
56 limit 55 to (english or french) (616)
57 limit 56 to yr="2003-Current" (498)
58 remove duplicates from 57 (490)

Other Source: CADTH Grey Matters International Guidelines from CADTH Grey Matters checklist: https://www.cadth.ca/resources/finding-evidence/grey-matters
Date of Search: 06 Jun 2020
Guidelines Sites:
Aetna – Clinical Policy Bulletins (Medical)
American Association for Clinical Chemistry
Best Practice Advocacy Centre New Zealand
CDC Guidelines Database
The Regulation and Quality Improvement Authority (UK)
French National Authority for Health Practice guidelines
Institute for Clinical Systems Improvement guidelines (UK)
ECRI Guidelines Trust
National Health and Medical Research Council – CPG portal (Australia)
NICE Guidelines (UK)
SIGN Guidelines (UK)

Keyword search terms on guidelines sites:
brain death
brainstem death
cardiac death
cardiorespiratory arrest
cardiorespiratory death
cessation of brain function
cessation of circulation and breathing
cessation of function with no possibility to resume
cessation of neurological or circulatory function
circulatory death
controlled donor
dead
death
death criteria
death determination
décès
decreased heart beating donors
dying
end-of-life
irreversible coma
mort

mourant
neurological death
neurological morbidity
non-heart-beating donors
permanent loss of capacity for consciousness and loss of all brainstem functions
uncontrolled donor
[RF: not all terms/phrases searched on all sites]

Other Source: Google (English)
Date of Search: 6 Jun 2020
URL: https://www.google.ca/
Strategy:
Search 1
(death criteria | death determination | death diagnosis) (consensus | guideline | pathway | "position statement" | policy | protocol | recommendation | standard | statement)

[RF note: reviewed first 5 pages of results. Kept 8 records]

Search 2
("controlled donor" | death | "decreased heart beating donor" | dying | "neurological morbidity" | "uncontrolled donor") (criteria | determination | declaration | definition | diagnosis) (consensus | guideline | pathway | "position statement" | policy | protocol | recommendation | standard | statement)

[RF note: reviewed first 5 pages of results. Kept 1 record]

Search 3
(academy | association | committee | "consensus development" | subcommittee | "working group") (brain stem death | "cessation of brain function" | death | dying | loss of capacity for consciousness) (consensus | guideline || "position statement" | policy | protocol | recommendation | standard | statement)

[RF note: reviewed first two pages of results – only 13 records retrieved. Kept 4 records]

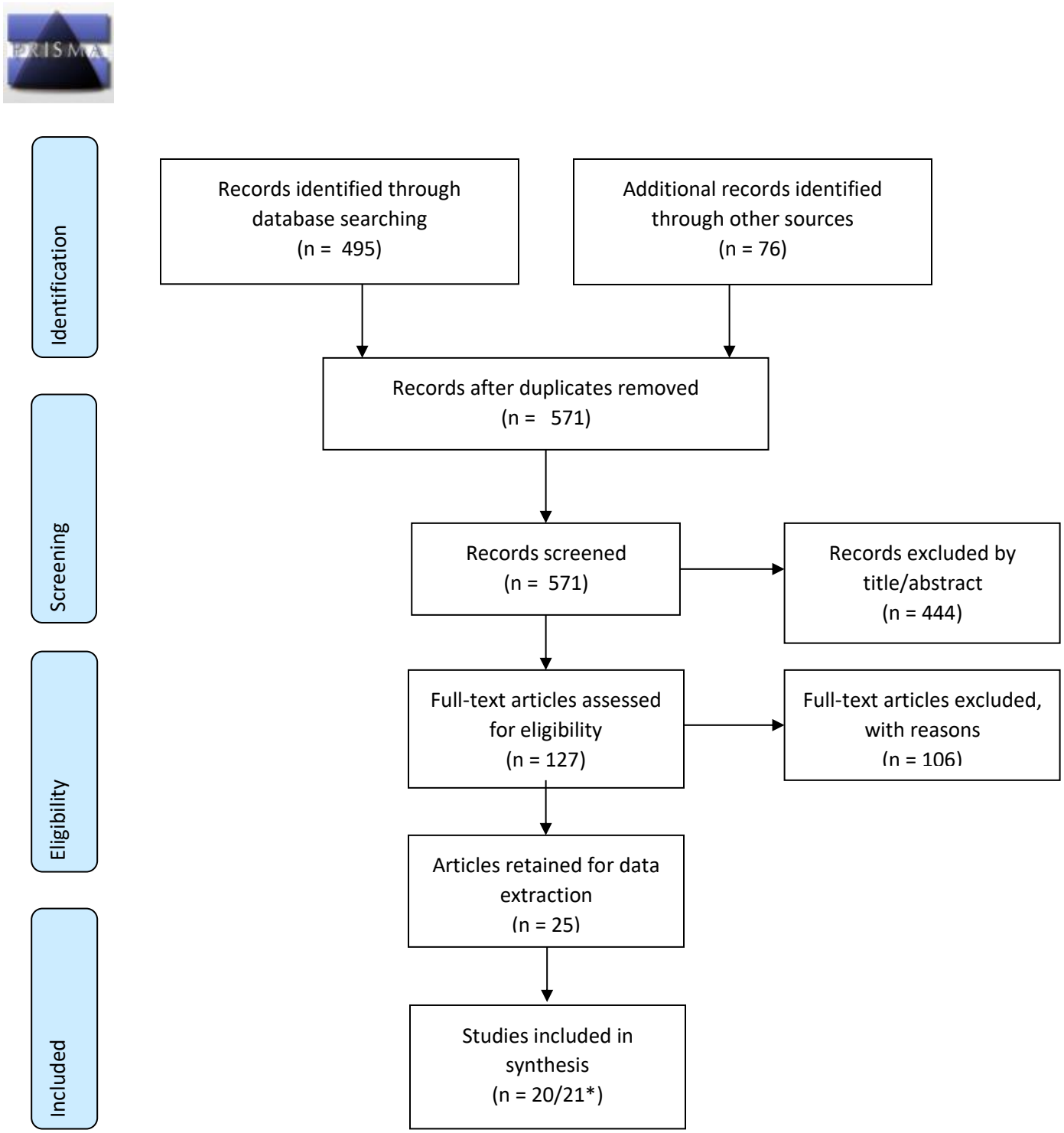
Other Source: Google (French)
Date of Search: 6 Jun 2020
URL: https://www.google.fr/
Strategy:
Search 1
(critère de décès | determiner la mort | détermination de la mort)

[RF note: reviewed first 5 pages of results. Kept 0 records]

Search 2
(mort cardiaque | mort cardiocirculatoire | mort circulatoire | mort cérébrale | mort encéphalique | mort neurologique) (critère | déclaration | définition | determiner | détermination) (directives | politique | protocole | recommandation)

[RF note: reviewed first 5 pages of results. Kept 1 record]

Appendix 2: PRISMA Flow Diagram



**Supplementary Guidance for the Diagnosis of Death using Neurological Criteria when the patient is supported with extracorporeal membrane oxygenation (ECMO) 2018* was counted as a separate article in PRISMA flow diagram but merged with *A code of practice for the diagnosis and confirmation of death: Academy of Medical Royal Colleges; 2008*, for the data extraction and analysis.

eAppendix 3 Definitions of death in national and international guidelines and legislation

1. Current Canadian Definitions

Definition of "Brain Death/Neurological Death"	Reference
1. Irreversible loss of the capacity for consciousness combined with the irreversible loss of all brain stem functions, including the capacity to breathe	Shemie, Doig, Dickens et al, Severe brain injury to neurological determination of death: Canadian forum recommendations. CMAJ, 2006; 174: S1-13.
Definition of "Cardiac Death/Circulatory Death"	**Reference**
2. Permanent loss of capacity for consciousness and all brainstem function, as a consequence of permanent cessation of circulation. • Permanence is defined as loss of function that will not resume spontaneously and will not be restored through intervention. Function refers to the primary and fundamental purpose of the brain 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 or groups of cells that can be measured by laboratory means.	Weiss, Hornby, Rochwerg et al, Canadian Guidelines for Controlled Pediatric Donation After Circulatory Determination of Death: Summary Report. Pediatric Critical Care Medicine, 2017; 18: 1035-46.
Definition of "Death" in Legislation	**Reference**
3. The death of a person takes place at the time at which irreversible cessation of all that person's brain function occurs (Manitoba) 4. The irreversible cessation of the functioning of the organism as a whole as determined by the irreversible loss of the brain's ability to control and co-ordinate the organism's critical functions (Nova Scotia) 5. In all other provinces, death is legally defined 'in accordance with accepted medical practice"	Canada (Manitoba): Vital Statistics Act Canada (Nova Scotia): Human Organ and Tissue Donation Act, comes into force Jan 18, 2021

2. International Death Determination Guidelines

Definition of "Death"	Reference
6. Irreversible cessation of all function of the brain of the person or the irreversible cessation of circulation of blood in the body of the person • Irreversible: may be taken to mean either that the relevant vital function is not able to be reversed or that no attempt will be made to reverse it	The ANZICS Statement on Death and Organ Donation: Australian and New Zealand Intensive Care Society, 2019. (4th edition)

Definition of "Death"	Reference
7. Irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe	The diagnosis of death by neurological criteria in infants less than two months old. Royal College of Paediatrics and Child Health, 2015
8. Permanent loss of capacity for consciousness and all brainstem functions • Permanent refers to loss of function that cannot resume spontaneously and will not be restored through intervention	Shemie, Hornby, Baker et al, International guideline development for the determination of death. Intensive care medicine, 2014; 40: 788-97.
9. Is irreversible and should be regarded as a state in which a patient has permanently lost the capacity for consciousness and brain stem function	Transplantation from deceased donors after circulatory death. British Transplantation Society Guidelines, compiled by a Working Party of The British Transplantation Society, July 2013.
10. Irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brainstem	Nakagawa, Ashwal, Mathur et al, 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. Irreversible and simultaneous loss of both the capacity to breathe and the capacity for consciousness	Organ Donation after Circulatory Death: Report of a consensus meeting. The Intensive Care Society, British Transplantation Society, National Health Service Blood and Transplant, June 2010.
12. Irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe	A code of practice for the diagnosis and confirmation of death. Academy of Medical Royal Colleges (UK), 2008.

Definitions of "Brain Death/Neurological Death"	Reference
13. The complete and permanent loss of brain function (as defined by an unresponsive coma with loss of capacity for consciousness, brainstem reflexes and the ability to breathe independently) • 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 • This may result from permanent cessation of circulation to the brain, after devastating brain injury, or both. Persistence of cellular-level neuronal and neuroendocrine activity does not preclude the determination. In the context of death determination, "permanent" refers to	Greer, Shemie, Lewis et al, Determination of Brain Death/Death by Neurologic Criteria, The World Brain Death Project. JAMA, 2020.

Definitions of "Brain Death/Neurological Death"	Reference
loss of function that cannot resume spontaneously and will not be restored through intervention.	
14. Irreversible cessation of all functions of the brain, including the brain stem	Brain Death Determination. Government of Dubai Health Regulation Sector, Dubai Health Authority, 2020.
15. Cessation of all functions of the entire brain, including the brain stem	Wijdicks, Varelas, Gronseth et al, 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.
16. Brain death is defined as the irreversible destruction of all the brain functions in a subject with a beating heart	Boulard, Guit, Pottecher et al, Prise en charge des sujets en état de mort encéphalique dans l'optique d'un prélèvement d'organes. Ann Fr Anesth Réanim, 2005; 24 : 836-43.

Definitions of "Cardiac Death/Circulatory Death"	Reference
17. Irreversible cessation of the functions of the brain, including the brainstem	Medical-ethical guidelines: Determination of death with regard to organ transplantation and preparations for organ removal. Swiss Academy of Medical Sciences, Swiss Medical Weekly, 2018; 148: w14524.
18. Irreversible cessation of circulatory and respiratory function	Reich, Mulligan, Abt et al, ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. American Journal of Transplantation, 2009; 9: 2004-11.

3. International Legislation

Definitions of Death	Reference
19. The irreversible cessation of circulatory or brain functions	Argentina: Organ, Tissue and Cell Transplant Act, 2018
20. Brain death, a complete and irreversible cessation of the brain's vital activity, which is recorded in the condition of ventricular heart and lung ventilation. The death of the brain is equivalent to the death of a human being.	Armenia: Law of the Republic of Armenia About Organ Transplantation and (or) Tissues of the Person, 2002
21. A person has died when there has occurred (a) irreversible cessation of all function of the brain of the person; or (b) irreversible cessation of circulation of blood in the body of the person	Australia: Transplantation and Anatomy Act, 1979 Human Tissue Act, 1982, 1983, 1985

Definitions of Death	Reference
	Death (Definition) Act, 1983
22. The complete and irreversible loss of brain functions, as defined by cessation of cortical and brainstem activities, characterizes brain death and death of the person	Brazil: Resolution of the Federal Council of Medicine, 2017
23. When all functions of the brain have stopped irreversibly and active heart function, death shall be detected	Bulgaria: Law on Transplantation of Organs, Tissues and Cells, 2007
24. Brain death shall be granted where the total and irreversible abolition of all brain functions has been verified	Chile: Regulation Establishing the Norms on Transplantation and Organ Donation under Law, 1996
25. Irreversible cessation of circulatory and respiratory functions, irreversible cessation of functions of the entire brain, including those of the brainstem • Brain death: irreversible cessation of the functions of all neurological structures located above the foramen magnum (brainstem and cerebral cortex)	Costa Rica: Regulation to the Law on Donation and Transplantation of Human Organs and Tissues Law, 2016
26. Complete and irreversible cessation of brain circulation has occurred or irreversible cessation of the function of the cerebrum, the cerebellum and the brain stem	Croatia: Ordinance on the Method, Procedure and Medical Criteria for Determining the Death of a Person Whose Body Parts May be Taken for Transplantation, 2005
27. The irreversible loss of function of the entire brain, including the brain stem, or irreversible collateral blood circulation	Czech Republic: Law for a Donation, Subscription and Transplantation of Tissues and Organs and Amending Some Laws (The Transplant Law), 2002
28. Irreparable cessation of breathing and heart activity or by irreversible cessation of all brain function	Denmark: The Health Act, 2005
29. Complete and irreversible cessation of the brain function	Estonia: Regulation on the conditions and procedure for the establishment of death of a person and the standard format for statements on the establishment of death, 2015
30. A person is considered to be dead when brain function has totally ceased	Finland: Act on the Medical Use of Human Organs, Tissues and Cells, 2001
31. If the person has persistent cardiac and respiratory arrest, the death can only be established if the following three clinical criteria are simultaneously present: (1) total absence of consciousness and spontaneous motor activity; (2) abolition of all brainstem reflexes; (3) total absence of spontaneous ventilation	France: Decree on the Determination of Death Prior to the Removal of Organs, Tissues, and Cells for Therapeutic or Scientific Purposes, and Amending the Public Health Code, 1996
32. The final, unrecoverable failure of the overall function of the cerebrum, the cerebellum and the brainstem	Germany: Law on The Donation, Removal and Transfer of Organs and Tissues, 2007

Definitions of Death	Reference
33. *Death:* beginning of irreversible autolysis of the organism due to entire cessation of respiration, circulation and brain functions • *Brain death:* entire, permanent, and irreversible cessation of functions of the brain, including the brain stem	Hungary: Organ and Tissue Transplantation, 1997
34. The stage at which all functions of the brain stem have permanently and irreversibly ceased Permanent disappearance of all evidence of life occurs, by reason of brain-stem death or in a cardiopulmonary sense, at any time after live birth has taken place	India: The Transplantation of Human Organs Act, 1994
35. A person's brain, breathing, and/or heart function has stopped	Indonesia: Clinical Surgery and Anatomic Surgery and Surgery Transplantation of Human Body or Network, 1981
36. The time of death shall be the time at which cerebral-respiratory or cardiac-respiratory death is determined under the provisions of this Act	Israel: Cerebro-Respiratory Death Act, 2008
37. The irreversible cessation of all brain functions	Italy: Rules for ascertaining and certifying death, 1993
38. A person who is judged to have irreversibly stopped functioning of the whole brain including the brainstem	Japan: Act on transplantation or organs, 1997
39. Irreversible interruption of human blood flow and respiration or brain death Death is the time when a person's blood flow and breathing are irreversibly interrupted or when all structures of the human brain are permanently disrupted Death is the irreversible death of the human body as a whole An irreversible outcome of all brain structures, although some which human organs and organ systems are still working	Lithuania: Law on the Determination of Human Death and Critical Condition of the Republic of Lithuania, 1997 On Criteria for the Death of Degree and they Amendment of the Determination Procedure, 2015
40. The loss of life occurs when death occurs encephalic or irreversible cardiac arrest	Mexico: General Law of Health, 1984
41. A person dies when there are certain signs of total destruction of the brain with a complete and irreversible cessation of all functions in the cerebrum, cerebellum and brain stem. Permanent cardiac and respiratory arrest are sure signs of total brain damage.	Norway: Regulations on the Definition of Death by Donation of Organs, Cells and Tissues, 2015
42. The state of the brain determines the life or death of a human being…brain death is based on the finding of irreversible lack of function the brain	Poland: Notice on Criteria and How to Establish a Permanent Irreversible Cessation of Brain Activities, 2007

Definitions of Death	Reference
43. Irreversible cessation of the heart and respiratory system, or irreversible cessation of all functions of the brain	Qatar: Human Organs Transplants Law, 1997
44. The moment of death of a person is the moment of death of his brain or his biological death (irreversible death of a person). • Brain death occurs with the complete and irreversible cessation of all its functions, registered with a working heart and mechanical ventilation	Russia: Law on the Basis of the Protection of Public Health in the Russian Federation, 2011
45. Irreversible cessation of circulation of blood and respiration in the body of the person; or total and irreversible cessation of all functions of the brain of the person	Singapore: Interpretation Act,2002
46. Persistent cessation of breathing and cardiac activity in the person, who was brought dead or after failed resuscitation	Slovakia: Professional guidance on donation, donations of human organs from the bodies of living and dead donors, on donor testing and the transfer of human organs to the recipient, Ministry of Health of the Slovak Republic, 2007
47. Death means brain death	South Africa: National Health Act, 2003
48. The brain is diagnosed as having irreversibly and completely ceased to function	South Korea: Internal Organs, Transplant Act, 2013
49. The irreversible cessation of the circulatory and respiratory functions or the brain functions	Spain: Royal Decree 1723 (related to organs destined for transplantation), 2012
50. The death of a person occurs when an irreversible cessation of all functions of the brain of such person has occurred. The irreversible cessation of the functions of the brain may be determined by the prolonged absence of spontaneous circulatory and respiratory functions. When the determination of the prolonged absence of spontaneous circulatory and respiratory functions is made impossible by the use of artificial means of support, the irreversible cessation of brain functions shall be determined.	Sri Lanka: Transplantation of Human Tissues Act, 1987
51. A person is dead when all the functions of the brain have completely and irreversibly fallen away	Sweden: Law on Criteria for Determining Human Death, 1987
52. A person is dead if the functions of his or her brain, including the brain stem, have ceased irreversibly	Switzerland: Federal Act on the Transplantation of Organs, Tissues and Cells (Transplantation Act), 2004
53. A person is considered dead when there has occurred (a) irreversible cessation of all functions of the brain stem of that person; or (b) irreversible cessation of circulation of blood in the body of that person	Trinidad and Tobago: Human Tissue Transplant Act, 2000

Definitions of Death	Reference
54. Irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem	United States: Adopted from Uniform Determination of Death Act (approved 1981) into State Law (except Arizona, Idaho, Washington, Puerto Rico)
55. Absolute and irreversible loss of all functions encephalic and brainstem	Venezuela: Law on Donation and Organ Transplantation, Tissues and Cells in Human Beings
56. Brain death is the state when the whole brain is severely damaged, the brain stops functioning and the brain-dead person cannot be revived	Vietnam: Law on Donation, Removal and Transplantation of Human Tissues and Organs and Donation and Recovery of Cadavers, 2006

eAppendix 4 Search strategies

Search Methods – Death Determination by Circulatory Criteria and Death Determination by Neurologic Criteria: Robin Featherstone (RF), an information specialist and health librarian experienced in the conduct of literature searches for systematic reviews, designed, executed, and prepared search results for primary screening for 12 literature reviews for the Circulatory and Neurological Death Determination working groups. A second information specialist, Dagmara Chojecki, peer reviewed all strategies according to the PRESS Peer Review of Electronic Search Strategies 2015 Guideline Statement[1]. Where applicable, RF applied search filters to remove animal studies and limited results to references published in English or French.

Between April 18, 2021, and August 21, 2021, RF searched the following databases:
- MEDLINE Ovid (1946 to present)
- Embase Ovid (1947 to present)
- Cochrane Central Register of Controlled Trials (CENTRAL; inception to present) via EBM Reviews Ovid
- Science Citation Index Expanded via Web of Science (1900 to present)

Conference proceedings were retrieved by the Embase search, and trial registry records from ClinicalTrials.gov and the World Health Organization International Clinical Trial Registry Platform (ICTRP) were retrieved by the CENTRAL search.

Search Methods – Ancillary Investigation: The search strategy for a systematic review of ancillary testing in the neurological determination of death was designed and executed by Risa Shorr in May 2019 and peer reviewed according to the PRESS Peer guidelines. The ancillary testing systematic review search was updated by Daniela Ziegler (DZ) in April 2020. The original search methods and April 2020 update results are published separately[2]. For the Ancillary Testing working group, DZ and RF updated the search on September 18, 2021, and RF updated the search on February 5, 2022. These update searches were conducted in the databases above (excluding Science Citation Index), and in CINAHL Ebsco (1981 to present).

For a literature review of pediatric patients, RF modified the ancillary testing systematic review search by adding a pediatrics concept. RF executed the pediatrics ancillary testing search on June 26, 2021min the databases reported above for the 12 reviews conducted for the Circulatory and Neurological Death Determination working group. RF applied search filters to remove animal studies and case reports, and limited results to references published in English or French.

Search Methods – All Groups: RF exported results to EndNote X9 (Clarivate Analytics), removed duplicate records, and submitted references collections for the 14 literature review in RIS format for screening in Covidence.

[1] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. Journal of clinical epidemiology. 2016 Jul 1;75:40-6.
[2] Chassé M, Glen P, Doyle MA, McIntyre L, English SW, Knoll G, Lizé JF, Shemie SD, Martin C, Turgeon AF, Lauzier F. Ancillary testing for diagnosis of brain death: a protocol for a systematic review and meta-analysis. Systematic reviews. 2013 Dec;2(1):1-8.

Death Determination by Circulatory Criteria

Review question: *In all patients who are potential organ donors undergoing death determination by circulatory criteria, should alternate means of measuring circulation (palpable pulse, ECG, point of care echocardiography, doppler, auscultation, pulse oximeter, tissue perfusion measurement) vs continuous arterial line monitoring be used for confirmation of cessation of circulation?*

Notes: Results were screened in stages by date of publication.

Results of the search: The search retrieved a total of 8124 references and 5136 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique): all dates*	Results (unique): 1948-2004	Results (unique): 2005-2021
MEDLINE	2977	2972	1008	1964
Embase	3357	1426	240	1186
CENTRAL	545	309	43	266
Web of Science	1245	429	137	292
Total:	**8124**	**5136**	**1428**	**3708**

* 49 pre-2018 conference proceedings removed manually from EndNote

Database: Ovid MEDLINE(R) ALL 1946 to April 26, 2021
Date search conducted: April 27, 2021
Strategy:

1 exp *Heart Arrest/ (36249)
2 ((arrest$1 or dead or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw,kf. (95494)
3 asystol*.tw,kf. (4407)
4 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw,kf. (237)
5 ((cessation or terminat*) adj3 cardi* resuscitation).tw,kf. (43)
6 or/1-5 [Set 1: cardiac arrest or circulatory death] (107656)
7 Monitoring, Physiologic/ (56086)
8 "Sensitivity and Specificity"/ (353899)
9 Vital Signs/ (1516)
10 detect*.tw,kf. (2454927)
11 measurement*.ti. (188631)
12 measurement*.ab. /freq=2 (262819)
13 monitor*.tw,kf. (852063)
14 vital sign$1.tw,kf. (15764)
15 or/7-14 [Set 2: vital signs monitoring] (3653026)
16 Arterial Pressure/ (6045)
17 Blood Pressure/ph [Physiology] (53044)
18 Blood Pressure Determination/ (28681)
19 ABP*.tw,kf. (10939)
20 ((arter* or aortic) adj3 (pressure$1 or tension$1)).tw,kf. (123551)
21 arterial line$1.tw,kf. (1451)
22 or/16-21 [Set 3: arterial line] (197650)
23 exp Auscultation/ (9235)
24 *Echocardiography/ (29695)
25 exp Echocardiography, Doppler/ (28957)
26 *Electrocardiography/ (67040)
27 Oximetry/ (13386)

28 Palpation/ (7710)
29 Perfusion Index/ (30)
30 Pulse/ (17022)
31 (absen* adj2 (breath sound$1 or breathing or heart sound$1 or pulse)).tw,kf. (366)
32 auscultat*.tw,kf. (6697)
33 (echo-cardiogra* or echocardiogra*).ti. (46775)
34 (echo-cardiogra* or echocardiogra*).ab. /freq=2 (53417)
35 (ECG* or EKG* or electro-cardiogra* or electrocardiogra*).ti. (44596)
36 (ECG* or EKG* or electro-cardiogra* or electrocardiogra*).ab. /freq=2 (47641)
37 (oximet* adj3 pulse).tw,kf. (9142)
38 (palpa* adj3 pulse).tw,kf. (572)
39 palpat*.tw,kf. (15554)
40 (perfusion adj2 (measur* or index)).tw,kf. (4831)
41 or/23-40 [Set 4: alternate means of measuring circulation] (269889)
42 and/6,15,22 [Sets 1 and 2 and 3] (739)
43 and/6,15,41 [Sets 1 and 2 and 4] (2710)
44 42 or 43 (3326)
45 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4819180)
46 ((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2178262)
47 45 or 46 (5186992)
48 44 not 47 [exclude animal studies] (2980)
49 remove duplicates from 48 [MEDLINE results for export] (2977)

Database: Ovid Embase Classic+Embase 1947 to April 26
Date search conducted: April 27, 2021
Strategy:
1 exp *heart arrest/ (40552)
2 ((arrest$1 or dead or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw,kw. (159504)
3 asystol*.tw,kw. (7840)
4 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw,kw. (375)
5 ((cessation or terminat*) adj3 cardi* resuscitation).tw,kw. (64)
6 or/1-5 [Set 1: cardiac arrest or circulatory death] (170024)
7 physiologic monitoring/ (5787)
8 "sensitivity and specificity"/ (393851)
9 vital sign/ (26094)
10 detect*.tw,kw. (3258606)
11 monitor*.tw,kw. (1204958)
12 vital sign$1.tw,kw. (31899)
13 or/7-12 [Set 2: vital signs monitoring] (4472611)
14 exp *arterial pressure/ (13354)
15 blood pressure monitoring/ (50751)
16 ABP*.tw,kw. (18788)
17 ((arter* or aortic) adj3 (pressure$1 or tension$1)).tw,kw. (183809)
18 arterial line$1.tw,kw. (2796)
19 or/14-18 [Set 3: arterial line] (244869)
20 exp auscultation/ (19395)
21 exp Doppler echocardiography/ (29685)
22 *echocardiography/ (43444)

23 *electrocardiography/ (50717)
24 palpation/ (21787)
25 perfusion index/ (265)
26 pulse oximetry/ (16729)
27 *pulse rate/ (6322)
28 (absen* adj2 (breath sound$1 or breathing or heart sound$1 or pulse)).tw,kw. (815)
29 auscultat*.tw,kw. (11523)
30 (echo-cardiogra* or echocardiogra*).ti. (69029)
31 (echo-cardiogra* or echocardiogra*).ab. /freq=2 (97131)
32 (ECG* or EKG* or electro-cardiogra* or electrocardiogra*).ti. (57837)
33 (ECG* or EKG* or electro-cardiogra* or electrocardiogra*).ab. /freq=2 (84302)
34 (oximet* adj3 pulse).tw,kw. (13752)
35 (palpa* adj3 pulse).tw,kw. (1051)
36 palpat*.tw,kw. (26892)
37 (perfusion adj2 (measur* or index)).tw,kw. (7017)
38 or/20-37 [Set 4: alternate means of measuring circulation] (378053)
39 and/6,13,19 [Sets 1 and 2 and 3] (1321)
40 and/6,13,38 [Sets 1 and 2 and 4] (4426)
41 39 or 40 (5522)
42 (exp animals/ or exp animal experiment/ or exp animal experimentation/ or exp models animal/ or nonhuman/ or exp vertebrate/ or exp vertebrates/) not (exp humans/ or exp human experiment/ or exp human experimentation/) (7555078)
43 ((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2590176)
44 42 or 43 (7833758)
45 41 not 44 [exclude animal studies] (4993)
46 (Conference Abstract or Conference Paper or Conference Review).pt. (4874389)
47 45 and 46 (2242)
48 limit 47 to yr="2018-2021" (689)
49 45 not 46 [exclude conference proceedings] (2751)
50 48 or 49 [add proceedings from last 3 yrs] (3440)
51 remove duplicates from 50 [Embase results for export] (3357)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials March 2021
Date search conducted: April 27, 2021
Strategy:
1 exp Heart Arrest/ (1998)
2 ((arrest$1 or dead or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw. (14791)
3 asystol*.tw. (312)
4 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw. (16)
5 ((cessation or terminat*) adj3 cardi* resuscitation).tw. (0)
6 or/1-5 [Set 1: cardiac arrest or circulatory death] (15477)
7 Monitoring, Physiologic/ (2256)
8 "Sensitivity and Specificity"/ (9350)
9 Vital Signs/ (98)
10 detect*.tw. (93291)
11 measurement*.tw. (130467)
12 monitor*.tw. (91508)
13 vital sign$1.tw. (15003)
14 or/7-13 [Set 2: vital signs monitoring] (299199)

15 Arterial Pressure/ (443)
16 Blood Pressure/ph [Physiology] (0)
17 Blood Pressure Determination/ (1123)
18 ABP*.tw. (2112)
19 ((arter* or aortic) adj3 (pressure$1 or tension$1)).tw. (20487)
20 arterial line$1.tw. (495)
21 or/15-20 [Set 3: arterial line] (23778)
22 exp Auscultation/ (174)
23 Echocardiography/ (2771)
24 exp Echocardiography, Doppler/ (1127)
25 Electrocardiography/ (7746)
26 Oximetry/ (824)
27 Palpation/ (354)
28 Perfusion Index/ (1)
29 Pulse/ (1425)
30 (absen* adj2 (breath sound$1 or breathing or heart sound$1 or pulse)).tw. (72)
31 auscultat*.tw. (858)
32 (echo-cardiogra* or echocardiogra*).ti. (2253)
33 (echo-cardiogra* or echocardiogra*).ab. /freq=2 (4442)
34 (ECG* or EKG* or electro-cardiogra* or electrocardiogra*).ti. (1957)
35 (ECG* or EKG* or electro-cardiogra* or electrocardiogra*).ab. /freq=2 (8134)
36 (oximet* adj3 pulse).tw. (3449)
37 (palpa* adj3 pulse).tw. (112)
38 palpat*.tw. (2343)
39 (perfusion adj2 (measur* or index)).tw. (789)
40 or/22-39 [Set 4: alternate means of measuring circulation] (30672)
41 and/6,14,21 [Sets 1 and 2 and 3] (152)
42 and/6,14,40 [Sets 1 and 2 and 4] (436)
43 41 or 42 (550)
44 remove duplicates from 43 [CENTRAL results for export] (545)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: April 27, 2021
Strategy:

# 9	**1,245**	#7 NOT #8 *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**2,767,504**	TI=((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin * or mouse or mice or nonhuman* or "non human*" or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep) not (adults or children or human or humans or infants or patient or patients or people or seniors)) *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**1,414**	#6 OR #5 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**886**	#4 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**555**	#3 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*

# 4	**130,485**	TS=((absen* NEAR/2 ("breath sound*" or breathing or "heart sound*" or pulse)) or auscultat* or (oximet* NEAR/3 pulse) or (palpa* NEAR/3 pulse) or palpat* or (perfusion NEAR/2 (measur* or index))) or TI=("echo cardiogra*" or echocardiogra* or ECG* or EKG* or "electro cardiogra *" or electrocardiogra*) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**98,128**	TS=(((arter* or aortic) NEAR/3 (pressur* or tension*)) or "arterial line*") *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**4,613,668**	TS=(detect* or monitor* or "vital sign*") or TI=measurement* *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**111,910**	TS=(((arrest* or dead or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart)) or asystol* or (cessation NEAR/5 ("cardiac rhythm*" or circulat* or "heart function*")) or ((cessation or terminat*) NEAR/3 "cardi* resuscitation")) *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In all patients who are potential organ donors undergoing death determination by circulatory criteria, should a pulseless arterial pressure of more than 0 mmHg (i.e. 5, 10, 20, 40) vs a pulseless arterial pressure of 0 mmHg be used for confirmation of cessation of circulation?*

Note: Baseline search conducted April 18, 2021; update search conducted August 21, 2021. Results were screened in stages, with animal studies screened separately.

Results of the search: The baseline search retrieved a total of 6488 references (4731 human studies and 1757 animal studies) and 4118 unique references (3140 human studies and 978 animal studies) (duplicates removed). The update search retrieved a total of 6654 reference (4838 human studies and 1816 animal studies), and 188 unique references (149 human studies and 39 animal studies) after duplicates and previously screened records were removed. The update search combined with the baseline search retrieved a total of 4306 unique references for primary screening (3289 human studies and 1017 animal studies).

Search summary:

Source	**Results (w. duplicates) – Human studies**	**Results (unique) – Human studies**	**Results (w. duplicates) – Animal studies**	**Results (unique) – Animal studies**
MEDLINE	1108	1090	517	399
Embase	2288	1485	900	443
CENTRAL	258	116	1	0
Web of Science	1077	449	339	136
Total:	**4731**	**3140***	**1757**	**978**

*51 animal studies were identified in EndNote and moved to the other set of results during duplicate removal.

Update search summary:

Source	**Results (w. duplicates) – Human studies**	**Results (unique) – Human studies**	**Results (w. duplicates) – Animal studies**	**Results (unique) – Animal studies**
MEDLINE	1122	25	548	9
Embase	2341	97	923	28
CENTRAL	268	9	1	0
Web of Science	1107	18	344	2
Total:	**4838**	**149***	**1816**	**39**

*3 animal studies were identified in EndNote and moved to the other set of results during duplicate removal

Database: Ovid MEDLINE(R) ALL 1946 to August 20, 2021

Date update search conducted: August 21, 2021

Strategy:

1 Death/ and Blood Circulation/ (55)
2 exp *Heart Arrest/ (37450)
3 ((arrest$1 or dead or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw,kf. (97902)
4 asystol*.tw,kf. (4486)
5 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw,kf. (240)
6 ((cessation or terminat*) adj3 cardi* resuscitation).tw,kf. (43)
7 or/1-6 [Set 1: cardiac arrest or circulatory death] (110258)
8 Organ Transplantation/mo (332)
9 (cDCD or DCD or DCDD).ti. (343)
10 dead donor rule*.tw,kf. (162)
11 ((donor* or donation*) adj3 non heart beating).tw,kf. (1173)
12 or/8-11 [Set 2: Donation after cardiac death] (1986)
13 (auto-resuscitat* or autoresuscitat*).tw,kf. (169)
14 Lazarus.ti. (165)

15 Lazarus phenomenon.tw,kf. (46)
16 "return of circulation".tw,kf. (172)
17 or/13-16 [Set 3: autoresuscitation] (491)
18 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kf. [Set 4: death determination] (10010)
19 Monitoring, Physiologic/ (56768)
20 "Sensitivity and Specificity"/ (357677)
21 Vital Signs/ (1625)
22 detect*.tw,kf. (2503759)
23 measurement*.ti. (191131)
24 measurement*.ab. /freq=2 (268116)
25 (mm Hg or mmHg).tw,kf. (157525)
26 monitor*.tw,kf. (872900)
27 vital sign$1.tw,kf. (16299)
28 or/19-27 [Set 5: vital signs monitoring] (3847486)
29 Arterial Pressure/ (6272)
30 Blood Pressure/ph [Physiology] (53572)
31 Blood Pressure Determination/ (28923)
32 ((arter* or aortic) adj3 (pressure$1 or tension$1)).tw,kf. (124788)
33 arterial line$1.tw,kf. (1470)
34 or/29-33 [Set 6: arterial pressure] (191067)
35 and/7,28,34 [Sets 1 and 5 and 6] (1593)
36 and/12,28,34 [Sets 2 and 5 and 6] (15)
37 and/17,28,34 [Sets 3 and 5 and 6] (14)
38 18 and 34 [Sets 4 and 6] (80)
39 or/35-38 (1671)
40 remove duplicates from 39 [MEDLINE results with animal studies] (1670)
41 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4878956)
42 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2283101)
43 41 or 42 [animal filter] (5261835)
44 40 not 43 [MEDLINE results for export - exclude animal studies] (1122)
45 40 not 44 [MEDLINE results for export - animal studies] (548)

Database: Ovid Embase Classic+Embase 1947 to 2021 August 19
Date update search conducted: August 21, 2021
Strategy:
1 exp *heart arrest/ (41073)
2 heart death/ (29574)
3 ((arrest$1 or dead or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw,kw. (161467)
4 asystol*.tw,kw. (7893)
5 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw,kw. (373)
6 ((cessation or terminat*) adj3 cardi* resuscitation).tw,kw. (64)
7 or/1-6 [Set 1: cardiac arrest or circulatory death] (180914)
8 (cDCD or DCD or DCDD).ti. (1202)
9 dead donor rule*.tw,kw. (177)
10 ((donor* or donation*) adj3 non heart beating).tw,kw. (1639)
11 or/8-10 [Set 2: Donation after cardiac death] (2983)
12 autoresuscitation/ (31)

13 (auto-resuscitat* or autoresuscitat*).tw,kw. (228)
14 Lazarus.ti. (176)
15 Lazarus phenomenon.tw,kw. (63)
16 "return of circulation".tw,kw. (345)
17 or/12-16 [Set 3: autoresuscitation] (738)
18 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kw. [Set 4: death determination] (16151)
19 physiologic monitoring/ (6008)
20 "sensitivity and specificity"/ (402938)
21 vital sign/ (26747)
22 detect*.tw,kw. (3277546)
23 measurement*.ti. (223007)
24 measurement*.ab. /freq=2 (350193)
25 (mm Hg or mmHg).tw,kw. (250300)
26 monitor*.tw,kw. (1218007)
27 vital sign$1.tw,kw. (32621)
28 or/19-27 [Set 5: vital signs monitoring] (5070322)
29 exp arterial pressure/ (138196)
30 blood pressure monitoring/ (51415)
31 ((arter* or aortic) adj3 (pressure$1 or tension$1)).tw,kw. (182458)
32 arterial line$1.tw,kw. (2798)
33 or/29-32 [Set 6: arterial pressure] (273337)
34 and/7,28,33 [Sets 1 and 5 and 6] (3126)
35 and/11,28,33 [Sets 2 and 5 and 6] (41)
36 and/17,28,33 [Sets 3 and 5 and 6] (33)
37 18 and 33 [Sets 4 and 6] (183)
38 or/34-37 (3304)
39 remove duplicates from 38 [Embase results with animal studies] (3264)
40 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5936616)
41 ((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2582689)
42 40 or 41 [animal filter] (6281919)
43 39 not 42 [Embase results for export - exclude animal studies] (2341)
44 39 not 43 [Embase results for export - animal studies] (923)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials July 2021
Date update search conducted: August 21, 2021
Strategy:
1 Death/ and Blood Circulation/ (0)
2 exp Heart Arrest/ (2050)
3 ((arrest$1 or dead or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw. (15163)
4 asystol*.tw. (317)
5 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw. (16)
6 ((cessation or terminat*) adj3 cardi* resuscitation).tw. (1)
7 or/1-6 [Set 1: cardiac arrest or circulatory death] (15855)
8 Organ Transplantation/mo (0)
9 (cDCD or DCD or DCDD).ti. (54)
10 dead donor rule*.tw. (0)
11 ((donor* or donation*) adj3 non heart beating).tw. (39)

12 or/8-11 [Set 2: Donation after cardiac death] (93)
13 (auto-resuscitat* or autoresuscitat*).tw. (1)
14 Lazarus.ti. (10)
15 Lazarus phenomenon.tw. (0)
16 "return of circulation".tw. (32)
17 or/13-16 [Set 3: autoresuscitation] (43)
18 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw. [Set 4: death determination] (1100)
19 Monitoring, Physiologic/ (2278)
20 "Sensitivity and Specificity"/ (9381)
21 Vital Signs/ (105)
22 detect*.tw. (95669)
23 measurement*.ti. (6375)
24 measurement*.ab. /freq=2 (45677)
25 (mm Hg or mmHg).tw. (37498)
26 monitor*.tw. (94016)
27 vital sign$1.tw. (15573)
28 or/19-27 [Set 5: vital signs monitoring] (266292)
29 Arterial Pressure/ (458)
30 Blood Pressure/ph [Physiology] (0)
31 Blood Pressure Determination/ (1140)
32 ((arter* or aortic) adj3 (pressure$1 or tension$1)).tw. (20894)
33 arterial line$1.tw. (502)
34 or/29-33 [Set 6: arterial pressure] (22358)
35 and/7,28,34 [Sets 1 and 5 and 6] (262)
36 and/12,28,34 [Sets 2 and 5 and 6] (0)
37 and/17,28,34 [Sets 3 and 5 and 6] (0)
38 18 and 34 [Sets 4 and 6] (22)
39 or/35-38 (281)
40 remove duplicates from 39 [CENTRAL results with animal studies] (269)
41 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (16)
42 ((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or mouse or mice or nonhuman* or non human* or pig or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or sheep) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (5031)
43 41 or 42 [animal filter] (5047)
44 40 not 43 [CENTRAL results for export - exclude animal studies] (268)
45 40 not 44 [CENTRAL results for export - animal studies] (1)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present ; Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
Date update search conducted: August 21, 2021
Strategy:

# 14	**344**	#11 NOT #13 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 13	**1,107**	#11 NOT #12 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 12	**2,837,919**	TI=((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapi

		n* or mouse or mice or nonhuman* or "non human*" or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rod ent* or swine* or sheep) not (adults or children or human or humans or infants or patient or patients or people or seniors)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 11	**1,451**	#10 OR #9 OR #8 OR #7 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 10	**90**	#6 AND #4 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 9	**10**	#6 AND #5 AND #3 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 8	**9**	#6 AND #5 AND #2 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 7	**1,369**	#6 AND #5 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 6	**101,756**	TS=(((arter* or aortic) NEAR/3 (pressur* or tension*)) or "arterial line*") *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 5	**5,687,660**	TS=(detect* or "mm Hg" or mmHg or monitor* or "vital sign*") or TI=(measurement*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 4	**13,128**	TS=((confirm* or criteri* or declar* or determin* or diagnos*) NEAR/2 death*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 3	**561**	TS=("auto resuscitat*" or autoresuscitat* or "Lazarus phenomenon" or "return of circulati on") or TI=(Lazarus) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 2	**2,834**	TS=("dead donor rule*" or ((donor* or donation*) NEAR/3 "non heart beating")) or TI=(cDCD or DCD or DCDD) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 1	**116,179**	TS=(((arrest* or dead or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart)) or asystol* or (cessation NEAR/5 ("cardiac rhythm*" or circulat* or "heart function*")) or ((cessation or terminat*) NEAR/3 "cardi* resuscitation")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

Review question: *In all patients who are potential organ donors undergoing death determination by circulatory criteria, should a shorter or longer period of hands-off time vs a 5 min hands-off time be used for confirmation of cessation of circulation?*

Note: Baseline search conducted May 28, 2021; update search conducted August 28, 2021.

Results of the search: The baseline search retrieved a total of 5988 references and 3651 unique references (duplicates removed). The update search retrieved a total of 6120 references and 90 unique references after duplicates and previously screened records were removed. The update search combined with the baseline search retrieved a total of 3741 unique references for primary screening.

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	1504	3651
Embase	2133	843
CENTRAL	415	279*
Web of Science	1936	1047
Total:	**5988**	**3651**

* 75 pre-2018 conference proceedings removed manually from EndNote

Update search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	1531	35
Embase	2183	19
CENTRAL	422	7
Web of Science	1984	29
Total:	**6120**	**90**

Database: Ovid MEDLINE(R) ALL 1946 to August 27, 2021
Date search conducted: August 28, 2021
Strategy:
1 Death/ and Blood Circulation/ (55)
2 Death/ and exp Heart Arrest/ (388)
3 (((arrest$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)) and (dead or death$1)).tw,kf. (10363)
4 ((dead or death$1) adj2 (cardi* or circulat* or heart)).tw,kf. (50272)
5 asystol*.tw,kf. (4494)
6 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw,kf. (240)
7 ((cessation or terminat*) adj3 cardi* resuscitation).tw,kf. (43)
8 or/1-7 [Set 1: cardiac death] (62288)
9 Donor Selection/ (3551)
10 exp Organ Transplantation/ (220173)
11 "Tissue and Organ Harvesting"/ (9490)
12 exp "Tissue and Organ Procurement"/ (22407)
13 exp Tissue Transplantation/ (194018)
14 exp Tissue Donors/ (77186)
15 (allocat* adj2 (organ$1 or tissue*)).tw,kf. (1784)
16 ((body or organ$1 or tissue*) adj2 (donor* or donation*)).tw,kf. (20853)
17 ((cardiac or heart$1 or heart-lung or hepatic or intestin$ or kidney$1 or kidney-pancreas or liver$1 or lung$1 or lung-heart or multiorgan or organ$1 or pancreas or renal or thoracic or tissue$1) adj2 transplant*).tw,kf. (234761)
18 (cDCD or DCD or DCDD).ti. (345)
19 dead donor rule*.tw,kf. (162)

20 deceased donor*.tw,kf. (6666)
21 "donation after circulatory death".tw,kf. (946)
22 ((donor* or donation*) adj3 non heart beating).tw,kf. (1173)
23 (donor adj2 (exclu* or select* or screen*)).tw,kf. (4684)
24 (organ$1 adj2 (harvest* or procur* or retriev* or scarc*)).tw,kf. (5973)
25 (tissue adj2 (harvest* or procur* or retriev*)).tw,kf. (3541)
26 or/9-25 [Set 2: Organ donation] (476087)
27 (auto-resuscitat* or autoresuscitat*).tw,kf. (169)
28 Lazarus.ti. (165)
29 Lazarus phenomen*.tw,kf. (48)
30 Lazarus syndrome*.tw,kf. (20)
31 (("return of" or recover* or restor* or resum*) adj2 (cardiac activity or circulation)).ti. (97)
32 or/27-31 [Set 3: autoresuscitation] (427)
33 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kf. [Set 4: death determination] (10028)
34 *Time Factors/ (3017)
35 ("5 minute" or "5 minutes" or "5 min" or "5 mins" or five min*).tw,kf. (91753)
36 delay*.ti. (78230)
37 delay*.ab. /freq=2 (117261)
38 hands off tim*.tw,kf. (120)
39 "how long".tw,kf. (7340)
40 (min or mins or minute$1).ti. (11955)
41 (min or mins or minute$1).ab. /freq=2 (424344)
42 ((observ* or wait*) adj3 (period$1 or tim*)).tw,kf. (103509)
43 (time or timing$1).ti. (290834)
44 time point$1.tw,kf. (127558)
45 or/34-44 [Set 5: time factors] (1103701)
46 and/8,26,45 [Sets 1 and 2 and 5] (932)
47 33 and 45 [Sets 4 and 5] (654)
48 or/32,46-47 (1913)
49 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4881364)
50 ((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2202025)
51 49 or 50 [animal filter] (5251161)
52 48 not 51 [exclude animal studies] (1534)
53 remove duplicates from 52 [MEDLINE results for export] (1531)

Database: Ovid Embase Classic+Embase 1947 to 2021 August 27
Date update search conducted: August 28, 2021
Strategy:
1 heart death/ (29614)
2 (((arrest$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)) and (dead or death$1)).tw,kw. (18876)
3 ((dead or death$1) adj2 (cardi* or circulat* or heart)).tw,kw. (86468)
4 asystol*.tw,kw. (7898)
5 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw,kw. (373)
6 ((cessation or terminat*) adj3 cardi* resuscitation).tw,kw. (64)
7 or/1-6 [Set 1: cardiac death] (116278)
8 deceased donor/ (4317)
9 donor selection/ (6338)

10 non heart beating donor/ (924)
11 exp organ transplantation/ (428590)
12 exp tissue transplantation/ (560385)
13 (allocat* adj2 (organ$1 or tissue*)).tw,kw. (3080)
14 ((body or organ$1 or tissue*) adj2 (donor* or donation*)).tw,kw. (31850)
15 ((cardiac or heart$1 or heart-lung or hepatic or intestin$ or kidney$1 or kidney-pancreas or liver$1 or lung$1 or lung-heart or multiorgan or organ$1 or pancreas or renal or thoracic or tissue$1) adj2 transplant*).tw,kw. (378229)
16 (cDCD or DCD or DCDD).ti. (1205)
17 dead donor rule*.tw,kw. (177)
18 deceased donor*.tw,kw. (15424)
19 "donation after circulatory death".tw,kw. (1642)
20 ((donor* or donation*) adj3 non heart beating).tw,kw. (1639)
21 (donor adj2 (exclu* or select* or screen*)).tw,kw. (8779)
22 (organ$1 adj2 (harvest* or procur* or retriev* or scarc*)).tw,kw. (9625)
23 (organ$1 adj2 (harvest* or procur* or retriev* or scarc*)).tw,kw. (9625)
24 (tissue adj2 (harvest* or procur* or retriev*)).tw,kw. (6132)
25 or/8-24 [Set 2: organ donation] (1050829)
26 autoresuscitation/ (31)
27 (auto-resuscitat* or autoresuscitat*).tw,kw. (229)
28 Lazarus.ti. (176)
29 Lazarus phenomen*.tw,kw. (65)
30 Lazarus syndrome*.tw,kw. (24)
31 (("return of" or recover* or restor* or resum*) adj2 (cardiac activity or circulation)).ti. (103)
32 or/26-31 [Set 3: autoresuscitation] (509)
33 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kw. [Set 4: death determination] (16163)
34 *time factor/ (1401)
35 ("5 minute" or "5 minutes" or "5 min" or "5 mins" or five min*).tw,kw. (133074)
36 delay*.ti. (97886)
37 delay*.ab. /freq=2 (170163)
38 hands off tim*.tw,kw. (211)
39 "how long".tw,kw. (10649)
40 (min or mins or minute$1).ti. (15267)
41 (min or mins or minute$1).ab. /freq=2 (634806)
42 ((observ* or wait*) adj3 (period$1 or tim*)).tw,kw. (158339)
43 (time or timing$1).ti. (348621)
44 time point$1.tw,kw. (203433)
45 or/34-44 [Set 5: time factors] (1551907)
46 and/7,25,45 [Sets 1 and 2 and 5] (2501)
47 33 and 45 [Sets 4 and 5] (1241)
48 or/32,46-47 (4037)
49 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5942339)
50 ((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2584704)
51 49 or 50 [animal filter] (6287819)
52 48 not 51 [exclude animal studies] (3342)
53 (Conference Abstract or Conference Paper or Conference Review).pt. (4933664)
54 52 and 53 (1586)

55 limit 54 to yr="2018-2021" (468)
56 52 not 53 [exclude conference proceedings] (1756)
57 55 or 56 [add proceedings from last 3 yrs] (2224)
58 remove duplicates from 57 [Embase results for export] (2183)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials July 2021
Date update search conducted: August 28, 2021
Strategy:
1 Death/ and Blood Circulation/ (0)
2 Death/ and exp Heart Arrest/ (51)
3 (((arrest$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)) and (dead or death$1)).tw. (1187)
4 ((dead or death$1) adj2 (cardi* or circulat* or heart)).tw. (10789)
5 asystol*.tw. (317)
6 (cessation adj5 (cardiac rhythm$1 or circulat* or heart function*)).tw. (16)
7 ((cessation or terminat*) adj3 cardi* resuscitation).tw. (1)
8 or/1-7 [Set 1: cardiac death] (11842)
9 Donor Selection/ (38)
10 exp Organ Transplantation/ (5723)
11 "Tissue and Organ Harvesting"/ (391)
12 exp "Tissue and Organ Procurement"/ (141)
13 exp Tissue Transplantation/ (4399)
14 exp Tissue Donors/ (1285)
15 (allocat* adj2 (organ$1 or tissue*)).tw. (56)
16 ((body or organ$1 or tissue*) adj2 (donor* or donation*)).tw. (773)
17 ((cardiac or heart$1 or heart-lung or hepatic or intestin$ or kidney$1 or kidney-pancreas or liver$1 or lung$1 or lung-heart or multiorgan or organ$1 or pancreas or renal or thoracic or tissue$1) adj2 transplant*).tw. (18304)
18 (cDCD or DCD or DCDD).ti. (54)
19 dead donor rule*.tw. (0)
20 deceased donor*.tw. (688)
21 "donation after circulatory death".tw. (48)
22 ((donor* or donation*) adj3 non heart beating).tw. (39)
23 (donor adj2 (exclu* or select* or screen*)).tw. (274)
24 (organ$1 adj2 (harvest* or procur* or retriev* or scarc*)).tw. (173)
25 (tissue adj2 (harvest* or procur* or retriev*)).tw. (283)
26 or/9-25 [Set 2: Organ donation] (23725)
27 (auto-resuscitat* or autoresuscitat*).tw. (1)
28 Lazarus.ti. (10)
29 Lazarus phenomen*.tw. (0)
30 Lazarus syndrom*.tw. (0)
31 (("return of" or recover* or restor* or resum*) adj2 (cardiac activity or circulation)).ti. (22)
32 or/27-31 [Set 3: autoresuscitation] (33)
33 ((declar* or determin*) adj2 death$1).tw. [Set 4: death determination] (334)
34 Time Factors/ (66356)
35 ("5 minute" or "5 minutes" or "5 min" or "5 mins" or five min*).tw. (355818)
36 delay*.ti. (6328)
37 delay*.ab. /freq=2 (11625)
38 hands off tim*.tw. (113)
39 "how long".tw. (143531)
40 (min or mins or minute$1).ti. (1100)
41 (min or mins or minute$1).ab. /freq=2 (50554)
42 ((observ* or wait*) adj3 (period$1 or tim*)).tw. (21725)
43 (time or timing$1).ti. (19567)
44 time point$1.tw. (32665)

45 or/34-44 [Set 5: time factors] (581458)
46 and/8,26,45 [Sets 1 and 2 and 5] (246)
47 33 and 45 [Sets 4 and 5] (158)
48 or/32,46-47 (431)
49 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (16)
50 ((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (5196)
51 49 or 50 (5212)
52 48 not 51 [exclude animal studies] (431)
53 remove duplicates from 52 [CENTRAL records for export] (422)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date update search conducted: August 28, 2021
Strategy:

# 10	**1,984**	#8 NOT #9 *Indexes=SCI-EXPANDED Timespan=All years*
# 9	**2,792,811**	TI=((ape or apes or animal* or baboon* or beagle* or cat or cats or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or mouse or mice or nonhuman* or "non human*" or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep) not (adults or children or human or humans or infants or patient or patients or people or seniors)) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**2,218**	#7 OR #6 OR #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**611**	#5 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**698**	#5 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**1,248,020**	TS=("5 minute" or "5 minutes" or "5 min" or "5 mins" or "five min*" or "hands off tim*" or "how long" or ((observ* or wait*) NEAR/3 (period* or tim*)) or "time point*") or TI=(delay* or min or mins or minute* or time or timing*) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**12,922**	TS=((confirm* or criteri* or declar* or determin* or diagnos*) NEAR/2 death*) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**979**	TS=("auto-resuscitat*" or autoresuscitat* or "Lazarus phenomen*" or "Lazarus syndrome*") or TI=(("return of" or recover* or restor* or resum*) NEAR/2 ("cardiac activity" or circulation)) or Lazarus) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**349,249**	TS=((allocat* NEAR/2 (organ* or tissue*)) or ((body or organ* or tissue*) NEAR/2 (donor* or donation*)) or ((cardiac or heart* or "heart-lung" or hepatic or intestin* or kidney* or "kidney-pancreas" or liver* or lung* or "lung-heart" or multiorgan or organ* or pancreas or renal or thoracic or

		tissue*) NEAR/2 transplant*) or "dead donor rule*" or "deceased donor*" or "donation af ter circulatory death" or ((donor* or donation*) NEAR/3 "non heart beating") or (donor NEAR/2 (exclu* or select* or screen*)) or (organ* NEAR/2 (harvest* or procur* or retriev* or scarc*)) or (tissue NEAR/2 (harvest* or procur* or retriev*))) or TI=(cDCD or DCD or DCDD) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**114,878**	TS=(((arrest* or dead or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart)) or asystol* or (cessation NEAR/5 ("cardiac rhythm*" or circulat* or "heart function*")) or ((cessation or terminat*) NEAR/3 "cardi* resuscitation")) *Indexes=SCI-EXPANDED Timespan=All years*

Death Determination by Neurologic Criteria

Review question: *In all patients without imaging demonstrating catastrophic brain injury but appearing to meet criteria for neurological determination of death, does delaying neurological determination of death 12 or 24 or 48 hours from the time of first clinical suspicion of neurological determination of death, compared to immediate determination, improve the accuracy of neurological determination of death?*

Results of the search: The search retrieved a total of 1179 references and 691 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	486	486
Embase	445	174
CENTRAL	53	3*
Web of Science	195	28
Total:	**1179**	**691**

* 9 pre-2018 conference proceedings removed manually from EndNote

Database: Ovid MEDLINE(R) ALL 1946 to May 06, 2021
Date search conducted: May 08, 2021
Strategy:

1 Carbon Monoxide Poisoning/ (5507)
2 exp Heart Arrest/ (49958)
3 exp Hypoglycemia/ (29000)
4 asystol*.tw,kf. (4412)
5 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kf. (95612)
6 carbon monoxide.tw,kf. (28828)
7 (hypo glyc?emi* or hypoglyc?emi*).tw,kf. (59900)
8 or/1-7 [Set 1: cardiac arrest of specific causes of neurological death] (212157)
9 Brain Death/ (8847)
10 Persistent Vegetative State/ (3017)
11 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
12 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
13 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11812)
14 cerebral performance categor*.tw,kf. (1392)
15 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (44)
16 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
17 (loss of brain* adj1 (function* or reflex*)).tw,kf. (190)
18 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (327)
19 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kf. (1253)
20 or/9-19 [Set 2: brain death or persistent loss of neurological function] (20441)
21 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kf. [Set 3: Death determination] (9810)
22 Outcome Assessment, Health Care/ (75868)
23 Predictive Value of Tests/ (210507)
24 Prognosis/ (532742)
25 Recovery of Function/ (55347)
26 exp "Sensitivity and Specificity"/ (605342)
27 accura*.ti. (71733)
28 accura*.ab. /freq=2 (236453)
29 ((false or true) adj (neg* or pos*)).tw,kf. (85680)

30 (neuroprognos* or neuro-prognos*).tw,kf. (118)
31 predict*.ti. (356486)
32 predict*.ab. /freq=2 (626889)
33 prognos*.ti. (168546)
34 prognos*.ab. /freq=2 (201015)
35 ((recover* or regain*) adj3 (consciousness or function*)).tw,kf. (53482)
36 reliab*.ti. (51884)
37 reliab*.ab. /freq=2 (106258)
38 ROC curve.tw,kf. (30439)
39 sensitiv*.ti. (180934)
40 sensitiv*.ab. /freq=2 (421632)
41 specifi*.ti. (335233)
42 specifi*.ab. /freq=2 (877929)
43 or/22-42 [Set 4: Prognosis] (3460211)
44 Time Factors/ (1206770)
45 ("12 h" or 12h or 12 hour* or 12 hr* or 12hr* or twelve hour* or twelve hr*).tw,kf. (98441)
46 ("24 h" or 24h or 24 hour* or 24 hr* or 24hr* or twenty?four hour* or twenty?four hr*).tw,kf. (449877)
47 ("48 h" or 48h or 48 hour* or 48 hr* or 48hr* or forty?eight hour* or forty?eight hr*).tw,kf. (164579)
48 delay*.ti. (76816)
49 delay*.ab. /freq=2 (114888)
50 (hours or hrs).ti. (11603)
51 (hours or hrs).ab. /freq=2 (155828)
52 "how long".tw,kf. (7173)
53 ((observ* or wait*) adj3 (period$1 or tim*)).tw,kf. (101447)
54 (time or timing$1).ti. (284711)
55 time point$1.tw,kf. (124126)
56 or/44-55 [Set 5: Time factors] (2329561)
57 and/8,20,43,56 (487)
58 and/8,21,43,56 (48)
59 57 or 58 (522)
60 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4824057)
61 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2262709)
62 60 or 61 (5206453)
63 59 not 62 [exclude animal studies] (502)
64 limit 63 to (english or french) (487)
65 remove duplicates from 64 [MEDLINE results for export] (486)

Database: Ovid Embase Classic+Embase 1947 to 2021 May 06
Date search conducted: May 08, 2021
Strategy:
1 carbon monoxide intoxication/ (7236)
2 exp heart arrest/ (108113)
3 hypoglycemia/ (90940)
4 exp hypoglycemic coma/ (1346)
5 asystol*.tw,kw. (7845)
6 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kw. (159217)
7 carbon monoxide.tw,kw. (37754)
8 (hypo glyc?emi* or hypoglyc?emi*).tw,kw. (99392)

9 or/1-8 [Set 1: cardiac arrest of specific causes of neurological death] (364225)
10 brain death/ (15815)
11 persistent vegetative state/ (5205)
12 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (90)
13 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (54)
14 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18795)
15 cerebral performance categor*.tw,kw. (2904)
16 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (56)
17 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
18 (loss of brain* adj1 (function* or reflex*)).tw,kw. (298)
19 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (496)
20 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kw. (1696)
21 or/10-20 [Set 2: brain death or persistent loss of neurological function] (32660)
22 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kw. [Set 3: Death determination] (15903)
23 predictive value/ (190884)
24 prognosis/ (658627)
25 exp "sensitivity and specificity"/ (394708)
26 accura*.ti. (89827)
27 accura*.ab. /freq=2 (317309)
28 ((false or true) adj (neg* or pos*)).tw,kw. (123350)
29 (neuroprognos* or neuro-prognos*).tw,kw. (202)
30 predict*.ti. (517299)
31 predict*.ab. /freq=2 (904610)
32 prognos*.ti. (242101)
33 prognos*.ab. /freq=2 (319998)
34 ((recover* or regain*) adj3 (consciousness or function*)).tw,kw. (78924)
35 reliab*.ti. (63851)
36 reliab*.ab. /freq=2 (135823)
37 ROC curve.tw,kw. (54060)
38 sensitiv*.ti. (220952)
39 sensitiv*.ab. /freq=2 (573761)
40 specifi*.ti. (409195)
41 specifi*.ab. /freq=2 (1181050)
42 or/23-41 [Set 4: Prognosis] (4326053)
43 time factor/ (39582)
44 ("12 h" or 12h or 12 hour* or 12 hr* or 12hr* or twelve hour* or twelve hr*).tw,kw. (141530)
45 ("24 h" or 24h or 24 hour* or 24 hr* or 24hr* or twenty?four hour* or twenty?four hr*).tw,kw. (687585)
46 ("48 h" or 48h or 48 hour* or 48 hr* or 48hr* or forty?eight hour* or forty?eight hr*).tw,kw. (257487)
47 delay*.ti. (97059)
48 delay*.ab. /freq=2 (168120)
49 (hours or hrs).ti. (15973)
50 (hours or hrs).ab. /freq=2 (273086)
51 "how long".tw,kw. (10534)
52 ((observ* or wait*) adj3 (period$1 or tim*)).tw,kw. (156870)
53 (time or timing$1).ti. (344509)
54 time point$1.tw,kw. (199912)
55 or/43-54 [Set 5: Time factors] (1953800)
56 and/9,21,42,55 (715)
57 and/9,22,42,55 (52)
58 56 or 57 (745)
59 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5953557)

60 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2679360)
61 59 or 60 (6316845)
62 58 not 61 [exclude animal studies] (728)
63 (Conference Abstract or Conference Paper or Conference Review).pt. (4875877)
64 62 and 63 (371)
65 limit 64 to yr="2018-2021" (114)
66 62 not 63 [exclude conference proceedings] (357)
67 65 or 66 [add proceedings from last 3 yrs] (471)
68 limit 67 to (english or french) (453)
69 remove duplicates from 68 [Embase results for export] (445)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials April 2021
Date search conducted: 08 May 2021
Strategy:
1 Carbon Monoxide Poisoning/ (61)
2 exp Heart Arrest/ (2004)
3 exp Hypoglycemia/ (2267)
4 asystol*.tw. (312)
5 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw. (14806)
6 carbon monoxide.tw. (2359)
7 (hypo glyc?emi* or hypoglyc?emi*).tw. (12783)
8 or/1-7 [Set 1: cardiac arrest of specific causes of neurological death] (30727)
9 Brain Death/ (84)
10 Persistent Vegetative State/ (70)
11 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
12 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
13 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (826)
14 cerebral performance categor*.tw. (286)
15 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
16 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
17 (loss of brain* adj1 (function* or reflex*)).tw. (8)
18 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
19 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw. (35)
20 or/9-19 [Set 2: brain death or persistent loss of neurological function] (1218)
21 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw. [Set 3: Death determination] (1076)
22 Outcome Assessment, Health Care/ (7803)
23 Predictive Value of Tests/ (7459)
24 Prognosis/ (14537)
25 Recovery of Function/ (5379)
26 exp "Sensitivity and Specificity"/ (16724)
27 accura*.ti. (3760)
28 accura*.ab. /freq=2 (11729)
29 ((false or true) adj (neg* or pos*)).tw. (3604)
30 (neuroprognos* or neuro-prognos*).tw. (3)
31 predict*.ti. (23907)
32 predict*.ab. /freq=2 (41498)
33 prognos*.ti. (8206)
34 prognos*.ab. /freq=2 (11117)

35 ((recover* or regain*) adj3 (consciousness or function*)).tw. (8608)
36 reliab*.ti. (2779)
37 reliab*.ab. /freq=2 (6416)
38 ROC curve.tw. (1605)
39 sensitiv*.ti. (8830)
40 sensitiv*.ab. /freq=2 (24039)
41 specifi*.ti. (10195)
42 specifi*.ab. /freq=2 (37329)
43 or/22-42 [Set 4: Prognosis] (174318)
44 Time Factors/ (65916)
45 ("12 h" or 12h or 12 hour* or 12 hr* or 12hr* or twelve hour* or twelve hr*).tw. (22185)
46 ("24 h" or 24h or 24 hour* or 24 hr* or 24hr* or twenty?four hour* or twenty?four hr*).tw. (80075)
47 ("48 h" or 48h or 48 hour* or 48 hr* or 48hr* or forty?eight hour* or forty?eight hr*).tw. (27683)
48 delay*.ti. (6223)
49 delay*.ab. /freq=2 (11373)
50 (hours or hrs).ti. (1754)
51 (hours or hrs).ab. /freq=2 (55579)
52 "how long".tw. (140478)
53 ((observ* or wait*) adj3 (period$1 or tim*)).tw. (21217)
54 (time or timing$1).ti. (19068)
55 time point$1.tw. (31664)
56 or/44-55 [Set 5: Time factors] (372323)
57 and/8,20,43,56 (71)
58 and/8,21,43,56 (8)
59 57 or 58 (77)
60 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (16)
61 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (5565)
62 60 or 61 (5581)
63 59 not 62 [exclude animal studies] (77)
64 limit 63 to (english or french) (56)
65 remove duplicates from 64 [CENTRAL results for export] (53)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: 08 May 2021
Strategy:

# 10	**195**	(#8 not #9) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	**2,826,299**	(TI=((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**201**	#7 OR #6

		Indexes=SCI-EXPANDED Timespan=All years
# 7	**12**	#5 AND #4 AND #3 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**196**	#5 AND #4 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**1,632,727**	(TS=("12 h" or 12h or "12 hour*" or "12 hr*" or 12hr* or "twelve hour*" or "twelve hr*" or "24 h" or 24h or "24 hour*" or "24 hr*" or 24hr* or "twenty$four hour*" or "twenty$four hr*" or "48 h" or 48h or "48 hour*" or "48 hr*" or 48hr* or "forty$eight hour*" or "forty$eight hr*" or "how long" or ((observ* or wait*) NEAR/3 (period* or tim*)) or "time point*") or TI=(delay* or hours or hrs or time or timing*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**1,951,713**	(TS=(((false or true) NEAR/1 (neg* or pos*)) or neuroprognos* or "neuro prognos*" or ((recover* or regain*) NEAR/3 (consciousness or function*)) or "ROC curve") or TI=(accura* or predict* or prognos* or reliab* or sensitiv* or specifi*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**12,099**	(TS=((confirm* or criteri* or declar* or determin* or diagnos*) NEAR/2 death*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**16,424**	(TS=(("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or "cerebral performance categor*" or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**244,989**	(TS=(asystol* or ((arrest* or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart or postcardi*)) or "carbon monoxide" or "hypo glyc$emi*" or hypoglyc$emi*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients being considered for neurological determination of death, does ensuring a core body temperature of 36 degrees as compared to 34 degrees improve the accuracy of the neurological determination of death?*

Results of the search: The search retrieved a total of 1628 references and 896 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	477	477
Embase	592	234
CENTRAL	60	7*
Web of Science	499	178
Total:	**1628**	**896**

*1 pre-2018 conference proceedings removed manually from EndNote

Database: Ovid MEDLINE(R) ALL 1946 to May 14, 2021
Date search conducted: May 16, 2021
Strategy:

1 exp Heart Arrest/ (50003)
2 Hypothermia/ (14100)
3 asystol*.tw,kf. (4414)
4 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kf. (95765)
5 (hypo-therm* or hypotherm*).tw,kf. (44432)
6 or/1-5 [Set 1: cardiac arrest or hypothermia] (153724)
7 Brain Death/ (8845)
8 Persistent Vegetative State/ (3018)
9 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kf. (2113)
10 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
11 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
12 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11828)
13 cerebral performance categor*.tw,kf. (1396)
14 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (44)
15 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
16 (electro-cerebral silence or electrocerebral silence).tw,kf. (94)
17 (loss of brain* adj1 (function* or reflex*)).tw,kf. (191)
18 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (330)
19 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kf. (1253)
20 or/7-19 [Set 2: brain death or persistent loss of neurological function] (22535)
21 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kf. [Set 3: Death determination] (9821)
22 Body Temperature/ (47990)
23 Body Temperature Regulation/ (23504)
24 Cryotherapy/ (5275)
25 Hypothermia, Induced/ (20848)
26 Rewarming/ (1501)
27 Temperature/ (247334)
28 body temp*.ti. (5113)
29 (body temp* adj2 (low* or regulat*)).tw,kf. (3020)
30 cold therap*.tw,kf. (398)
31 (cryo-therap* or cryotherap*).tw,kf. (7845)
32 (hypo-thermi* or hypothermi*).tw,kf. (44201)

33 (manag* adj2 temp*).tw,kf. (2576)
34 (normo-therm* or normotherm*).tw,kf. (8924)
35 (re-warm* or rewarm*).tw,kf. (5299)
36 (thermo-regulat* or thermoregulat*).tw,kf. (13414)
37 treatment temperature*.tw,kf. (1192)
38 TTM.ti. (73)
39 or/22-38 [Set 4: body temperature regulation] (370800)
40 Evoked Potentials, Somatosensory/ (12432)
41 Outcome Assessment, Health Care/ (75928)
42 Predictive Value of Tests/ (210638)
43 Prognosis/ (533625)
44 Recovery of Function/ (55400)
45 exp "Sensitivity and Specificity"/ (605862)
46 accura*.ti. (71854)
47 accura*.ab. /freq=2 (236956)
48 ((false or true) adj (neg* or pos*)).tw,kf. (85779)
49 (neurophysiologic* monitor* or neuro-physiologic* monitor*).tw,kf. (1279)
50 (neuroprognos* or neuro-prognos*).tw,kf. (117)
51 predict*.tw,kf. (1705726)
52 prognos*.ti. (168869)
53 prognos*.ab. /freq=2 (201482)
54 ((recover* or regain*) adj3 (consciousness or function*)).tw,kf. (53561)
55 reliab*.ti. (51940)
56 reliab*.ab. /freq=2 (106444)
57 ROC curve.tw,kf. (30563)
58 sensitiv*.ti. (181128)
59 sensitiv*.ab. /freq=2 (422196)
60 specifi*.ti. (335493)
61 specifi*.ab. /freq=2 (878989)
62 or/40-61 [Set 5: Prognosis] (4198514)
63 and/6,20,39,62 (520)
64 and/6,21,39,62 (35)
65 63 or 64 (534)
66 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4827134)
67 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2264121)
68 66 or 67 (5209901)
69 65 not 68 [exclude animal studies] (498)
70 limit 69 to (english or french) (479)
71 remove duplicates from 70 [MEDLINE results for export] (477)

Database: Ovid Embase Classic+Embase 1947 to 2021 May 14
Date search conducted: May 16, 2021
Strategy:
1 accidental hypothermia/ (758)
2 exp heart arrest/ (107722)
3 hypothermia/ (43242)
4 asystol*.tw,kw. (7798)
5 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kw. (158347)

6 (hypo-therm* or hypotherm*).tw,kw. (61587)
7 or/1-6 [Set 1: cardiac arrest or hypothermia] (254494)
8 brain death/ (15632)
9 persistent vegetative state/ (5113)
10 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kw. (4306)
11 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (89)
12 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (53)
13 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18605)
14 cerebral performance categor*.tw,kw. (2904)
15 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (55)
16 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
17 (electro-cerebral silence or electrocerebral silence).tw,kw. (121)
18 (loss of brain* adj1 (function* or reflex*)).tw,kw. (294)
19 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (491)
20 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kw. (1652)
21 or/8-20 [Set 2: brain death or persistent loss of neurological function] (36456)
22 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kw. [Set 3: Death determination] (15788)
23 body temperature/ (62341)
24 cryotherapy/ (19570)
25 induced hypothermia/ (16696)
26 thermoregulation/ (30619)
27 warming/ (14077)
28 body temp*.ti. (6168)
29 (body temp* adj2 (low* or regulat*)).tw,kw. (3705)
30 cold therap*.tw,kw. (346)
31 (cryo-therap* or cryotherap*).tw,kw. (11917)
32 (hypo-thermi* or hypothermi*).tw,kw. (61205)
33 (manag* adj2 temp*).tw,kw. (3840)
34 (normo-therm* or normotherm*).tw,kw. (12802)
35 (re-warm* or rewarm*).tw,kw. (7943)
36 (thermo-regulat* or thermoregulat*).tw,kw. (17436)
37 treatment temperature*.tw,kw. (1231)
38 TTM.ti. (140)
39 or/23-38 [Set 4: body temperature regulation] (188420)
40 predictive value/ (190416)
41 prognosis/ (652248)
42 exp "sensitivity and specificity"/ (392467)
43 somatosensory evoked potential/ (2809)
44 accura*.ti. (89191)
45 accura*.ab. /freq=2 (315218)
46 ((false or true) adj (neg* or pos*)).tw,kw. (122198)
47 (neuroprognos* or neuro-prognos*).tw,kw. (204)
48 predict*.tw,kw. (2312241)
49 prognos*.ti. (240339)
50 prognos*.ab. /freq=2 (317725)
51 ((recover* or regain*) adj3 (consciousness or function*)).tw,kw. (78172)
52 reliab*.ti. (63242)
53 reliab*.ab. /freq=2 (134715)
54 ROC curve.tw,kw. (53786)
55 sensitiv*.ti. (218763)
56 sensitiv*.ab. /freq=2 (568019)
57 specifi*.ti. (404612)

58 specifi*.ab. /freq=2 (1169212)
59 or/40-58 [Set 5: Prognosis] (5230826)
60 and/7,21,39,59 (1035)
61 and/7,22,39,59 (60)
62 60 or 61 (1055)
63 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5891582)
64 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2650524)
65 63 or 64 (6251319)
66 62 not 65 [exclude animal studies] (1018)
67 (Conference Abstract or Conference Paper or Conference Review).pt. (4860431)
68 66 and 67 (510)
69 limit 68 to yr="2018-2021" (114)
70 66 not 67 [exclude conference proceedings] (508)
71 69 or 70 [add proceedings from last 3 yrs] (622)
72 limit 71 to (english or french) (601)
73 remove duplicates from 72 [Embase results for export] (592)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials April 2021
Date search conducted: May 16, 2021
Strategy:
1 exp Heart Arrest/ (2004)
2 Hypothermia/ (713)
3 asystol*.tw. (312)
4 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw. (14806)
5 (hypo-therm* or hypotherm*).tw. (3875)
6 or/1-5 [Set 1: cardiac arrest or hypothermia] (18772)
7 Brain Death/ (84)
8 Persistent Vegetative State/ (70)
9 ((absen* or lack* or loss of or no) adj2 reflex*).tw. (375)
10 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
11 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
12 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (826)
13 cerebral performance categor*.tw. (286)
14 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
15 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
16 (electro-cerebral silence or electrocerebral silence).tw. (1)
17 (loss of brain* adj1 (function* or reflex*)).tw. (8)
18 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
19 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw. (35)
20 or/7-19 [Set 2: brain death or persistent loss of neurological function] (1585)
21 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw. [Set 3: Death determination] (1076)
22 Body Temperature/ (2220)
23 Body Temperature Regulation/ (834)
24 Cryotherapy/ (680)
25 Hypothermia, Induced/ (933)
26 Rewarming/ (175)
27 Temperature/ (1394)

28 body temp*.ti. (438)
29 (body temp* adj2 (low* or regulat*)).tw. (245)
30 cold therap*.tw. (196)
31 (cryo-therap* or cryotherap*).tw. (1695)
32 (hypo-thermi* or hypothermi*).tw. (3869)
33 (manag* adj2 temp*).tw. (608)
34 (normo-therm* or normotherm*).tw. (1099)
35 (re-warm* or rewarm*).tw. (721)
36 (thermo-regulat* or thermoregulat*).tw. (812)
37 treatment temperature*.tw. (63)
38 TTM.ti. (51)
39 or/22-38 [Set 4: body temperature regulation] (11241)
40 Evoked Potentials, Somatosensory/ (341)
41 Outcome Assessment, Health Care/ (7803)
42 Predictive Value of Tests/ (7459)
43 Prognosis/ (14537)
44 Recovery of Function/ (5379)
45 exp "Sensitivity and Specificity"/ (16724)
46 accura*.ti. (3760)
47 accura*.ab. /freq=2 (11729)
48 ((false or true) adj (neg* or pos*)).tw. (3604)
49 (neurophysiologic* monitor* or neuro-physiologic* monitor*).tw. (52)
50 (neuroprognos* or neuro-prognos*).tw. (3)
51 predict*.tw. (107174)
52 prognos*.ti. (8206)
53 prognos*.ab. /freq=2 (11117)
54 ((recover* or regain*) adj3 (consciousness or function*)).tw. (8608)
55 reliab*.ti. (2779)
56 reliab*.ab. /freq=2 (6416)
57 ROC curve.tw. (1605)
58 sensitiv*.ti. (8830)
59 sensitiv*.ab. /freq=2 (24039)
60 specifi*.ti. (10195)
61 specifi*.ab. /freq=2 (37329)
62 or/40-61 [Set 5: Prognosis] (220662)
63 and/6,20,39,62 (85)
64 and/6,21,39,62 (3)
65 63 or 64 (85)
66 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (16)
67 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (5565)
68 66 or 67 (5581)
69 65 not 68 [exclude animal studies] (85)
70 (Conference Abstract or Conference Paper or Conference Review).pt. (17183)
71 69 and 70 (3)
72 limit 71 to yr="2018-2021" (0) [no indexed conference proceedings from the past 3 years]
73 69 not 70 [exclude conference proceedings] (82)
74 limit 73 to (english or french) (65)
75 remove duplicates from 74 [Embase results for export] (60)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: May 16, 2021
Strategy:

# 10	**499**	(#8 NOT #9) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	**2,828,162**	(TI=((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**512**	#7 OR #6 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**30**	#5 AND #4 AND #3 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**503**	#5 AND #4 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**4,097,699**	(TS=("evoked potential*" or ((false or true) NEAR/1 (neg* or pos*)) or "neurophysiologic* monitor*" or "neuro physiologic* monitor*" or neuroprognos * or "neuro prognos*" or predict* or ((recover* or regain*) NEAR/3 (consciousness or function*)) or "ROC curve") or TI=(accura* or prognos* or reliab* or sensitiv* or specifi*)) *A ND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**94,564**	(TS=(("body temp*" NEAR/2 (low* or regulat*)) or "cold therap*" or "cryo therap*" or cryotherap* or "hypo therm*" or hypother m* or (manag* NEAR/2 temp*) or "normo therm*" or normotherm* or "re warm*" or rewarm* or "thermo regulat* " or thermoregulat* or "treatment temperature*") or TI=("body temp*" or TTM)) *AND* **LAN GUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**12,127**	(TS=((confirm* or criteri* or declar* or determin* or diagnos*) NEAR/2 death*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**16,484**	(TS=(("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or "cerebral performance categor*" or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or "electro cerebral silence" or "electrocerebral silence" or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**141,118**	(TS=(asystol* or ((arrest* or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart or postcardi*)) or "hypo therm*" or hypotherm*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients being considered for neurological determination of death who are post therapeutic hypothermia, how long after achieving temperature target (see Q2) do you have to wait before performing the clinical exam for death determination?*

Results of the search: The search retrieved a total of 563 references and 314 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	202	202
Embase	211	81
CENTRAL	34	1*
Web of Science	116	30
Total:	**563**	**314**

*5 pre-2018 conference proceedings removed manually from EndNote

Database: Ovid MEDLINE(R) ALL 1946 to May 14, 2021
Date search conducted: May 15, 2021
Strategy:

1 exp Heart Arrest/ (50003)
2 asystol*.tw,kf. (4414)
3 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kf. (95765)
4 or/1-3 [Set 1: cardiac arrest] (115726)
5 Brain Death/ (8845)
6 Persistent Vegetative State/ (3018)
7 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
8 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
9 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11828)
10 cerebral performance categor*.tw,kf. (1396)
11 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (44)
12 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
13 (loss of brain* adj1 (function* or reflex*)).tw,kf. (191)
14 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (330)
15 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kf. (1253)
16 or/5-15 [Set 2: brain death or persistent loss of neurological function] (20467)
17 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kf. [Set 3: Death determination] (9821)
18 Body Temperature/ (47990)
19 Body Temperature Regulation/ (23504)
20 Cryotherapy/ (5275)
21 Hypothermia, Induced/ (20848)
22 Rewarming/ (1501)
23 Temperature/ (247334)
24 body temp*.ti. (5113)
25 (body temp* adj2 (low* or regulat*)).tw,kf. (3020)
26 cold therap*.tw,kf. (398)
27 (cryo-therap* or cryotherap*).tw,kf. (7845)
28 (hypo-thermi* or hypothermi*).tw,kf. (44201)
29 (manag* adj2 temp*).tw,kf. (2576)
30 (normo-therm* or normotherm*).tw,kf. (8924)
31 (re-warm* or rewarm*).tw,kf. (5299)
32 (thermo-regulat* or thermoregulat*).tw,kf. (13414)

33 treatment temperature*.tw,kf. (1192)
34 TTM.ti. (73)
35 or/18-34 [Set 4: body temperature regulation] (370800)
36 Outcome Assessment, Health Care/ (75928)
37 Predictive Value of Tests/ (210638)
38 Prognosis/ (533625)
39 Recovery of Function/ (55400)
40 exp "Sensitivity and Specificity"/ (605862)
41 accura*.ti. (71854)
42 accura*.ab. /freq=2 (236956)
43 ((false or true) adj (neg* or pos*)).tw,kf. (85779)
44 (neuroprognos* or neuro-prognos*).tw,kf. (117)
45 predict*.ti. (357287)
46 predict*.ab. /freq=2 (628256)
47 prognos*.ti. (168869)
48 prognos*.ab. /freq=2 (201482)
49 ((recover* or regain*) adj3 (consciousness or function*)).tw,kf. (53561)
50 reliab*.ti. (51940)
51 reliab*.ab. /freq=2 (106444)
52 ROC curve.tw,kf. (30563)
53 sensitiv*.ti. (181128)
54 sensitiv*.ab. /freq=2 (422196)
55 specifi*.ti. (335493)
56 specifi*.ab. /freq=2 (878989)
57 or/36-56 [Set 5: Prognosis] (3464944)
58 Time Factors/ (1207209)
59 ("12 h" or 12h or 12 hour* or 12 hr* or 12hr* or twelve hour* or twelve hr*).tw,kf. (98510)
60 ("24 h" or 24h or 24 hour* or 24 hr* or 24hr* or twenty?four hour* or twenty?four hr*).tw,kf. (450213)
61 ("48 h" or 48h or 48 hour* or 48 hr* or 48hr* or forty?eight hour* or forty?eight hr*).tw,kf. (164731)
62 delay*.ti. (76923)
63 delay*.ab. /freq=2 (115065)
64 (hours or hrs).ti. (11609)
65 (hours or hrs).ab. /freq=2 (155952)
66 "how long".tw,kf. (7187)
67 ((observ* or wait*) adj3 (period$1 or tim*)).tw,kf. (101570)
68 (time or timing$1).ti. (285107)
69 time point$1.tw,kf. (124337)
70 or/58-69 [Set 6: Time factors] (2331361)
71 and/4,16,35,57,70 [Sets 1 and 2 and 4 and 5 and 6: cardiac arrest and brain death and temperature regulation and prognosis and time factors] (218)
72 and/4,17,35,57,70 [Sets 1 and 3 and 4 and 5 and 6: cardiac arrest and death determination and temperature regulation and prognosis and time factors] (3)
73 71 or 72 (219)
74 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4827134)
75 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2264121)
76 74 or 75 (5209901)
77 73 not 76 [exclude animal studies] (206)
78 limit 77 to (english or french) (203)

79 remove duplicates from 78 [MEDLINE results for export] (202)

Database: Ovid Embase Classic+Embase 1947 to 2021 May 14
Date search conducted: May 15, 2021
Strategy:
1 exp heart arrest/ (107722)
2 asystol*.tw,kw. (7798)
3 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kw. (158347)
4 or/1-3 [Set 1: cardiac arrest] (196667)
5 brain death/ (15632)
6 persistent vegetative state/ (5113)
7 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (89)
8 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (53)
9 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18605)
10 cerebral performance categor*.tw,kw. (2904)
11 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (55)
12 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
13 (loss of brain* adj1 (function* or reflex*)).tw,kw. (294)
14 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (491)
15 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kw. (1652)
16 or/5-15 [Set 2: brain death or persistent loss of neurological function] (32287)
17 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw,kw. [Set 3: Death determination] (15788)
18 body temperature/ (62341)
19 cryotherapy/ (19570)
20 induced hypothermia/ (16696)
21 thermoregulation/ (30619)
22 warming/ (14077)
23 body temp*.ti. (6168)
24 (body temp* adj2 (low* or regulat*)).tw,kw. (3705)
25 cold therap*.tw,kw. (346)
26 (cryo-therap* or cryotherap*).tw,kw. (11917)
27 (hypo-thermi* or hypothermi*).tw,kw. (61205)
28 (manag* adj2 temp*).tw,kw. (3840)
29 (normo-therm* or normotherm*).tw,kw. (12802)
30 (re-warm* or rewarm*).tw,kw. (7943)
31 (thermo-regulat* or thermoregulat*).tw,kw. (17436)
32 treatment temperature*.tw,kw. (1231)
33 TTM.ti. (140)
34 or/18-33 [Set 4: body temperature regulation] (188420)
35 predictive value/ (190416)
36 prognosis/ (652248)
37 exp "sensitivity and specificity"/ (392467)
38 accura*.ti. (89191)
39 accura*.ab. /freq=2 (315218)
40 ((false or true) adj (neg* or pos*)).tw,kw. (122198)
41 (neuroprognos* or neuro-prognos*).tw,kw. (204)
42 predict*.ti. (514476)
43 predict*.ab. /freq=2 (899477)
44 prognos*.ti. (240339)
45 prognos*.ab. /freq=2 (317725)
46 ((recover* or regain*) adj3 (consciousness or function*)).tw,kw. (78172)
47 reliab*.ti. (63242)

48 reliab*.ab. /freq=2 (134715)
49 ROC curve.tw,kw. (53786)
50 sensitiv*.ti. (218763)
51 sensitiv*.ab. /freq=2 (568019)
52 specifi*.ti. (404612)
53 specifi*.ab. /freq=2 (1169212)
54 or/35-53 [Set 5: Prognosis] (4288425)
55 time factor/ (39370)
56 ("12 h" or 12h or 12 hour* or 12 hr* or 12hr* or twelve hour* or twelve hr*).tw,kw. (139916)
57 ("24 h" or 24h or 24 hour* or 24 hr* or 24hr* or twenty?four hour* or twenty?four hr*).tw,kw. (680715)
58 ("48 h" or 48h or 48 hour* or 48 hr* or 48hr* or forty?eight hour* or forty?eight hr*).tw,kw. (254826)
59 delay*.ti. (96183)
60 delay*.ab. /freq=2 (166817)
61 (hours or hrs).ti. (15819)
62 (hours or hrs).ab. /freq=2 (271025)
63 "how long".tw,kw. (10425)
64 ((observ* or wait*) adj3 (period$1 or tim*)).tw,kw. (155446)
65 (time or timing$1).ti. (341501)
66 time point$1.tw,kw. (198639)
67 or/55-66 [Set 6: Time factors] (1935842)
68 and/4,16,34,54,67 [Sets 1 and 2 and 4 and 5 and 6: cardiac arrest and brain death and temperature regulation and prognosis and time factors] (387)
69 and/4,17,34,54,67 [Sets 1 and 3 and 4 and 5 and 6: cardiac arrest and death determination and temperature regulation and prognosis and time factors] (6)
70 68 or 69 (389)
71 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5891582)
72 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2650524)
73 71 or 72 (6251319)
74 70 not 73 [exclude animal studies] (380)
75 (Conference Abstract or Conference Paper or Conference Review).pt. (4860431)
76 74 and 75 (210)
77 limit 76 to yr="2018-2021" (47)
78 74 not 75 [exclude conference proceedings] (170)
79 77 or 78 [add proceedings from last 3 yrs] (217)
80 limit 79 to (english or french) (214)
81 remove duplicates from 80 [Embase results for export] (211)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials April 2021
Date search conducted: May 15, 2021
Strategy:
1 exp Heart Arrest/ (2004)
2 asystol*.tw. (312)
3 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw. (14806)
4 or/1-3 [Set 1: cardiac arrest] (15478)
5 Brain Death/ (84)
6 Persistent Vegetative State/ (70)
7 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
8 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)

9 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (826)
10 cerebral performance categor*.tw. (286)
11 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
12 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
13 (loss of brain* adj1 (function* or reflex*)).tw. (8)
14 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
15 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw. (35)
16 or/5-15 [Set 2: brain death or persistent loss of neurological function] (1218)
17 ((confirm* or criteri* or declar* or determin* or diagnos*) adj2 death$1).tw. [Set 3: Death determination] (1076)
18 Body Temperature/ (2220)
19 Body Temperature Regulation/ (834)
20 Cryotherapy/ (680)
21 Hypothermia, Induced/ (933)
22 Rewarming/ (175)
23 Temperature/ (1394)
24 body temp*.ti. (438)
25 (body temp* adj2 (low* or regulat*)).tw. (245)
26 cold therap*.tw. (196)
27 (cryo-therap* or cryotherap*).tw. (1695)
28 (hypo-thermi* or hypothermi*).tw. (3869)
29 (manag* adj2 temp*).tw. (608)
30 (normo-therm* or normotherm*).tw. (1099)
31 (re-warm* or rewarm*).tw. (721)
32 (thermo-regulat* or thermoregulat*).tw. (812)
33 treatment temperature*.tw. (63)
34 TTM.ti. (51)
35 or/18-34 [Set 4: body temperature regulation] (11241)
36 Outcome Assessment, Health Care/ (7803)
37 Predictive Value of Tests/ (7459)
38 Prognosis/ (14537)
39 Recovery of Function/ (5379)
40 exp "Sensitivity and Specificity"/ (16724)
41 accura*.ti. (3760)
42 accura*.ab. /freq=2 (11729)
43 ((false or true) adj (neg* or pos*)).tw. (3604)
44 (neuroprognos* or neuro-prognos*).tw. (3)
45 predict*.ti. (23907)
46 predict*.ab. /freq=2 (41498)
47 prognos*.ti. (8206)
48 prognos*.ab. /freq=2 (11117)
49 ((recover* or regain*) adj3 (consciousness or function*)).tw. (8608)
50 reliab*.ti. (2779)
51 reliab*.ab. /freq=2 (6416)
52 ROC curve.tw. (1605)
53 sensitiv*.ti. (8830)
54 sensitiv*.ab. /freq=2 (24039)
55 specifi*.ti. (10195)
56 specifi*.ab. /freq=2 (37329)
57 or/36-56 [Set 5: Prognosis] (174318)
58 Time Factors/ (65916)
59 ("12 h" or 12h or 12 hour* or 12 hr* or 12hr* or twelve hour* or twelve hr*).tw. (22185)
60 ("24 h" or 24h or 24 hour* or 24 hr* or 24hr* or twenty?four hour* or twenty?four hr*).tw. (80075)

61 ("48 h" or 48h or 48 hour* or 48 hr* or 48hr* or forty?eight hour* or forty?eight hr*).tw. (27683)
62 delay*.ti. (6223)
63 delay*.ab. /freq=2 (11373)
64 (hours or hrs).ti. (1754)
65 (hours or hrs).ab. /freq=2 (55579)
66 "how long".tw. (140478)
67 ((observ* or wait*) adj3 (period$1 or tim*)).tw. (21217)
68 (time or timing$1).ti. (19068)
69 time point$1.tw. (31664)
70 or/58-69 [Set 6: Time factors] (372323)
71 and/4,16,35,57,70 [Sets 1 and 2 and 4 and 5 and 6: cardiac arrest and brain death and temperature regulation and prognosis and time factors] (45)
72 and/4,17,35,57,70 [Sets 1 and 3 and 4 and 5 and 6: cardiac arrest and death determination and temperature regulation and prognosis and time factors] (0)
73 71 or 72 (45)
74 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (16)
75 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (5565)
76 74 or 75 (5581)
77 73 not 76 [exclude animal studies] (45)
78 limit 77 to (english or french) (36)
79 remove duplicates from 78 [CENTRAL results for export] (34)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: May 15, 2021
Strategy:

# 11	**116**	(#9 NOT #10) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 10	**2,827,905**	(TI=((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	**119**	#8 OR #7 *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**1**	#6 AND #5 AND #4 AND #3 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**119**	#6 AND #5 AND #4 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**1,634,841**	(TS=("12 h" or 12h or "12 hour*" or "12 hr*" or 12hr* or "twelve hour*" or "twelve hr*" or "24 h" or 24h or "24 hour*" or "24 hr*" or 24hr* or "twenty$four hour*" or "twenty$four hr*" or "48 h" or 48h or "48 hour*" or "48 hr*" or 48hr* or "forty$eight hour*" or "forty$eight hr*" or "how long" or ((observ* or wait*) NEAR/3 (period* or

		tim*)) or "time point*") or TI=(delay* or hours or hrs or time or timing*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**1,954,565**	(TS=(((false or true) NEAR/1 (neg* or pos*)) or neuroprognos* or "neuro prognos*" or ((recover* or regain*) NEAR/3 (consciousness or function*)) or "ROC curve") or TI=(accura* or predict* or prognos* or reliab* or sensitiv* or specifi*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**94,288**	(TS=(("body temp*" NEAR/2 (low* or regulat*)) or "cold therap*" or "cryo therap*" or cryotherap* or "hypo thermi*" or hypothermi* or (manag* NEAR/2 temp*) or "normo therm*" or normotherm* or "re warm*" or rewarm* or "thermo regulat*" or thermoregulat* or "treatment temperature*") or TI=("body temp*" or TTM)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**12,124**	(TS=((confirm* or criteri* or declar* or determin* or diagnos*) NEAR/2 death*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**16,441**	(TS=(("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or "cerebral performance categor*" or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**108,336**	(TS=(asystol* or ((arrest* or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart or postcardi*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients who appear to meet criteria for neurological determination of death, does use of pupillometry compared with routine clinical pupil assessment improve the accuracy of neurological determination of death?*

Results of the search: The search retrieved a total of 1930 references and 995 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	656	656
Embase	740	239
CENTRAL	74	24*
Web of Science	460	76
Total:	**1930**	**995**

*13 pre-2018 conference proceedings removed manually from EndNote

Database: Ovid MEDLINE(R) ALL 1946 to May 28, 2021
Date search conducted: May 29, 2021
Strategy:
1 (Diagnostic Techniques, Neurological/is or Neurologic Examination/is, me or Neurophysiological Monitoring/is) and (Pupil/ or Reflex, Pupillary/) [Coordinated concept] (17)
2 (automat* pupil* adj (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)).tw,kf. (12)
3 neuro* pupil* ind*.tw,kf. (50)
4 pupil?omet*.tw,kf. (1763)
5 (quantitative pupil* adj (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)).tw,kf. (9)
6 or/2-5 [Set 1: pupillometry] (1767)
7 Pupil/ and (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*).tw,kf. (4708)
8 Reflex, Pupillary/ and (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*).tw,kf. (1430)
9 ((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) adj5 (pupil or pupillary or pupils)).tw,kf. (5007)
10 (((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) adj2 (clinical* or manual* or standard* or subjective*)) and pupil*).tw,kf. (1216)
11 or/7-10 [Set 2: clinical pupil assessment] (9241)
12 Diagnosis/ (17439)
13 Predictive Value of Tests/ (211065)
14 Reproducibility of Results/ (416538)
15 exp "Sensitivity and Specificity"/ (607964)
16 di.fs. (2665873)
17 accura*.tw,kf. (868983)
18 clinical utility.tw,kf. (28097)
19 diagnos*.tw,kf. (2671617)
20 ((false or true) adj (neg* or pos*)).tw,kf. (85963)
21 neuroprognos*.tw,kf. (109)
22 precis*.tw,kf. (386327)
23 predict*.tw,kf. (1711402)
24 prognos*.tw,kf. (666078)
25 reliab*.tw,kf. (518054)
26 reproducib*.tw,kf. (171226)
27 ROC curve.tw,kf. (30765)

28 sensitiv*.tw,kf. (1465289)
29 specifi*.tw,kf. (3355542)
30 valid*.tw,kf. (810026)
31 or/12-30 [Set 3: diagnostic accuracy] (10456656)
32 and/6,11,31 [Sets 1 and 2 and 3] (703)
33 1 or 32 [Coordinated concept added to combined set] (710)
34 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4837077)
35 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2266668)
36 34 or 35 (5219073)
37 33 not 36 [exclude animal studies] (686)
38 limit 37 to (english or french) (658)
39 remove duplicates from 38 [MEDLINE results for export] (656)

Database: Ovid Embase Classic+Embase 1947 to 2021 May 28
Date search conducted: May 29, 2021
Strategy:
1 pupillometry/ (1647)
2 (automat* pupil* adj (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)).tw,kw. (17)
3 neuro* pupil* ind*.tw,kw. (103)
4 pupil?omet*.tw,kw. (2356)
5 (quantitative pupil* adj (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)).tw,kw. (15)
6 or/1-5 [Set 1: pupillometry] (2665)
7 pupil/ and (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*).tw,kw. (6706)
8 pupil reflex/ and (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*).tw,kw. (3448)
9 ((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) adj5 (pupil or pupillary or pupils)).tw,kw. (7310)
10 (((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) adj2 (clinical* or manual* or standard* or subjective*)) and pupil*).tw,kw. (1958)
11 or/7-10 [Set 2: clinical pupil assessment] (14654)
12 diagnostic accuracy/ (266423)
13 predictive value/ (191541)
14 prognosis/ (654263)
15 reproducibility/ (231217)
16 exp "sensitivity and specificity"/ (394385)
17 accura*.tw,kw. (1143470)
18 clinical utility.tw,kw. (41748)
19 diagnos*.tw,kw. (4039081)
20 ((false or true) adj (neg* or pos*)).tw,kw. (122687)
21 neuroprognos*.tw,kw. (184)
22 precis*.tw,kw. (497252)
23 predict*.tw,kw. (2324093)
24 prognos*.tw,kw. (1048926)
25 reliab*.tw,kw. (679002)
26 reproducib*.tw,kw. (226999)
27 ROC curve.tw,kw. (54152)

28 sensitiv*.tw,kw. (1913988)
29 specifi*.tw,kw. (4362386)
30 valid*.tw,kw. (1143516)
31 or/12-30 [Set 3: diagnostic accuracy] (12380931)
32 and/6,11,31 [Sets 1 and 2 and 3] (975)
33 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5907601)
34 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2657732)
35 33 or 34 (6268501)
36 32 not 35 [exclude animal studies] (937)
37 (Conference Abstract or Conference Paper or Conference Review).pt. (4872803)
38 36 and 37 (250)
39 limit 38 to yr="2018-2021" (96)
40 36 not 37 [exclude conference proceedings] (687)
41 39 or 40 [add proceedings from last 3 yrs] (783)
42 limit 41 to (english or french) (751)
43 remove duplicates from 42 [Embase results for export] (740)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials April 2021
Date search conducted: May 29, 2021
Strategy:
1 (automat* pupil* adj (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)).tw. (1)
2 neuro* pupil* ind*.tw. (3)
3 pupil?omet*.tw. (323)
4 (quantitative pupil* adj (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)).tw. (3)
5 or/1-4 [Set 1: pupillometry] (324)
6 Pupil/ and (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*).tw. (531)
7 Reflex, Pupillary/ and (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*).tw. (80)
8 ((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) adj5 (pupil or pupillary or pupils)).tw. (1237)
9 (((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) adj2 (clinical* or manual* or standard* or subjective*)) and pupil*).tw. (419)
10 or/6-9 [Set 2: clinical pupil assessment] (1797)
11 Diagnosis/ (65)
12 Predictive Value of Tests/ (7459)
13 Reproducibility of Results/ (11965)
14 exp "Sensitivity and Specificity"/ (16724)
15 accura*.tw. (35656)
16 clinical utility.tw. (2296)
17 diagnos*.tw. (167119)
18 ((false or true) adj (neg* or pos*)).tw. (3604)
19 neuroprognos*.tw. (3)
20 precis*.tw. (11101)
21 predict*.tw. (107174)
22 prognos*.tw. (38220)
23 reliab*.tw. (27494)
24 reproducib*.tw. (6565)
25 ROC curve.tw. (1605)

26 sensitiv*.tw. (72613)
27 specifi*.tw. (149604)
28 valid*.tw. (59879)
29 or/11-28 [Set 3: diagnostic accuracy] (492628)
30 and/5,10,29 [Sets 1 and 2 and 3] (76)
31 remove duplicates from 30 [CENTRAL records for export] (74)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: May 29, 2021
Strategy:

# 6	**460**	(#4 NOT #5) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**2,831,912**	(TI=((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**469**	#3 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**11,842,354**	(TS=(accura* or "clinical utility" or diagnos* or ((false or true) NEAR/1 (neg* or pos*)) or neuroprognos* or precis* or predict* or prognos* or reliab* or reproducib* or "R OC curve" or sensitiv* or specifi* or valid*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**5,119**	(TS=(((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) NEAR/5 (pupil or pupillary or pupils)) or (((assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*) NEAR/2 (clinical* or manual* or standard* or subjective*)) and pupil*))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**1,789**	(TS=(("automat* pupil*" NEAR/1 (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)) or "neuro* pupil* ind*" or pupil$omet* or ("quantitative pupil*" NEAR/1 (assess* or evaluat* or exam* or measur* or monitor* or prognosticat* or test*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients who appear to meet criteria for neurological determination of death, does the combination of oculocephalic reflex (OCR) testing and vestibulo-ocular reflex (VOR, or cold-calorics testing) testing, compared to VOR alone, improve the accuracy of neurological determination of death?*

Results of the search: The search retrieved a total of 1730 references and 1144 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	551	551
Embase	850	502
CENTRAL	24	8
Web of Science	305	83
Total:	**1730**	**1144**

Database: Ovid MEDLINE(R) ALL 1946 to June 04, 2021
Date protocol search conducted: Jun 5, 2021
Strategy:

1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Eye Movements/ or Fixation, Ocular/ or Reflex, Vestibulo-Ocular/ or exp Vestibular Function Tests/) [Coordinated concept] (15)
2 Brain Injuries, Traumatic/ (7921)
3 exp Brain Ischemia/ (113280)
4 Coma/ (12639)
5 Coma, Post-Head Injury/ (125)
6 exp Heart Arrest/ (50265)
7 exp Hypoxia, Brain/ (13196)
8 exp Stroke/ (144473)
9 apoplex*.tw,kf. (3347)
10 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kf. (96177)
11 asystol*.tw,kf. (4426)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kf. (72723)
13 brain trauma*.tw,kf. (2879)
14 cerebral circulatory arrest$1.tw,kf. (152)
15 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kf. (13999)
16 coma*.tw,kf. (42866)
17 devastating brain injur*.tw,kf. (51)
18 stroke$1.tw,kf. (271089)
19 (TBI* or traumatic brain injur*).tw,kf. (49174)
20 or/2-19 [Set 1: causes of neurological death] (568525)
21 Brain Death/ (8872)
22 Brain Injuries/mo (2076)
23 Persistent Vegetative State/ (3026)
24 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kf. (2114)
25 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
26 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
27 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11857)
28 cerebral performance categor*.tw,kf. (1406)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (45)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
31 (electro-cerebral silence or electrocerebral silence).tw,kf. (94)
32 (loss of brain* adj1 (function* or reflex*)).tw,kf. (193)

33 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (330)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kf. (1255)
35 or/21-34 [Set 2: brain death or persistent loss of neurological function] (24534)
36 Brain Death/di (1846)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 death$1).tw,kf. (20376)
38 36 or 37 [Set 3: Death determination] (21266)
39 Caloric Tests/ (2089)
40 Head Impulse Test/ (358)
41 Reflex, Vestibulo-Ocular/ (3808)
42 Vestibular Function Tests/ (6714)
43 Barany* test*.tw,kf. (11)
44 (caloric$1 adj2 (irrigat* or reflex* or respon* or stimul* or test*)).tw,kf. (3001)
45 cold caloric$1.tw,kf. (70)
46 (doll* eye* adj1 (maneuver* or phenom* or reflex* or respon* or test*)).tw,kf. (22)
47 head impulse test*.tw,kf. (901)
48 head heave test*.tw,kf. (4)
49 head thrust test*.tw,kf. (52)
50 (OCR adj3 (maneuver* or respon* or test*)).tw,kf. (51)
51 (oculocephalic or oculo-cephalic).tw,kf. (163)
52 (oculovestibular or oculo-vestibular).tw,kf. (75)
53 (OVR adj3 (maneuver* or respon* or test*)).tw,kf. (5)
54 ((vestibuloocular or vestibulo-ocular) adj2 (maneuver* or reflex* or respon* or stimul* or test*)).tw,kf. (3458)
55 (VOR adj3 (maneuver* or respon* or test*)).tw,kf. (407)
56 or/39-55 [Set 4: VOR or OCR testing] (14101)
57 and/20,56 [Sets 1 and 4] (639)
58 and/35,56 [Sets 2 and 4] (101)
59 and/38,56 [Sets 3 and 4] (18)
60 or/1,57-59 (707)
61 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4840052)
62 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2268724)
63 61 or 62 (5222916)
64 60 not 63 [exclude animal studies] (683)
65 limit 64 to (english or french) (551)
66 remove duplicates from 65 [MEDLINE results for export] (551)

Database: Ovid Embase Classic+Embase 1947 to 2021 June 04
Date search conducted: June 5, 2021
Strategy:
1 (brain death/di or neurophysiological monitoring/) and (eye fixation/ or eye movement/ or vestibular function/ or exp vestibular test/ or vestibular stimulation/ or vestibuloocular reflex/) [Coordinated concept] (13)
2 brain hypoxia/ (12335)
3 exp brain ischemia/ (201214)
4 exp cerebrovascular accident/ (234554)
5 coma/ (35736)
6 exp heart arrest/ (108390)
7 exp traumatic brain injury/ (55134)

8 apoplex*.tw,kw. (4816)
9 apoplex*.tw,kw. (4816)
10 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kw. (159254)
11 asystol*.tw,kw. (7825)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kw. (106410)
13 brain trauma*.tw,kw. (4324)
14 cerebral circulatory arrest$1.tw,kw. (246)
15 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kw. (24552)
16 coma*.tw,kw. (63872)
17 devastating brain injur*.tw,kw. (83)
18 stroke$1.tw,kw. (441168)
19 (TBI* or traumatic brain injur*).tw,kw. (76685)
20 or/2-19 [Set 1: causes of neurological death] (942018)
21 brain death/ (15667)
22 persistent vegetative state/ (5123)
23 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kw. (4316)
24 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (89)
25 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (54)
26 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18658)
27 cerebral performance categor*.tw,kw. (2925)
28 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (55)
29 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
30 (electro-cerebral silence or electrocerebral silence).tw,kw. (121)
31 (loss of brain* adj1 (function* or reflex*)).tw,kw. (298)
32 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (498)
33 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kw. (1654)
34 or/21-33 [Set 2: brain death or persistent loss of neurological function] (36567)
35 brain death/di (564)
36 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 death$1).tw,kw. (31357)
37 35 or 36 [Set 3: Death determination] (31700)
38 exp vestibular test/ (9927)
39 vestibular stimulation/ (2447)
40 vestibuloocular reflex/ (5271)
41 Barany* test*.tw,kw. (31)
42 (caloric$1 adj2 (irrigat* or reflex* or respon* or stimul* or test*)).tw,kw. (4633)
43 cold caloric$1.tw,kw. (143)
44 (doll* eye* adj1 (maneuver* or phenom* or reflex* or respon* or test*)).tw,kw. (46)
45 head impulse test*.tw,kw. (1139)
46 head heave test*.tw,kw. (4)
47 head thrust test*.tw,kw. (74)
48 (OCR adj3 (maneuver* or respon* or test*)).tw,kw. (90)
49 (oculocephalic or oculo-cephalic).tw,kw. (264)
50 (oculovestibular or oculo-vestibular).tw,kw. (118)
51 (OVR adj3 (maneuver* or respon* or test*)).tw,kw. (10)
52 ((vestibuloocular or vestibulo-ocular) adj2 (maneuver* or reflex* or respon* or stimul* or test*)).tw,kw. (4191)
53 (VOR adj3 (maneuver* or respon* or test*)).tw,kw. (479)
54 or/38-53 [Set 4: VOR or OCR testing] (18954)
55 and/20,54 [Sets 1 and 4] (923)
56 and/34,54 [Sets 2 and 4] (191)
57 and/37,54 [Sets 3 and 4] (54)
58 or/1,55-57 (1017)

59 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5905542)
60 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2656544)
61 59 or 60 (6266400)
62 58 not 61 [exclude animal studies] (990)
63 limit 62 to (english or french) (868)
64 remove duplicates from 63 [Embase results for export] (850)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials May 2021
Date search conducted: Jun 5, 2021
Strategy:
1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Eye Movements/ or Fixation, Ocular/ or Reflex, Vestibulo-Ocular/ or exp Vestibular Function Tests/) [Coordinated concept] (0)
2 Brain Injuries, Traumatic/ (619)
3 exp Brain Ischemia/ (3682)
4 Coma/ (205)
5 Coma, Post-Head Injury/ (4)
6 exp Heart Arrest/ (2011)
7 exp Hypoxia, Brain/ (313)
8 exp Stroke/ (10246)
9 apoplex*.tw. (353)
10 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw. (14989)
11 asystol*.tw. (313)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw. (6308)
13 brain trauma*.tw. (190)
14 cerebral circulatory arrest$1.tw. (1)
15 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw. (2223)
16 coma*.tw. (3585)
17 devastating brain injur*.tw. (4)
18 stroke$1.tw. (57283)
19 (TBI* or traumatic brain injur*).tw. (5449)
20 or/2-19 [Set 1: causes of neurological death] (82387)
21 Brain Death/ (84)
22 Brain Injuries/mo (0)
23 Persistent Vegetative State/ (70)
24 ((absen* or lack* or loss of or no) adj2 reflex*).tw. (377)
25 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
26 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
27 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (832)
28 cerebral performance categor*.tw. (287)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
31 (electro-cerebral silence or electrocerebral silence).tw. (1)
32 (loss of brain* adj1 (function* or reflex*)).tw. (8)
33 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw. (35)
35 or/21-34 [Set 2: brain death or persistent loss of neurological function] (1594)
36 Brain Death/di (0)

37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 death$1).tw. (2008)
38 36 or 37 [Set 3: Death determination] (2008)
39 Caloric Tests/ (46)
40 Head Impulse Test/ (6)
41 Reflex, Vestibulo-Ocular/ (88)
42 Vestibular Function Tests/ (137)
43 Barany* test*.tw. (0)
44 (caloric$1 adj2 (irrigat* or reflex* or respon* or stimul* or test*)).tw. (244)
45 cold caloric$1.tw. (3)
46 (doll* eye* adj1 (maneuver* or phenom* or reflex* or respon* or test*)).tw. (0)
47 head impulse test*.tw. (61)
48 head heave test*.tw. (0)
49 head thrust test*.tw. (3)
50 (OCR adj3 (maneuver* or respon* or test*)).tw. (13)
51 (oculocephalic or oculo-cephalic).tw. (1)
52 (oculovestibular or oculo-vestibular).tw. (3)
53 (OVR adj3 (maneuver* or respon* or test*)).tw. (1)
54 ((vestibuloocular or vestibulo-ocular) adj2 (maneuver* or reflex* or respon* or stimul* or test*)).tw. (132)
55 (VOR adj3 (maneuver* or respon* or test*)).tw. (25)
56 or/39-55 [Set 4: VOR or OCR testing] (560)
57 and/20,56 [Sets 1 and 4] (24)
58 and/35,56 [Sets 2 and 4] (0)
59 and/38,56 [Sets 3 and 4] (0)
60 or/1,57-59 (24)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: June 5, 2021
Strategy:

# 10	**305**	(#8 NOT #9) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	**2,834,000**	(TI=((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or "non human*" or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**316**	#7 OR #6 OR #5 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**10**	#4 AND #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**53**	#4 AND #2 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**282**	#4 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**6,996**	(TS=("Barany* test*" or ((caloric or calorics) NEAR/2 (irrigat* or reflex* or respon* or stimul* or test*)) or "cold caloric*" or ("doll* eye*" NEAR/1 (maneuver* or phenom* or reflex* or respon* or

		test*)) or "head impulse test*" or "head heave test*" or "head thrust test*" or (OCR NEAR/3 (maneuver* or respon* or test*)) or oculocephalic or "oculo-cephalic" or oculovestibular or "oculo-vestibular" or (OVR NEAR/3 (maneuver* or respon* or test*)) or ((vestibuloocular or "vestibulo-ocular") NEAR/2 (maneuver* or reflex* or respon* or stimul* or test*)) or (VOR NEAR/3 (maneuver* or respon* or test*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**21,756**	(TS=((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) NEAR/3 death*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**19,094**	(TS=(((absen* or lack* or "loss of") NEAR/2 reflex*) or ("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or "cerebral performance categor*" or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or "electro-cerebral silence" or "electrocerebral silence" or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**579,653**	(TS=(apoplex* or ((arrest* or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart or postcardi*)) or asystol* or ((brain* or cerebral) NEAR/2 (hypoxi* or infarct* or isch$emi*)) or "brain trauma*" or "cerebral circulatory arrest*" or (("cerebro-vascular" or cerebrovascular) NEAR/1 (accident* or event*)) or coma* or "devastating brain injur*" or stroke* or TBI* or "traumatic brain injur*")) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients who are undergoing apnea testing as part of neurological determination of death, does using a pCO2 threshold of 60mmHg as compared to 80mmHg or 90mmHg improve the accuracy of neurological determination of death?*

Results of the search: The search retrieved a total of 424 references and 263 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	149	148
Embase	191	103
CENTRAL	13	6
Web of Science	71	7
Total:	**424**	**263**

Database: Ovid MEDLINE(R) ALL 1946 to June 15, 2021
Date search conducted: June 16, 2021
Strategy:

1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Blood Gas Analysis/ or Carbon Dioxide/bl) [Coordinated concept] (41)
2 Brain Injuries, Traumatic/ (8006)
3 exp Brain Ischemia/ (113435)
4 Coma/ (12644)
5 Coma, Post-Head Injury/ (125)
6 exp Heart Arrest/ (50313)
7 exp Hypoxia, Brain/ (13217)
8 exp Stroke/ (144779)
9 apoplex*.tw,kf. (3352)
10 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kf. (96395)
11 asystol*.tw,kf. (4432)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kf. (72862)
13 brain trauma*.tw,kf. (2880)
14 cerebral circulatory arrest$1.tw,kf. (152)
15 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kf. (14032)
16 coma*.tw,kf. (42921)
17 devastating brain injur*.tw,kf. (51)
18 stroke$1.tw,kf. (271748)
19 (TBI* or traumatic brain injur*).tw,kf. (49297)
20 or/2-19 [Set 1: causes of neurological death] (569661)
21 Brain Death/ (8880)
22 Brain Injuries/mo (2076)
23 Persistent Vegetative State/ (3030)
24 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kf. (2115)
25 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
26 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
27 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11869)
28 cerebral performance categor*.tw,kf. (1414)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (45)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
31 (electro-cerebral silence or electrocerebral silence).tw,kf. (94)
32 (loss of brain* adj1 (function* or reflex*)).tw,kf. (193)
33 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (330)

34 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kf. (1255)
35 or/21-34 [Set 2: brain death or persistent loss of neurological function] (24559)
36 Brain Death/di (1851)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 (dead or death$1)).tw,kf. (21898)
38 36 or 37 [Set 3: Death determination] (22777)
39 Apnea/di (872)
40 Apnea/ and (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*).mp. (4140)
41 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kf. (4412)
42 or/39-41 [Set 4: Apnea test] (7934)
43 Blood Gas Analysis/ (22199)
44 Carbon Dioxide/bl (23942)
45 Partial Pressure/ (17115)
46 blood gas*.tw,kf. (27747)
47 ((carbon dioxide or CO2) adj2 challenge).tw,kf. (311)
48 ((carbon dioxide or CO2) adj2 pressure).tw,kf. (5679)
49 ((carbon dioxide or CO2) adj2 tension).tw,kf. (3139)
50 ((h?emo-dynamic or h?emodynamic) adj1 (assess* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kf. (13218)
51 mmHG.tw,kf. (85458)
52 (paCO2 or p CO2 or p CO 2 or pCO2 or pvCO2).tw,kf. (20793)
53 partial pressure of carbon dioxide.tw,kf. (1664)
54 partial pressure of CO2.tw,kf. (736)
55 or/43-54 [Set 5: PCO2] (174644)
56 and/20,42,55 [Sets 1 and 4 and 5] (63)
57 and/35,42,55 [Sets 2 and 4 and 5] (102)
58 and/38,42,55 [Sets 3 and 4 and 5] (92)
59 or/1,56-58 (149)
60 remove duplicates from 59 [MEDLINE results for export] (149)

Database: Ovid Embase Classic+Embase 1947 to 2021 June 15
Date search conducted: June 16, 2021
Strategy:
1 brain death/di and (carbon dioxide blood level/ or exp carbon dioxide tension/) (1)
2 brain hypoxia/ (12352)
3 exp brain ischemia/ (201415)
4 exp cerebrovascular accident/ (235141)
5 coma/ (35773)
6 exp heart arrest/ (108637)
7 exp traumatic brain injury/ (55317)
8 apoplex*.tw,kw. (4828)
9 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kw. (159583)
10 asystol*.tw,kw. (7832)
11 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kw. (106627)
12 brain trauma*.tw,kw. (4330)
13 cerebral circulatory arrest$1.tw,kw. (246)
14 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kw. (24601)
15 coma*.tw,kw. (63989)
16 devastating brain injur*.tw,kw. (83)
17 stroke$1.tw,kw. (442179)
18 (TBI* or traumatic brain injur*).tw,kw. (76912)

19 or/2-18 [Set 1: causes of neurological death] (944092)
20 brain death/ (15688)
21 persistent vegetative state/ (5129)
22 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kw. (4319)
23 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (90)
24 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (54)
25 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18703)
26 cerebral performance categor*.tw,kw. (2935)
27 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (55)
28 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
29 (electro-cerebral silence or electrocerebral silence).tw,kw. (121)
30 (loss of brain* adj1 (function* or reflex*)).tw,kw. (299)
31 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (499)
32 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kw. (1656)
33 or/20-32 [Set 2: brain death or persistent loss of neurological function] (36637)
34 brain death/di (564)
35 ((confirm* or criteri* or declar* or determin* or diagnos* or exam*) adj3 (dead or death$1)).tw,kw. (32922)
36 34 or 35 [Set 3: Death determination] (33261)
37 apnea/di (753)
38 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kw. (7568)
39 37 or 38 [Set 4: Apnea test] (8169)
40 blood gas analysis/ (23716)
41 carbon dioxide blood level/ (1130)
42 exp carbon dioxide tension/ (33498)
43 partial pressure/ (2663)
44 blood gas*.tw,kw. (41582)
45 ((carbon dioxide or CO2) adj2 challenge).tw,kw. (485)
46 ((carbon dioxide or CO2) adj2 pressure).tw,kw. (7760)
47 ((carbon dioxide or CO2) adj2 tension).tw,kw. (4761)
48 ((h?emo-dynamic or h?emodynamic) adj1 (assess* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kw. (20295)
49 mmHG.tw,kw. (155872)
50 (paCO2 or p CO2 or p CO 2 or pCO2 or pvCO2).tw,kw. (32836)
51 partial pressure of carbon dioxide.tw,kw. (2039)
52 partial pressure of CO2.tw,kw. (1031)
53 or/40-52 [Set 5: PCO2] (264918)
54 and/19,39,53 [Sets 1 and 4 and 5] (99)
55 and/33,39,53 [Sets 2 and 4 and 5] (176)
56 and/36,39,53 [Sets 3 and 4 and 5] (142)
57 or/1,54-56 (197)
58 remove duplicates from 57 [Embase results for export] (191)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials May 2021
Date search conducted: June 16, 2021
Strategy:
1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Blood Gas Analysis/ or Carbon Dioxide/bl) [Coordinated concept] (0)
2 Brain Injuries, Traumatic/ (619)
3 exp Brain Ischemia/ (3682)
4 Coma/ (205)
5 Coma, Post-Head Injury/ (4)
6 exp Heart Arrest/ (2011)

7 exp Hypoxia, Brain/ (313)
8 exp Stroke/ (10246)
9 apoplex*.tw. (353)
10 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw. (14989)
11 asystol*.tw. (313)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw. (6308)
13 brain trauma*.tw. (190)
14 cerebral circulatory arrest$1.tw. (1)
15 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw. (2223)
16 coma*.tw. (3585)
17 devastating brain injur*.tw. (4)
18 stroke$1.tw. (57283)
19 (TBI* or traumatic brain injur*).tw. (5449)
20 or/2-19 [Set 1: causes of neurological death] (82387)
21 Brain Death/ (84)
22 Brain Injuries/mo (0)
23 Persistent Vegetative State/ (70)
24 ((absen* or lack* or loss of or no) adj2 reflex*).tw. (377)
25 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
26 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
27 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (832)
28 cerebral performance categor*.tw. (287)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
31 (electro-cerebral silence or electrocerebral silence).tw. (1)
32 (loss of brain* adj1 (function* or reflex*)).tw. (8)
33 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw. (35)
35 or/21-34 [Set 2: brain death or persistent loss of neurological function] (1594)
36 Brain Death/di (0)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 (dead or death$1)).tw. (2074)
38 36 or 37 [Set 3: Death determination] (2074)
39 Apnea/di (0)
40 Apnea/ and (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*).tw. (732)
41 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw. (1169)
42 or/39-41 [Set 4: Apnea test] (1779)
43 Blood Gas Analysis/ (1247)
44 Carbon Dioxide/bl (0)
45 Partial Pressure/ (673)
46 blood gas*.tw. (5526)
47 ((carbon dioxide or CO2) adj2 challenge).tw. (120)
48 ((carbon dioxide or CO2) adj2 pressure).tw. (1135)
49 ((carbon dioxide or CO2) adj2 tension).tw. (479)
50 ((h?emo-dynamic or h?emodynamic) adj1 (assess* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw. (2855)
51 mmHG.tw. (21909)
52 (paCO2 or p CO2 or p CO 2 or pCO2 or pvCO2).tw. (3062)
53 partial pressure of carbon dioxide.tw. (397)
54 partial pressure of CO2.tw. (58)
55 or/43-54 [Set 5: PCO2] (32403)

56 and/20,42,55 [Sets 1 and 4 and 5] (8)
57 and/35,42,55 [Sets 2 and 4 and 5] (6)
58 and/38,42,55 [Sets 3 and 4 and 5] (6)
59 or/1,56-58 (13)
60 remove duplicates from 59 [CENTRAL results for export] (13)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: June 16, 2021
Strategy:

# 9	71	#8 OR #7 OR #6 *Indexes=SCI-EXPANDED Timespan=All years*
# 8	50	#5 AND #4 AND #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	59	#5 AND #4 AND #2 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	34	#5 AND #4 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	118,842	TS=("blood gas*" or (("carbon dioxide" or CO2) NEAR/2 (challenge or pressure or tension)) or (("h$emo dynamic" or h$emodynamic) NEAR/1 (assess* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)) or mmHG or paCO2 or "p CO2" or "p CO 2" or "pCO2" or pvCO2 or "partial pressure o f carbon dioxide" or "partial pressure of CO2") *Indexes=SCI-EXPANDED Timespan=All years*
# 4	5,693	TS=((apne* or apnoe*) NEAR/3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	24,753	TS=((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) NEAR /3 (dead or death*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	20,476	TS=(((absen* or lack* or "loss of" or no) NEAR/2 reflex*) or ("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or "cerebral performance categor*" or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or "electro cerebral silence" or "electrocerebral silence" or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware*))) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	587,804	TS=(apoplex* or ((arrest* or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart or postcardi*)) or asystol* or ((brain* or cerebral) NEAR/2 (hypoxi* or infarct* or isch$emi*)) or "brain trauma*" or "cerebral circulatory arrest*" or (("cerebro-vascular" or cerebrovascular) NEAR/1 (accident* or event*)) or coma* or "devastating brain injur*" or stroke* or "traumatic brain injur*") *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients who are undergoing apnea testing as part of neurological determination of death, does using any CO2 insufflation as compared to not using CO2 insufflation improve the ability to complete the apnea test or influence the accuracy of neurological determination of death?*

Results of the search: The search retrieved a total of 1372 references and 743 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	452	451
Embase	574	230
CENTRAL	23	11
Web of Science	323	51
Total:	**1372**	**743**

Database: Ovid MEDLINE(R) ALL 1946 to June 15, 2021
Date search conducted: June 19, 2021
Strategy:
1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Carbon Dioxide/ or Insufflation/) [Coordinated concept] (42)
2 Brain Death/ (8882)
3 Brain Injuries/mo (2076)
4 Persistent Vegetative State/ (3028)
5 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kf. (2117)
6 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
7 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
8 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11879)
9 cerebral performance categor*.tw,kf. (1415)
10 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (45)
11 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
12 (electro-cerebral silence or electrocerebral silence).tw,kf. (94)
13 (loss of brain* adj1 (function* or reflex*)).tw,kf. (193)
14 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (330)
15 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kf. (1255)
16 or/2-15 [Set 1: brain death or persistent loss of neurological function] (24570)
17 Brain Death/di (1852)
18 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 (dead or death$1)).tw,kf. (21915)
19 17 or 18 [Set 2: Death determination] (22794)
20 Apnea/di (871)
21 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kf. (4413)
22 20 or 21 [Set 3: Apnea test] (5036)
23 *Carbon Dioxide/ (35846)
24 Carbon Dioxide/ad, ae (2830)
25 Carbon Dioxide/ and Insufflation/ (864)
26 Insufflation/ and (carbon dioxide or CO2).tw,kf. (906)
27 (carbon dioxide or CO2).ti. (44842)
28 ((carbon dioxide or CO2) adj2 administ*).tw,kf. (230)
29 ((carbon dioxide or CO2) adj2 aerat*).tw,kf. (66)
30 ((carbon dioxide or CO2) adj2 augment*).tw,kf. (89)
31 ((carbon dioxide or CO2) adj2 blend*).tw,kf. (36)

32 ((carbon dioxide or CO2) adj2 deliver*).tw,kf. (262)
33 ((carbon dioxide or CO2) adj5 insufflat*).tw,kf. (1998)
34 or/23-33 [Set 4: CO2 insufflation] (61075)
35 and/16,34 [Sets 1 and 4] (62)
36 and/19,22 [Sets 2 and 3] (341)
37 and/19,34 [Sets 2 and 4] (44)
38 and/22,34 [Sets 3 and 4] (63)
39 or/1,35-38 (452)
40 remove duplicates from 39 [MEDLINE results for export] (452)

Database: Ovid Embase Classic+Embase 1947 to 2021 June 18
Date search conducted: June 19, 2021
Strategy:
1 brain death/di and (aeration/ or carbon dioxide/) [Coordinated concept] (1)
2 brain death/ (15711)
3 persistent vegetative state/ (5132)
4 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kw. (4321)
5 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (90)
6 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (54)
7 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18726)
8 cerebral performance categor*.tw,kw. (2939)
9 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (55)
10 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
11 (electro-cerebral silence or electrocerebral silence).tw,kw. (122)
12 (loss of brain* adj1 (function* or reflex*)).tw,kw. (300)
13 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (500)
14 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kw. (1660)
15 or/2-14 [Set 1: brain death or persistent loss of neurological function] (36686)
16 brain death/di (564)
17 ((confirm* or criteri* or declar* or determin* or diagnos* or exam*) adj3 (dead or death$1)).tw,kw. (32954)
18 16 or 17 [Set 2: Death determination] (33293)
19 apnea/di (753)
20 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kw. (7569)
21 19 or 20 [Set 3: Apnea test] (8170)
22 *carbon dioxide/ (41824)
23 carbon dioxide/ad (510)
24 carbon dioxide/ and aeration/ (1959)
25 aeration/ and (carbon dioxide or CO2).tw,kw. (2427)
26 (carbon dioxide or CO2).ti. (48864)
27 ((carbon dioxide or CO2) adj2 administ*).tw,kw. (473)
28 ((carbon dioxide or CO2) adj2 aerat*).tw,kw. (96)
29 ((carbon dioxide or CO2) adj2 augment*).tw,kw. (125)
30 ((carbon dioxide or CO2) adj2 blend*).tw,kw. (55)
31 ((carbon dioxide or CO2) adj2 deliver*).tw,kw. (414)
32 ((carbon dioxide or CO2) adj5 insufflat*).tw,kw. (3298)
33 or/22-32 [Set 4: CO2 insufflation] (64989)
34 and/15,33 [Sets 1 and 4] (71)
35 and/18,21 [Sets 2 and 3] (456)
36 and/18,33 [Sets 2 and 4] (46)
37 and/21,33 [Sets 3 and 4] (71)
38 or/1,34-37 (585)
39 remove duplicates from 38 [Embase results for export] (574)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials May 2021
Date search conducted: June 19, 2021
Strategy:
1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Carbon Dioxide/ or Insufflation/) [Coordinated concept] (0)
2 Brain Death/ (84)
3 Brain Injuries/mo (0)
4 Persistent Vegetative State/ (70)
5 ((absen* or lack* or loss of or no) adj2 reflex*).tw. (377)
6 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
7 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
8 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (832)
9 cerebral performance categor*.tw. (287)
10 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
11 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
12 (electro-cerebral silence or electrocerebral silence).tw. (1)
13 (loss of brain* adj1 (function* or reflex*)).tw. (8)
14 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
15 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw. (35)
16 or/2-15 [Set 1: brain death or persistent loss of neurological function] (1594)
17 Brain Death/di (0)
18 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 (dead or death$1)).tw. (2074)
19 17 or 18 [Set 2: Death determination] (2074)
20 Apnea/di (0)
21 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw. (1169)
22 20 or 21 [Set 3: Apnea test] (1169)
23 *Carbon Dioxide/ (0)
24 Carbon Dioxide/ad, ae (0)
25 Carbon Dioxide/ and Insufflation/ (143)
26 Insufflation/ and (carbon dioxide or CO2).tw. (150)
27 (carbon dioxide or CO2).ti. (2306)
28 ((carbon dioxide or CO2) adj2 administ*).tw. (62)
29 ((carbon dioxide or CO2) adj2 aerat*).tw. (3)
30 ((carbon dioxide or CO2) adj2 augment*).tw. (10)
31 ((carbon dioxide or CO2) adj2 blend*).tw. (1)
32 ((carbon dioxide or CO2) adj2 deliver*).tw. (48)
33 ((carbon dioxide or CO2) adj5 insufflat*).tw. (662)
34 or/23-33 [Set 4: CO2 insufflation] (2677)
35 and/16,34 [Sets 1 and 4] (5)
36 and/19,22 [Sets 2 and 3] (13)
37 and/19,34 [Sets 2 and 4] (4)
38 and/22,34 [Sets 3 and 4] (7)
39 or/1,35-38 (23)
40 remove duplicates from 39 [CENTRAL results for export] (23)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: June 19, 2021
Strategy:

# 9	**323**	#8 OR #7 OR #6 OR #5 *Indexes=SCI-EXPANDED Timespan=All years*

# 8	**43**	#4 AND #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**35**	#4 AND #2 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**246**	#3 AND #2 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**34**	#4 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**179,899**	TI=("carbon dioxide" or CO2) or TS=(("carbon dioxide" or CO2) NEAR/2 (administ* or aerat* or augment* or blend* or deliver* or insufflat*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**5,695**	TS=((apne* or apnoe*) NEAR/3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**24,769**	TS=((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) NEAR/3 (dead or death*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**20,492**	TS=(((absen* or lack* or "loss of" or no) NEAR/2 reflex*) or ("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or "cerebral performance categor*" or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or "electro cerebral silence" or "electrocerebral silence" or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware*))) *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients who are undergoing apnea testing as part of neurological determination of death, does using passive oxygenation (CPAP or continuous oxygen insufflation) as compared to not using passive oxygenation improve the ability to complete the apnea test or influence the accuracy of neurological determination of death?*

Results of the search: The search retrieved a total of 814 references and 523 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	195	194
Embase	313	185
CENTRAL	134	90
Web of Science	172	54
Total:	**814**	**523**

Database: Ovid MEDLINE(R) ALL 1946 to June 11, 2021
Date search conducted: June 12, 2021
Strategy:

1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Continuous Positive Airway Pressure/ or Noninvasive Ventilation/) [Coordinated concept] (13)
2 Brain Injuries, Traumatic/ (7979)
3 exp Brain Ischemia/ (113375)
4 Coma/ (12642)
5 Coma, Post-Head Injury/ (125)
6 exp Heart Arrest/ (50292)
7 exp Hypoxia, Brain/ (13212)
8 exp Stroke/ (144660)
9 apoplex*.tw,kf. (3350)
10 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kf. (96306)
11 asystol*.tw,kf. (4429)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kf. (72818)
13 brain trauma*.tw,kf. (2879)
14 cerebral circulatory arrest$1.tw,kf. (152)
15 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kf. (14023)
16 coma*.tw,kf. (42902)
17 devastating brain injur*.tw,kf. (51)
18 stroke$1.tw,kf. (271506)
19 (TBI* or traumatic brain injur*).tw,kf. (49249)
20 or/2-19 [Set 1: causes of neurological death] (569234)
21 Brain Death/ (8876)
22 Brain Injuries/mo (2076)
23 Persistent Vegetative State/ (3029)
24 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kf. (2114)
25 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
26 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
27 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11864)
28 cerebral performance categor*.tw,kf. (1410)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (45)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
31 (electro-cerebral silence or electrocerebral silence).tw,kf. (94)
32 (loss of brain* adj1 (function* or reflex*)).tw,kf. (193)

33 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (330)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kf. (1255)
35 or/21-34 [Set 2: brain death or persistent loss of neurological function] (24548)
36 Brain Death/di (1849)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 (dead or death$1)).tw,kf. (21879)
38 36 or 37 [Set 3: Death determination] (22758)
39 Apnea/di (872)
40 Apnea/ and (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*).mp. (4140)
41 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kf. (4406)
42 or/39-41 [Set 4: Apnea test] (7928)
43 Continuous Positive Airway Pressure/ (7749)
44 Noninvasive Ventilation/ (2640)
45 Positive Pressure Ventilation/ (17576)
46 CIO.tw,kf. (522)
47 (continuous adj1 (flow of oxygen or oxygen flow)).tw,kf. (64)
48 (continuous adj3 insufflation).tw,kf. (102)
49 (continuous positive adj2 pressure).tw,kf. (10946)
50 ((nasal* or mask*) adj2 (respirat* or ventilat*)).tw,kf. (4348)
51 (nCPAP* or CPAP*).tw,kf. (10000)
52 ((noninvasive or non-invasive) adj5 (respirat* or ventilat*)).tw,kf. (10575)
53 NPPV.tw,kf. (589)
54 passive oxygen*.tw,kf. (36)
55 (positive pressure adj2 (respirat* or ventilat*)).tw,kf. (6981)
56 or/43-55 [Set 5: Passive oxygenation] (45042)
57 and/20,42,56 [Sets 1 and 4 and 5] (70)
58 and/35,56 [Sets 2 and 5] (96)
59 and/38,56 [Sets 3 and 5] (81)
60 or/1,57-59 (195)
61 remove duplicates from 60 [MEDLINE results for export] (195)

Database: Ovid Embase Classic+Embase 1947 to 2021 June 11
Date search conducted: June 12, 2021
Strategy:
1 brain hypoxia/ (12352)
2 exp brain ischemia/ (201388)
3 exp cerebrovascular accident/ (235044)
4 coma/ (35767)
5 exp heart arrest/ (108603)
6 exp traumatic brain injury/ (55258)
7 apoplex*.tw,kw. (4822)
8 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw,kw. (159531)
9 asystol*.tw,kw. (7829)
10 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kw. (106585)
11 brain trauma*.tw,kw. (4328)
12 cerebral circulatory arrest$1.tw,kw. (246)
13 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kw. (24593)
14 coma*.tw,kw. (63965)
15 devastating brain injur*.tw,kw. (83)
16 stroke$1.tw,kw. (441970)
17 (TBI* or traumatic brain injur*).tw,kw. (76839)

18 or/1-17 [Set 1: causes of neurological death] (943714)
19 brain death/ (15684)
20 persistent vegetative state/ (5129)
21 ((absen* or lack* or loss of or no) adj2 reflex*).tw,kw. (4319)
22 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (90)
23 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (54)
24 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18695)
25 cerebral performance categor*.tw,kw. (2930)
26 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (55)
27 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
28 (electro-cerebral silence or electrocerebral silence).tw,kw. (121)
29 (loss of brain* adj1 (function* or reflex*)).tw,kw. (299)
30 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (499)
31 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw,kw. (1656)
32 or/19-31 [Set 2: brain death or persistent loss of neurological function] (36624)
33 brain death/di (564)
34 ((confirm* or criteri* or declar* or determin* or diagnos* or exam*) adj3 (dead or death$1)).tw,kw. (32911)
35 33 or 34 [Set 3: Death determination] (33250)
36 apnea/di (753)
37 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw,kw. (7567)
38 36 or 37 [Set 4: Apnea test] (8168)
39 exp continuous positive airway pressure/ (3109)
40 exp noninvasive positive pressure ventilation/ (475)
41 positive pressure ventilation/ (1025)
42 CIO.tw,kw. (587)
43 (continuous adj1 (flow of oxygen or oxygen flow)).tw,kw. (85)
44 (continuous adj3 insufflation).tw,kw. (141)
45 (continuous positive adj2 pressure).tw,kw. (16291)
46 ((nasal* or mask*) adj2 (respirat* or ventilat*)).tw,kw. (6415)
47 (nCPAP* or CPAP*).tw,kw. (18973)
48 ((noninvasive or non-invasive) adj5 (respirat* or ventilat*)).tw,kw. (19053)
49 NPPV.tw,kw. (943)
50 passive oxygen*.tw,kw. (58)
51 (positive pressure adj2 (respirat* or ventilat*)).tw,kw. (10689)
52 or/39-51 [Set 5: Passive oxygenation] (55597)
53 and/18,38,52 [Sets 1 and 4 and 5] (105)
54 and/32,52 [Sets 2 and 5] (150)
55 and/35,52 [Sets 3 and 5] (125)
56 or/53-55 (319)
57 remove duplicates from 56 [Embase results for export] (313)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials May 2021
Date search conducted: June 12, 2021
Strategy:
1 (Brain Death/di or Diagnostic Techniques, Neurological/me or Neurological Examination/me, st) and (Continuous Positive Airway Pressure/ or Noninvasive Ventilation/) [Coordinated concept] (0)
2 Brain Injuries, Traumatic/ (619)
3 exp Brain Ischemia/ (3682)
4 Coma/ (205)
5 Coma, Post-Head Injury/ (4)
6 exp Heart Arrest/ (2011)
7 exp Hypoxia, Brain/ (313)

8 exp Stroke/ (10246)
9 apoplex*.tw. (353)
10 ((arrest$1 or death$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart or postcardi*)).tw. (14989)
11 asystol*.tw. (313)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw. (6308)
13 brain trauma*.tw. (190)
14 cerebral circulatory arrest$1.tw. (1)
15 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw. (2223)
16 coma*.tw. (3585)
17 devastating brain injur*.tw. (4)
18 stroke$1.tw. (57283)
19 (TBI* or traumatic brain injur*).tw. (5449)
20 or/2-19 [Set 1: causes of neurological death] (82387)
21 Brain Death/ (84)
22 Brain Injuries/mo (0)
23 Persistent Vegetative State/ (70)
24 ((absen* or lack* or loss of or no) adj2 reflex*).tw. (377)
25 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
26 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
27 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (832)
28 cerebral performance categor*.tw. (287)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
31 (electro-cerebral silence or electrocerebral silence).tw. (1)
32 (loss of brain* adj1 (function* or reflex*)).tw. (8)
33 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware*)).tw. (35)
35 or/21-34 [Set 2: brain death or persistent loss of neurological function] (1594)
36 Brain Death/di (0)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) adj3 (dead or death$1)).tw. (2074)
38 36 or 37 [Set 3: Death determination] (2074)
39 Apnea/di (0)
40 Apnea/ and (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*).tw. (732)
41 ((apne* or apnoe*) adj3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)).tw. (1169)
42 or/39-41 [Set 4: Apnea test] (1779)
43 Continuous Positive Airway Pressure/ (1114)
44 Noninvasive Ventilation/ (264)
45 Positive Pressure Ventilation/ (1518)
46 CIO.tw. (15)
47 (continuous adj1 (flow of oxygen or oxygen flow)).tw. (30)
48 (continuous adj3 insufflation).tw. (21)
49 (continuous positive adj2 pressure).tw. (3980)
50 ((nasal* or mask*) adj2 (respirat* or ventilat*)).tw. (1663)
51 (nCPAP* or CPAP*).tw. (5133)
52 ((noninvasive or non-invasive) adj5 (respirat* or ventilat*)).tw. (3630)
53 NPPV.tw. (217)
54 passive oxygen*.tw. (7)
55 (positive pressure adj2 (respirat* or ventilat*)).tw. (1605)
56 or/43-55 [Set 5: Passive oxygenation] (11730)
57 and/20,42,56 [Sets 1 and 4 and 5] (81)

58 and/35,56 [Sets 2 and 5] (34)
59 and/38,56 [Sets 3 and 5] (31)
60 or/1,57-59 (135)
61 remove duplicates from 60 [CENTRAL results for export] (134)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: June 12, 2021
Strategy:

# 9	**172**	#8 OR #7 OR #6 *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**66**	#5 AND #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**67**	#5 AND #2 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**66**	#5 AND #4 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**34,811**	TS=(CIO or (continuous NEAR/1 ("flow of oxygen" or "oxygen flow")) or (continuous NEAR/3 insufflation) or ("continuous positive" NEAR/2 pressure) or ((nasal* or mask*) NEAR/2 (respirat* or ventilat*)) or nCPAP* or CPAP* or ((noninvasive or "non invasive") NEAR/5 (respirat* or ventilat*)) or NPPV or "passive oxygen*" or ("positive pressure" NEAR/2 (respirat* or ventilat*))) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**5,689**	TS=((apne* or apnoe*) NEAR/3 (assess* or diagnos* or evaluat* or exam* or finding* or measur* or monitor* or prognosticat* or test*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**24,740**	TS=((confirm* or criteri* or declar* or determin* or diagnos* or exam* or pronounc*) NEAR /3 (dead or death*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**20,467**	TS=(((absen* or lack* or "loss of" or no) NEAR/2 reflex*) or ("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or "cerebral performance categor*" or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or "electro cerebral silence" or "electrocerebral silence" or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware*))) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**587,356**	TS=(apoplex* or ((arrest* or death* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart or postcardi*)) or asystol* or ((brain* or cerebral) NEAR/2 (hypoxi* or infarct* or isch$emi*)) or "brain trauma*" or "cerebral circulatory arrest*" or (("cerebro-vascular" or cerebrovascular) NEAR/1 (accident* or event*)) or coma* or "devastating brain injur*" or stroke* or "traumatic brain injur*") *Indexes=SCI-EXPANDED Timespan=All years*

Review question: *In patients who appear to meet criteria for neurological determination of death, does addition of a separate neurological determination of death exam separated in time, compared to a single exam, improve the accuracy of neurological determination of death?*

Results of the search: The search retrieved a total of 1766 references and 1147 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	557	557
Embase	720	386
CENTRAL	42	15*
Web of Science	447	189
Total:	**1766**	**1147**

*11 pre-2018 conference proceedings removed manually from EndNote

Database: Ovid MEDLINE(R) ALL 1946 to May 21, 2021
Date search conducted: May 24, 2021
Strategy:

1 *Brain Death/di and (Diagnostic Techniques, Neurological/ or Neurophysiological Monitoring/ or Practice Patterns, Physicians/ or Practice Guidelines as Topic/) [Coordinated concept] (130)
2 Brain Injuries, Traumatic/ (7842)
3 exp Brain Ischemia/ (113058)
4 Carbon Monoxide Poisoning/ (5514)
5 exp Heart Arrest/ (50125)
6 exp Hypoglycemia/ (29052)
7 exp Hypoxia, Brain/ (13179)
8 exp Stroke/ (143917)
9 apoplex*.tw,kf. (3335)
10 ((arrest$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw,kf. (49580)
11 asystol*.tw,kf. (4416)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kf. (72548)
13 brain trauma*.tw,kf. (2872)
14 carbon monoxide.tw,kf. (28890)
15 cerebral circulatory arrest$1.tw,kf. (152)
16 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kf. (13958)
17 devastating brain injur*.tw,kf. (51)
18 (hypo glyc?emi* or hypoglyc?emi*).tw,kf. (60027)
19 stroke$1.tw,kf. (270095)
20 (TBI* or traumatic brain injur*).tw,kf. (48983)
21 or/2-20 [Set 1: causes of neurological death] (592443)
22 Brain Death/ (8858)
23 Persistent Vegetative State/ (3022)
24 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kf. (53)
25 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (45)
26 (absen* adj3 motor respons*).tw,kf. (104)
27 ((brain* or cerebral) adj2 arrest).tw,kf. (650)
28 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kf. (11839)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kf. (44)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kf. (13)
31 (loss of brain* adj1 (function* or reflex*)).tw,kf. (192)
32 (loss of neuro* adj1 (function* or reflex*)).tw,kf. (329)

33 never regain* consciousness.tw,kf. (31)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware* or unconscious*)).tw,kf. (1336)
35 or/22-34 [Set 2: brain death] (19821)
36 Brain Death/di (1841)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam*) adj3 death$1).tw,kf. (20009)
38 36 or 37 [Set 3: Death determination] (20899)
39 Diagnosis/ (17435)
40 Outcome Assessment, Health Care/ (76063)
41 Predictive Value of Tests/ (210890)
42 Prognosis/ (535429)
43 Recovery of Function/ (55485)
44 Reproducibility of Results/ (416039)
45 exp "Sensitivity and Specificity"/ (607414)
46 di.fs. (2662288)
47 accura*.tw,kf. (867583)
48 clinical utility.tw,kf. (28036)
49 diagnos*.tw,kf. (2668035)
50 ((false or true) adj (neg* or pos*)).tw,kf. (85872)
51 neuroprognos*.tw,kf. (109)
52 precis*.tw,kf. (385732)
53 predict*.tw,kf. (1708557)
54 prognos*.tw,kf. (664978)
55 ((recover* or regain*) adj3 (consciousness or function*)).tw,kf. (53633)
56 reliab*.tw,kf. (517324)
57 reproducib*.tw,kf. (171050)
58 reversal of findings.tw,kf. (51)
59 ROC curve.tw,kf. (30663)
60 sensitiv*.tw,kf. (1463736)
61 specifi*.tw,kf. (3351914)
62 valid*.tw,kf. (808468)
63 or/39-62 [Set 4: Diagnostic accuracy] (10637185)
64 Apnea/ and (assess* or evaluat* or exam* or measur* or prognosticat* or test*).tw,kf. (2629)
65 Diagnostic Techniques, Neurological/ (1517)
66 exp Neurologic Examination/ (170354)
67 Physical Examination/ (41644)
68 Reflex, Pupillary/ and (assess* or evaluat* or exam* or measur* or prognosticat* or test*).tw,kf. (1408)
69 apnea test*.tw,kf. (520)
70 ((assess* or evaluat* or exam* or measur* or prognosticat* or test*) adj5 (pupil or pupillary or pupils)).tw,kf. (4862)
71 ((bed side or bedside or clinical* or neuro* or physical) adj3 (assess* or evaluat* or exam* or finding* or test*)).tw,kf. (731129)
72 ((cornea* or pupil* or OCR or oculocephalic or oculovestibular or OVR) adj2 (reflex* or respon* or test*)).tw,kf. (6293)
73 ((gag or cough) adj3 (reflex* or respons* or test*)).tw,kf. (3711)
74 or/64-73 [Apnea test or clinical exam] (924297)
75 and/21,35,63,74 (473)
76 and/21,38,63,74 (274)
77 or/1,75-76 (690)
78 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4834121)
79 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or

raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2265633)
80 78 or 79 (5216119)
81 77 not 80 [exclude animal studies] (626)
82 limit 81 to (english or french) (557)
83 remove duplicates from 82 [MEDLINE results for export] (557)

Database: Ovid Embase Classic+Embase 1947 to 2021 May 21
Date search conducted: May 24, 2021
Strategy:
1 *brain death/di and (clinical practice/ or neurologic examination/ or neurophysiological monitoring/ or exp practice guideline/) [Coordinated concept] (65)
2 brain hypoxia/ (12325)
3 exp brain ischemia/ (200983)
4 carbon monoxide intoxication/ (7198)
5 exp cerebrovascular accident/ (233600)
6 exp heart arrest/ (108029)
7 exp hypoglycemia/ (93234)
8 exp traumatic brain injury/ (54945)
9 apoplex*.tw,kw. (4802)
10 ((arrest$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw,kw. (79270)
11 asystol*.tw,kw. (7812)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw,kw. (106182)
13 brain trauma*.tw,kw. (4318)
14 carbon monoxide.tw,kw. (37494)
15 cerebral circulatory arrest$1.tw,kw. (246)
16 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw,kw. (24510)
17 devastating brain injur*.tw,kw. (83)
18 (hypo glyc?emi* or hypoglyc?emi*).tw,kw. (98840)
19 stroke$1.tw,kw. (439833)
20 (TBI* or traumatic brain injur*).tw,kw. (76485)
21 or/2-20 [Set 1: causes of neurological death] (985779)
22 brain death/ (15650)
23 persistent vegetative state/ (5117)
24 (absence of brain* adj1 (activit* or function* or reflex*)).tw,kw. (89)
25 (absence of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (54)
26 (absen* adj3 motor respons*).tw,kw. (191)
27 ((brain* or cerebral) adj2 arrest).tw,kw. (996)
28 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw,kw. (18636)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw,kw. (55)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw,kw. (15)
31 (loss of brain* adj1 (function* or reflex*)).tw,kw. (296)
32 (loss of neuro* adj1 (function* or reflex*)).tw,kw. (493)
33 never regain* consciousness.tw,kw. (53)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware* or unconscious*)).tw,kw. (1761)
35 or/22-34 [Set 2: brain death] (30565)
36 brain death/di (564)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam*) adj3 death$1).tw,kw. (30844)
38 36 or 37 [Set 3: Death determination] (31187)
39 diagnostic accuracy/ (265834)
40 predictive value/ (190986)
41 prognosis/ (653350)
42 reproducibility/ (230741)

43 exp "sensitivity and specificity"/ (393487)
44 accura*.tw,kw. (1140710)
45 clinical utility.tw,kw. (41606)
46 diagnos*.tw,kw. (4030773)
47 ((false or true) adj (neg* or pos*)).tw,kw. (122437)
48 neuroprognos*.tw,kw. (184)
49 precis*.tw,kw. (496027)
50 predict*.tw,kw. (2318591)
51 prognos*.tw,kw. (1046581)
52 ((recover* or regain*) adj3 (consciousness or function*)).tw,kw. (78340)
53 reliab*.tw,kw. (677539)
54 reproducib*.tw,kw. (226559)
55 reversal of findings.tw,kw. (59)
56 ROC curve.tw,kw. (53985)
57 sensitiv*.tw,kw. (1910352)
58 specifi*.tw,kw. (4353482)
59 valid*.tw,kw. (1140557)
60 or/39-59 [Set 4: Diagnostic accuracy] (12405313)
61 apnea/ and (assess* or evaluat* or exam* or measur* or prognosticat* or test*).tw,kw. (12038)
62 corneal reflex test/ (75)
63 neurologic examination/ (72431)
64 physical examination/ (235280)
65 pupil reflex/ and (assess* or evaluat* or exam* or measur* or prognosticat* or test*).tw,kw. (3389)
66 apnea test*.tw,kw. (885)
67 ((assess* or evaluat* or exam* or measur* or prognosticat* or test*) adj5 (pupil or pupillary or pupils)).tw,kw. (7117)
68 ((bed side or bedside or clinical* or neuro* or physical) adj3 (assess* or evaluat* or exam* or finding* or test*)).tw,kw. (1130144)
69 ((cornea* or pupil* or OCR or oculocephalic or oculovestibular or OVR) adj2 (reflex* or respon* or test*)).tw,kw. (9228)
70 ((gag or cough) adj3 (reflex* or respons* or test*)).tw,kw. (6135)
71 or/61-70 [Apnea test or clinical exam] (1345496)
72 and/21,35,60,71 (938)
73 and/21,38,60,71 (481)
74 or/1,72-73 (1193)
75 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5899905)
76 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2654239)
77 75 or 76 (6260263)
78 74 not 77 [exclude animal studies] (1110)
79 (Conference Abstract or Conference Paper or Conference Review).pt. (4865522)
80 78 and 79 (394)
81 limit 80 to yr="2018-2021" (94)
82 78 not 79 [exclude conference proceedings] (716)
83 81 or 82 [add proceedings from last 3 yrs] (810)
84 limit 83 to (english or french) (734)
85 remove duplicates from 84 [Embase results for export] (720)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials April 2021
Date search conducted: May 24, 2021
Strategy:

1 *Brain Death/di and (Diagnostic Techniques, Neurological/ or Neurophysiological Monitoring/ or Practice Patterns, Physicians/ or Practice Guidelines as Topic/) [Coordinated concept] (0)
2 Brain Injuries, Traumatic/ (607)
3 exp Brain Ischemia/ (3663)
4 Carbon Monoxide Poisoning/ (61)
5 exp Heart Arrest/ (2004)
6 exp Hypoglycemia/ (2267)
7 exp Hypoxia, Brain/ (309)
8 exp Stroke/ (10169)
9 apoplex*.tw. (352)
10 ((arrest$1 or flat-lin* or flatlin*) adj2 (cardi* or circulat* or heart)).tw. (4720)
11 asystol*.tw. (312)
12 ((brain* or cerebral) adj2 (hypoxi* or infarct* or isch?emi*)).tw. (6272)
13 brain trauma*.tw. (189)
14 ((cerebro-vascular or cerebrovascular) adj1 (accident* or event*)).tw. (2202)
15 devastating brain injur*.tw. (4)
16 carbon monoxide.tw. (2359)
17 cerebral circulatory arrest$1.tw. (1)
18 (hypo glyc?emi* or hypoglyc?emi*).tw. (12783)
19 stroke$1.tw. (56712)
20 (TBI* or traumatic brain injur*).tw. (5372)
21 or/2-20 [Set 1: causes of neurological death] (87942)
22 Brain Death/ (84)
23 Persistent Vegetative State/ (70)
24 (absence of brain* adj1 (activit* or function* or reflex*)).tw. (0)
25 (absence of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
26 (absen* adj3 motor respons*).tw. (8)
27 ((brain* or cerebral) adj2 arrest).tw. (66)
28 ((brain* or cerebral or neurologic*) adj2 (dead or death$1)).tw. (826)
29 (cessation of brain* adj1 (activit* or function* or reflex*)).tw. (1)
30 (cessation of neuro* adj1 (activit* or function* or reflex*)).tw. (0)
31 (loss of brain* adj1 (function* or reflex*)).tw. (8)
32 (loss of neuro* adj1 (function* or reflex*)).tw. (17)
33 never regain* consciousness.tw. (0)
34 ((permanent* or persistent*) adj2 (vegetative* or unaware* or unconscious*)).tw. (42)
35 or/22-34 [Set 2: brain death] (1030)
36 Brain Death/di (0)
37 ((confirm* or criteri* or declar* or determin* or diagnos* or exam*) adj3 death$1).tw. (1958)
38 36 or 37 [Set 3: Death determination] (1958)
39 Diagnosis/ (65)
40 Outcome Assessment, Health Care/ (7803)
41 Predictive Value of Tests/ (7459)
42 Prognosis/ (14537)
43 Recovery of Function/ (5379)
44 Reproducibility of Results/ (11965)
45 exp "Sensitivity and Specificity"/ (16724)
46 accura*.tw. (35656)
47 clinical utility.tw. (2296)
48 diagnos*.tw. (167119)
49 ((false or true) adj (neg* or pos*)).tw. (3604)

50 neuroprognos*.tw. (3)
51 precis*.tw. (11101)
52 predict*.tw. (107174)
53 prognos*.tw. (38220)
54 ((recover* or regain*) adj3 (consciousness or function*)).tw. (8608)
55 reliab*.tw. (27494)
56 reproducib*.tw. (6565)
57 reversal of findings.tw. (1)
58 ROC curve.tw. (1605)
59 sensitiv*.tw. (72613)
60 specifi*.tw. (149604)
61 valid*.tw. (59879)
62 or/39-61 [Set 4: Diagnostic accuracy] (511547)
63 Apnea/ and (assess* or evaluat* or exam* or measur* or prognosticat* or test*).tw. (681)
64 Diagnostic Techniques, Neurological/ (48)
65 exp Neurologic Examination/ (23603)
66 Physical Examination/ (842)
67 Reflex, Pupillary/ and (assess* or evaluat* or exam* or measur* or prognosticat* or test*).tw. (80)
68 apnea test*.tw. (56)
69 ((assess* or evaluat* or exam* or measur* or prognosticat* or test*) adj5 (pupil or pupillary or pupils)).tw. (1211)
70 ((bed side or bedside or clinical* or neuro* or physical) adj3 (assess* or evaluat* or exam* or finding* or test*)).tw. (143020)
71 ((cornea* or pupil* or OCR or oculocephalic or oculovestibular or OVR) adj2 (reflex* or respon* or test*)).tw. (885)
72 ((gag or cough) adj3 (reflex* or respons* or test*)).tw. (1090)
73 or/63-72 [Apnea test or clinical exam] (167759)
74 and/21,35,62,73 (53)
75 and/21,38,62,73 (17)
76 or/1,74-75 (68)
77 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (16)
78 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (5565)
79 77 or 78 (5581)
80 76 not 79 [exclude animal studies] (67)
81 limit 80 to (english or french) (45)
82 remove duplicates from 81 [CENTRAL records for export] (42)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: May 24, 2021
Strategy:

# 10	**447**	(#8 NOT #9) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	**2,830,711**	(TI=((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or

		racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**489**	#7 OR #6 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**190**	#5 AND #4 AND #3 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**403**	#5 AND #4 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**678,897**	(TS=("apnea test*" or ((assess* or evaluat* or exam* or measur* or prognosticat* or test*) NEAR/5 (pupil or pupillary or pupils)) or (("bed side" or bedside or clinical* or neuro* or physical) NEAR/3 (assess* or evaluat* or exam* or finding* or test*)) or ((cornea* or pupil* or OCR or oculocephalic or oculovestibular or OVR) NEAR2 (reflex* or respon* or test*)) or ((gag or cough) NEAR/3 (reflex* or respons* or test*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**11,864,484**	(TS=(accura* or "clinical utility" or diagnos* or ((false or true) NEAR/1 (neg* or pos*)) or neuroprognos* or precis* or predict* or prognos* or ((recover* or regain*) NEAR/3 (consciousness or function*)) or reliab* or reproducib* or "reversal of findings" or "ROC curve" or sensitiv* or specifi* or valid*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**21,383**	(TS=((confirm* or criteri* or declar* or determin* or diagnos* or exam*) NEAR/3 death*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**16,294**	(TS=(("absence of brain*" NEAR/1 (activit* or function* or reflex*)) or ("absence of neuro*" NEAR/1 (activit* or function* or reflex*)) or (absen* NEAR/3 "motor respons*") or ((brain* or cerebral) NEAR/2 arrest) or ((brain* or cerebral or neurologic*) NEAR/2 (dead or death*)) or ("cessation of brain*" NEAR/1 (activit* or function* or reflex*)) or ("cessation of neuro*" NEAR/1 (activit* or function* or reflex*)) or ("loss of brain*" NEAR/1 (function* or reflex*)) or ("loss of neuro*" NEAR/1 (function* or reflex*)) or "never regain* consciousness" or ((permanent* or persistent*) NEAR/2 (vegetative* or unaware* or unconscious*)))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**622,362**	(TS=(apoplex* or ((arrest* or "flat lin*" or flatlin*) NEAR/2 (cardi* or circulat* or heart)) or asystol* or ((brain* or cerebral) NEAR/2 (hypoxi* or infarct* or isch$emi*)) or "brain trauma*" or "carbon monoxide" or "cerebral circulatory arrest*" or (" cerebro-vascular" or cerebrovascular) NEAR/1 (accident* or event*)) or "devastating brain injur*" or "hypo glyc$emi*" or hypoglyc$emi* or stroke* or " traumatic brain injur*")) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*

Ancillary Testing

Review question: *In patients appearing to meet criteria for neurological determination of death who require ancillary testing, which ancillary test should be performed to complete the neurological determination of death?*

Note: Baseline search conducted May 16, 2019; first update search conducted April 22, 2020; second update search conducted September 18, 2021; third update search conducted February 5, 2022

Results of the search: The September 18, 2021, update search retrieved a total of 1101 references and 763 unique references (duplicates removed). The February 5, 2022, update search retrieved a total of 1372 references and 193 unique references (1179 duplicates removed).

Search summary:

Source	Results (w. duplicates) Update 2 - Sept 2021	Results (unique) Update 2 - Sept 2021	Results (w. duplicates) Update 3 - Feb 2022	Results (unique) Update 3 - Feb 2022
MEDLINE	369	369	457	87
Embase	513	294	634	72
EBM Reviews	43	27	50	6
CINAHL	176	73	231	28
Total:	**1101**	**763**	**1372**	**193**

Database: Ovid MEDLINE(R) ALL 1946 to February 4, 2022
Date search conducted: February 5, 2022
Strategy:
1 Brain Death/ (9100)
2 (cerebral death or absence of neuro$ or cerebr$ circulatory arrest or braindea*).kw,sh,tw. (2216)
3 ((brain* or neurol*) adj3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or un-arous* or absen* or unresuscit*)).kw,sh,tw. (21586)
4 ((coma* or stupor) adj2 (irreversibl* or depasse* or unrespons* or un-respons* or unresuscit*)).kw,sh,tw. (306)
5 ((unarous* or un-arous*) adj2 (unrespons* or un-respons*)).kw,sh,tw. (2)
6 comatose patient*.kw,sh,tw. (1884)
7 or/1-6 (27463)
8 exp "Sensitivity and Specificity"/ (629809)
9 (sensitiv* or specificity or accurac*).kw,sh,tw. (2270870)
10 (predictive adj3 value*).kw,sh,tw. (124929)
11 ((true adj positive*) or (false adj positive*) or (false adj negative*) or (true adj negative*) or diagnos* determination of death or ((diagnos* or determination) adj2 death)).kw,sh,tw. (92044)
12 (observer adj variation*).kw,sh,tw. (1321)
13 (roc adj curve*).kw,sh,tw. (44016)
14 (likelihood adj3 ratio*).kw,sh,tw. (17989)
15 likelihood function/ (23138)
16 diagnosis, differential/ or exp Diagnostic errors/ (573368)
17 (diagnostic error* or misdiagnos*).kw,sh,tw. (73366)
18 or/8-17 (3076024)
19 four-vessel angiograph*.kw,sh,tw. (136)
20 Technetium Tc 99m Exametazime/ (2977)
21 Tomography, Emission-Computed, Single-Photon/ (31958)
22 (single photon emission computed tomography or single photon emission ct or spect).kw,sh,tw. (35350)
23 Angiography, Digital Subtraction/ (11196)
24 digital subtraction angiograph*.kw,sh,tw. (9316)

25 Positron-Emission Tomography/ (58517)
26 Radionuclide Angiography/ (1188)
27 (Xenon computed tomography or xenon ct).kw,sh,tw. (360)
28 Magnetic Resonance Angiography/ (24156)
29 (magnetic resonance angiography or magnetic resonance perfusion or mr perfusion).kw,sh,tw. (28413)
30 (computed tomography angiography or ct angiography).kw,sh,tw. (29959)
31 (computed tomography perfusion or ct perfusion).kw,sh,tw. (2697)
32 Ultrasonography, Doppler, Transcranial/ (7843)
33 Transcranial Doppler.kw,sh,tw. (8772)
34 ancillary test$.kw,sh,tw. (1749)
35 ((brain or cerebral) adj perfusion).kw,sh,tw. (14458)
36 Electroencephalography/ (154498)
37 (Electroencephalography or eeg).kw,sh,tw. (182040)
38 exp Evoked Potentials/ (121786)
39 (evoked potentials or evoked response).kw,sh,tw. (82262)
40 or/19-39 (462185)
41 7 and 18 (3687)
42 7 and 40 (3377)
43 41 or 42 [Ancillary testing for diagnosis of brain death SR search] (6157)
44 (case reports not review).pt. (2108675)
45 43 not 44 [Exclude case reports] (5318)
46 limit 45 to dt="20200401-20220205" [Create date limit April 1 2020 to current] (452)
47 limit 45 to yr="2021-2022" [Publication year date limit] (295)
48 limit 45 to ep="20200401-20220205" [Electronic publication date limit April 1 2020 to current] (340)
49 or/46-48 [Combined date limits] (457)
50 remove duplicates from 49 [Medline update results for export] (457)

Database: Ovid Embase Classic+Embase 1947 to 2022 February 03
Date search conducted: February 5, 2022
Strategy:
1 brain death/ (16023)
2 (cerebral death or absence of neuro$ or cerebr$ circulatory arrest or braindea*).kw,sh,tw. (3368)
3 ((brain* or neurol*) adj3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or un-arous* or absen* or unresuscit*)).kw,sh,tw. (68821)
4 ((coma* or stupor) adj2 (irreversibl* or depasse* or unrespons* or un-respons* or unresuscit*)).ti,ab. (432)
5 ((unarous* or un-arous*) adj2 (unrespons* or un-respons*)).kw,sh,tw. (1)
6 comatose patient*.kw,sh,tw. (4705)
7 or/1-6 (79058)
8 "sensitivity and specificity"/ (420601)
9 (sensitiv* or specificity or accurac*).ti,ab. (2709512)
10 (predictive adj3 value*).kw,sh,tw. (187405)
11 ((true adj positive*) or (false adj positive*) or (false adj negative*) or (true adj negative*) or diagnos* determination of death or ((diagnos* or determination) adj2 death)).kw,sh,tw. (175127)
12 (observer adj variation*).kw,sh,tw. (2053)
13 (roc adj curve*).kw,sh,tw. (75929)
14 (likelihood adj3 ratio*).kw,sh,tw. (24484)
15 differential diagnosis/ (411284)
16 Diagnostic errors/ (62447)
17 (diagnostic error* or misdiagnos*).kw,sh,tw. (101875)
18 or/8-17 (3493601)
19 four-vessel angiograph*.kw,sh,tw. (170)
20 hexamethylpropylene amine oxime technetium tc 99m/ (5146)
21 single photon emission computed tomography/ (13691)

22 (single photon emission computed tomography or single photon emission ct or spect).kw,sh,tw. (62187)
23 digital subtraction angiography/ (24901)
24 digital subtraction angiograph*.kw,sh,tw. (26979)
25 positron emission tomography/ (149893)
26 radionuclide ventriculography/ (651)
27 (Xenon computed tomography or xenon ct).kw,sh,tw. (459)
28 magnetic resonance angiography/ (39056)
29 (magnetic resonance angiography or magnetic resonance perfusion or mr perfusion).kw,sh,tw. (42373)
30 (computed tomography angiography or ct angiography).kw,sh,tw. (35078)
31 (computed tomography perfusion or ct perfusion).kw,sh,tw. (4875)
32 transcranial Doppler ultrasonography/ (2610)
33 Transcranial Doppler.kw,sh,tw. (14470)
34 ancillary test$.kw,sh,tw. (2769)
35 ((brain or cerebral) adj perfusion).kw,sh,tw. (21704)
36 electroencephalography/ (133171)
37 (Electroencephalography or eeg).kw,sh,tw. (224037)
38 exp Evoked Potentials/ (81078)
39 (evoked potentials or evoked response).kw,sh,tw. (81561)
40 or/19-39 (635766)
41 7 and 18 (12583)
42 7 and 40 (8210)
43 41 or 42 (18891)
44 case report/ (2804713)
45 43 not 44 [Exclude case reports] (16149)
46 limit 45 to embase (7461)
47 limit 46 to dd="20200401-20220205" [Date delivered date limit April 1 2020 to current] (59)
48 limit 46 to dc="20200401-20220205" [Date created date limit April 1 2020 to current] (634)
49 limit 46 to yr="2021-2022" (355)
50 or/47-49 [Combined date limits] (636)
51 remove duplicates from 50 [Embase records for export] (634)

Database: EBM Reviews - ACP Journal Club 1991 to November 2021, EBM Reviews - Cochrane Central Register of Controlled Trials November 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 02, 2021
Date search conducted: February 5, 2022
Strategy:
1 Brain Death/ (88)
2 (cerebral death or absence of neuro$ or cerebr$ circulatory arrest or braindea*).af. (159)
3 ((brain* or neurol*) adj3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or un-arous* or absen* or unresuscit*)).af. (1889)
4 ((coma* or stupor) adj2 (irreversibl* or depasse* or unrespons* or un-respons* or unresuscit*)).ti,ab. (7)
5 ((unarous* or un-arous*) adj2 (unrespons* or un-respons*)).af. (0)
6 comatose patient*.af. (294)
7 or/1-6 (2223)
8 exp "Sensitivity and Specificity"/ (16963)
9 (sensitiv* or specificity or accurac*).ti,ab. (98252)
10 (predictive adj3 value*).af. (18329)
11 ((true adj positive*) or (false adj positive*) or (false adj negative*) or (true adj negative*) or diagnos* determination of death or ((diagnos* or determination) adj2 death)).af. (6885)
12 (observer adj variation*).af. (2578)
13 (roc adj curve*).af. (3650)
14 (likelihood adj3 ratio*).af. (1555)
15 likelihood function/ (340)

16 diagnosis, differential/ or exp Diagnostic errors/ (4410)
17 (diagnostic error* or misdiagnos*).af. (1462)
18 or/8-17 (122960)
19 four-vessel angiograph*.af. (3)
20 Technetium Tc 99m Exametazime/ (101)
21 Tomography, Emission-Computed, Single-Photon/ (1033)
22 (single photon emission computed tomography or single photon emission ct or spect).af. (2622)
23 Angiography, Digital Subtraction/ (230)
24 digital subtraction angiograph*.af. (598)
25 Positron-Emission Tomography/ (1034)
26 Radionuclide Angiography/ (64)
27 (Xenon computed tomography or xenon ct).af. (28)
28 Magnetic Resonance Angiography/ (455)
29 (magnetic resonance angiography or magnetic resonance perfusion or mr perfusion).af. (1080)
30 (computed tomography angiography or ct angiography).af. (1965)
31 (computed tomography perfusion or ct perfusion).af. (357)
32 Ultrasonography, Doppler, Transcranial/ (459)
33 Transcranial Doppler.af. (1382)
34 ancillary test$.af. (58)
35 ((brain or cerebral) adj perfusion).af. (1469)
36 Electroencephalography/ (4863)
37 (Electroencephalography or eeg).af. (11973)
38 exp Evoked Potentials/ (3303)
39 (evoked potentials or evoked response).af. (5013)
40 or/19-39 (25429)
41 7 and 18 (256)
42 7 and 40 (255)
43 41 or 42 (445)
44 limit 43 to yr="2020-Current" (50)

Database: CINAHL Ebsco (1981 to February 4, 2022)
Date search conducted: February 5, 2022
Strategy:

#	Query	Limiters/Expanders	Results
S1	(MH "Brain Death") OR ((cerebral death or absence of neuro$ or cerebr$ circulatory arrest or braindea*)) OR (((brain* or neurol*) N3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or un-arous* or absen* or unresuscit*))) OR (((coma* or stupor) N2 (irreversibl* or depasse* or unrespons* or un-respons* or unresuscit*)).) OR (((unarous* or un-arous*) N2 (unrespons* or un-respons*))) OR comatose patient*	Search modes - Boolean/Phrase	7,590
S2	((MH "Sensitivity and Specificity") OR (MH "Diagnosis, Differential") OR (MH "Diagnostic Errors")) OR ((sensitiv* or specificity or accurac*)) OR (predictive N3 value*) OR (((true N positive*) or (false N positive*) or (false N negative*) or (true N negative*) or diagnos* determination of death or ((diagnos* or determination) N2 death))) OR (observer adj variation*) OR (roc adj	Search modes - Boolean/Phrase	457,289

	curve*) OR (likelihood adj3 ratio*) OR ((diagnostic error* or misdiagnos*))		
S3	(MH "Angiography, Digital Subtraction") OR (MH "Tomography, Emission-Computed") OR (MH "Radionuclide Ventriculography") OR (MH "Magnetic Resonance Angiography") OR (MH "Ultrasonography, Doppler, Transcranial") OR (MH "Electroencephalography") OR (MH "Evoked Potentials") OR (MH "Evoked Potentials, Auditory, Brainstem") OR (MH "Evoked Potentials, Motor") OR (MH "Evoked Potentials, Visual") OR (MH "Evoked Potentials, Somatosensory") OR (MH "Evoked Potentials, Auditory") OR (MH "Auditory Steady-State Response")	Search modes - Boolean/Phrase	56,760
S4	S1 AND S2	Search modes - Boolean/Phrase	1,724
S5	S1 AND S3	Search modes - Boolean/Phrase	578
S6	S4 OR S5	Search modes - Boolean/Phrase	2,046
S7	(MH "Case Studies")	Search modes - Boolean/Phrase	25,470
S8	TI((case N1 (report or study) NOT review)	Search modes - Boolean/Phrase	87,009
S9	S7 OR S8	Search modes - Boolean/Phrase	108,409
S10	S6 NOT S9	Search modes - Boolean/Phrase	2,014
S11	S6 NOT S9	Limiters - Published Date: 20200401-20221231 Search modes - Boolean/Phrase	231

Review question: *In pediatric patients (≤18 years of age) appearing to meet criteria for neurological determination of death who require ancillary testing, which ancillary test should be performed to complete the neurological determination of death?*

Results of the search: The search retrieved a total of 3601 references and 2632 unique references (duplicates removed).

Search summary:

Source	Results (w. duplicates)	Results (unique)
MEDLINE	1209	1208
Embase	1567	1034
CENTRAL	45	22
Web of Science	780	368
Total:	**3601**	**2632**

Database: Ovid MEDLINE(R) ALL 1946 to June 25, 2021
Date search conducted: June 26, 2021
Strategy:

1 Brain Death/ (8908)
2 (cerebral death or absence of neuro$ or cerebr$ circulatory arrest or braindea*).kw,sh,tw. (2169)
3 ((brain* or neurol*) adj3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or un-arous* or absen* or unresuscit*)).kw,sh,tw. (20932)
4 ((coma* or stupor) adj2 (irreversibl* or depasse* or unrespons* or un-respons* or unresuscit*)).kw,sh,tw. (298)
5 ((unarous* or un-arous*) adj2 (unrespons* or un-respons*)).kw,sh,tw. (2)
6 comatose patient*.kw,sh,tw. (1843)
7 or/1-6 (26726)
8 exp "Sensitivity and Specificity"/ (610911)
9 (sensitiv* or specificity or accurac*).kw,sh,tw. (2188304)
10 (predictive adj3 value*).kw,sh,tw. (119263)
11 ((true adj positive*) or (false adj positive*) or (false adj negative*) or (true adj negative*) or diagnos* determination of death or ((diagnos* or determination) adj2 death)).kw,sh,tw. (89054)
12 (observer adj variation*).kw,sh,tw. (1293)
13 (roc adj curve*).kw,sh,tw. (39623)
14 (likelihood adj3 ratio*).kw,sh,tw. (17127)
15 likelihood function/ (22614)
16 diagnosis, differential/ or exp Diagnostic errors/ (566209)
17 (diagnostic error* or misdiagnos*).kw,sh,tw. (70953)
18 or/8-17 (2974019)
19 four-vessel angiograph*.kw,sh,tw. (134)
20 Technetium Tc 99m Exametazime/ (2966)
21 Tomography, Emission-Computed, Single-Photon/ (31341)
22 (single photon emission computed tomography or single photon emission ct or spect).kw,sh,tw. (34467)
23 Angiography, Digital Subtraction/ (10947)
24 digital subtraction angiograph*.kw,sh,tw. (9018)
25 Positron-Emission Tomography/ (55784)
26 Radionuclide Angiography/ (1188)
27 (Xenon computed tomography or xenon ct).kw,sh,tw. (360)
28 Magnetic Resonance Angiography/ (23711)
29 (magnetic resonance angiography or magnetic resonance perfusion or mr perfusion).kw,sh,tw. (27845)
30 (computed tomography angiography or ct angiography).kw,sh,tw. (27963)

31 (computed tomography perfusion or ct perfusion).kw,sh,tw. (2536)
32 Ultrasonography, Doppler, Transcranial/ (7662)
33 Transcranial Doppler.kw,sh,tw. (8573)
34 ancillary test$.kw,sh,tw. (1649)
35 ((brain or cerebral) adj perfusion).kw,sh,tw. (14049)
36 Electroencephalography/ (150009)
37 (Electroencephalography or eeg).kw,sh,tw. (176796)
38 exp Evoked Potentials/ (119192)
39 (evoked potentials or evoked response).kw,sh,tw. (80756)
40 or/19-39 (448578)
41 7 and 18 (3566)
42 7 and 40 (3317)
43 41 or 42 [Ancillary testing for diagnosis of brain death SR search] (5998)
44 Adolescent/ (2101965)
45 exp Child/ (1982630)
46 Hospitals, Pediatric/ (14101)
47 exp Infant/ (1175377)
48 exp Infant Death/ (7891)
49 exp Infant Mortality/ (30675)
50 exp Infant, Newborn, Diseases/ (179082)
51 exp Infant, Premature, Diseases/ (45411)
52 exp Intensive Care Units, Pediatric/ (23864)
53 Minors/ (2646)
54 exp Pediatrics/ (60334)
55 Premature Birth/ (15787)
56 (adolescen* or boy* or girl* or minors or teen*).tw,kf. (546167)
57 (babies* or baby* or infan* or neo-nat* or neonat* or newborn* or post matur* or postmatur* or pre matur* or prematur* or post nat* or postnat* or pre term* or preterm*).tw,kf. (1020157)
58 (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).tw,jw,kf. (1599243)
59 ELBW*.tw,kf. (1527)
60 (elementary school* or grade school* or gradeschool* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).tw,kf. (75085)
61 low birth weight*.tw,kf. (29391)
62 p?ediatric*.tw,jw,kf. (793774)
63 (PICU* or NICU*).tw,kf. (18029)
64 (small* adj2 gestational age).tw,kf. (11416)
65 VLBW*.tw,kf. (4151)
66 or/44-65 [Pediatrics] (4711513)
67 and/43,66 [Pediatrics filter applied to ancillary testing search] (1726)
68 (case reports not review).pt. (2055679)
69 67 not 68 [Exclude case reports] (1435)
70 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (4854038)
71 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti,kf. (2271901)
72 70 or 71 (5235010)
73 69 not 72 [exclude animal studies] (1377)
74 limit 73 to (english or french) (1209)
75 remove duplicates from 74 [MEDLINE results for export] (1209)

Database: Ovid Embase Classic+Embase 1947 to 2021 June 25
Date search conducted: June 26, 2021
Strategy:

1 brain death/ (15692)
2 (cerebral death or absence of neuro$ or cerebr$ circulatory arrest or braindea*).kw,sh,tw. (3305)
3 ((brain* or neurol*) adj3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or un-arous* or absen* or unresuscit*)).kw,sh,tw. (67515)
4 ((coma* or stupor) adj2 (irreversibl* or depasse* or unrespons* or un-respons* or unresuscit*)).ti,ab. (424)
5 ((unarous* or un-arous*) adj2 (unrespons* or un-respons*)).kw,sh,tw. (1)
6 comatose patient*.kw,sh,tw. (4580)
7 or/1-6 (77417)
8 "sensitivity and specificity"/ (397350)
9 (sensitiv* or specificity or accurac*).ti,ab. (2614071)
10 (predictive adj3 value*).kw,sh,tw. (180430)
11 ((true adj positive*) or (false adj positive*) or (false adj negative*) or (true adj negative*) or diagnos* determination of death or ((diagnos* or determination) adj2 death)).kw,sh,tw. (171578)
12 (observer adj variation*).kw,sh,tw. (2472)
13 (roc adj curve*).kw,sh,tw. (70839)
14 (likelihood adj3 ratio*).kw,sh,tw. (23789)
15 differential diagnosis/ (403357)
16 Diagnostic errors/ (60268)
17 (diagnostic error* or misdiagnos*).kw,sh,tw. (98236)
18 or/8-17 (3376860)
19 four-vessel angiograph*.kw,sh,tw. (168)
20 hexamethylpropylene amine oxime technetium tc 99m/ (5115)
21 single photon emission computed tomography/ (11969)
22 (single photon emission computed tomography or single photon emission ct or spect).kw,sh,tw. (60288)
23 digital subtraction angiography/ (23726)
24 digital subtraction angiograph*.kw,sh,tw. (25807)
25 positron emission tomography/ (143534)
26 radionuclide ventriculography/ (599)
27 (Xenon computed tomography or xenon ct).kw,sh,tw. (468)
28 magnetic resonance angiography/ (37598)
29 (magnetic resonance angiography or magnetic resonance perfusion or mr perfusion).kw,sh,tw. (41009)
30 (computed tomography angiography or ct angiography).kw,sh,tw. (33665)
31 (computed tomography perfusion or ct perfusion).kw,sh,tw. (4647)
32 transcranial Doppler ultrasonography/ (2331)
33 Transcranial Doppler.kw,sh,tw. (14262)
34 ancillary test$.kw,sh,tw. (2611)
35 ((brain or cerebral) adj perfusion).kw,sh,tw. (21749)
36 electroencephalography/ (128799)
37 (Electroencephalography or eeg).kw,sh,tw. (217839)
38 exp Evoked Potentials/ (78177)
39 (evoked potentials or evoked response).kw,sh,tw. (81960)
40 or/19-39 (616770)
41 7 and 18 (12360)
42 7 and 40 (8045)
43 41 or 42 (18553)
44 limit 43 to embase (8979)
45 exp adolescent/ (1737974)
46 exp child/ (3169513)
47 exp child death/ (28001)

48 exp infant/ (1208707)
49 infant mortality/ (25573)
50 "minor (person)"/ (727)
51 neonatology/ (5119)
52 exp newborn disease/ (1810540)
53 newborn intensive care/ (26754)
54 pediatric hospital/ (26701)
55 pediatric intensive care unit/ (8517)
56 exp pediatrics/ (125788)
57 (adolescen* or boy* or girl* or minors or teen*).tw,kw. (752172)
58 (babies* or baby* or infan* or neo-nat* or neonat* or newborn* or post matur* or postmatur* or pre matur* or prematur* or post nat* or postnat* or pre term* or preterm*).tw,kw. (1338325)
59 (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).tw,kw. (2070481)
60 ELBW*.tw,kw. (2225)
61 (elementary school* or grade school* or gradeschool* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).tw,kw. (98172)
62 low birth weight*.tw,kw. (39331)
63 p?ediatric*.tw,kw. (635439)
64 (PICU* or NICU*).tw,kw. (34260)
65 (small* adj2 gestational age).tw,kw. (15676)
66 VLBW*.tw,kw. (5736)
67 or/45-66 [Pediatrics] (6134420)
68 and/44,67 [Pediatrics filter applied to ancillary testing search] (2465)
69 (case report/ or (case adj1 (report or study)).ti.) not review.pt. (2722423)
70 68 not 69 [Exclude case reports] (1915)
71 (exp animals/ or exp animal experimentation/ or exp models animal/ or exp vertebrates/) not (exp humans/ or exp human experimentation/) (5915331)
72 ((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or non human* or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors)).ti. (2661264)
73 71 or 72 (6277041)
74 70 not 73 [exclude animal studies] (1794)
75 (Conference Abstract or Conference Paper or Conference Review).pt. (4887732)
76 74 and 75 (45)
77 limit 76 to yr="2018-2021" (1)
78 74 not 75 [exclude conference proceedings] (1749)
79 77 or 78 [add proceedings from last 3 yrs] (1750)
80 limit 79 to (english or french) (1575)
81 remove duplicates from 80 [Embase results for export] (1567)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials May 2021
Date search conducted: June 26, 2021
Strategy:
1 Brain Death/ (84)
2 (cerebral death or absence of neuro$ or cerebr$ circulatory arrest or braindea*).af. (134)
3 ((brain* or neurol*) adj3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or un-arous* or absen* or unresuscit*)).af. (1545)
4 ((coma* or stupor) adj2 (irreversibl* or depasse* or unrespons* or un-respons* or unresuscit*)).ti,ab. (6)
5 ((unarous* or un-arous*) adj2 (unrespons* or un-respons*)).af. (0)
6 comatose patient*.af. (268)
7 or/1-6 (1849)

8 exp "Sensitivity and Specificity"/ (16749)
9 (sensitiv* or specificity or accurac*).ti,ab. (92662)
10 (predictive adj3 value*).af. (17206)
11 ((true adj positive*) or (false adj positive*) or (false adj negative*) or (true adj negative*) or diagnos* determination of death or ((diagnos* or determination) adj2 death)).af. (5681)
12 (observer adj variation*).af. (2482)
13 (roc adj curve*).af. (3320)
14 (likelihood adj3 ratio*).af. (1072)
15 likelihood function/ (335)
16 diagnosis, differential/ or exp Diagnostic errors/ (4381)
17 (diagnostic error* or misdiagnos*).af. (1199)
18 or/8-17 (115656)
19 four-vessel angiograph*.af. (3)
20 Technetium Tc 99m Exametazime/ (101)
21 Tomography, Emission-Computed, Single-Photon/ (1027)
22 (single photon emission computed tomography or single photon emission ct or spect).af. (2453)
23 Angiography, Digital Subtraction/ (228)
24 digital subtraction angiograph*.af. (540)
25 Positron-Emission Tomography/ (1007)
26 Radionuclide Angiography/ (64)
27 (Xenon computed tomography or xenon ct).af. (27)
28 Magnetic Resonance Angiography/ (451)
29 (magnetic resonance angiography or magnetic resonance perfusion or mr perfusion).af. (983)
30 (computed tomography angiography or ct angiography).af. (1791)
31 (computed tomography perfusion or ct perfusion).af. (325)
32 Ultrasonography, Doppler, Transcranial/ (452)
33 Transcranial Doppler.af. (1287)
34 ancillary test$.af. (44)
35 ((brain or cerebral) adj perfusion).af. (1320)
36 Electroencephalography/ (4761)
37 (Electroencephalography or eeg).af. (11126)
38 exp Evoked Potentials/ (3231)
39 (evoked potentials or evoked response).af. (4767)
40 or/19-39 (23806)
41 7 and 18 (180)
42 7 and 40 (170)
43 41 or 42 [Ancillary testing for diagnosis of brain death SR search] (308)
44 Adolescent/ (107543)
45 exp Child/ (57412)
46 Hospitals, Pediatric/ (209)
47 exp Infant/ (32372)
48 exp Infant Death/ (71)
49 exp Infant Mortality/ (547)
50 exp Infant, Newborn, Diseases/ (6465)
51 exp Infant, Premature, Diseases/ (3237)
52 exp Intensive Care Units, Pediatric/ (1059)
53 Minors/ (10)
54 exp Pediatrics/ (697)
55 Premature Birth/ (1497)
56 (adolescen* or boy* or girl* or minors or teen*).tw. (39434)
57 (babies* or baby* or infan* or neo-nat* or neonat* or newborn* or post matur* or postmatur* or pre matur* or prematur* or post nat* or postnat* or pre term* or preterm*).tw. (75795)
58 (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).tw. (140462)

59 ELBW*.tw. (271)
60 (elementary school* or grade school* or gradeschool* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).tw. (9646)
61 low birth weight*.tw. (4059)
62 p?ediatric*.tw. (36585)
63 (PICU* or NICU*).tw. (3645)
64 (small* adj2 gestational age).tw. (1044)
65 VLBW*.tw. (992)
66 or/44-65 [Pediatrics] (316178)
67 and/43,66 [Pediatrics filter applied to ancillary testing search] (48)
68 remove duplicates from 67 [CENTRAL results for export] (45)

Database: Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Date search conducted: June 26, 2021
Strategy:

# 12	**780**	(#10 NOT #11) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 11	**2,838,076**	(TI=((ape or apes or animal* or baboon* or beagle* or canine* or cat or cats or cattle or chicken or chickens or chimp* or dog or dogs or feline* or fish or hamster or hamsters or horse or horses or lapin* or macaque* or mouse or mice or nonhuman* or "non human*" or pig or piglet* or pigs or porcine or rabbit or rabbit or raccoon or raccoons or racehorse or racehorses or rat or rats or rodent* or swine* or sheep or zebrafish*) not (adults or children or human or humans or infants or patient or patients or people or seniors))) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 10	**819**	(#8 NOT #9) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	**280,970**	(TI=("case report" or "case study")) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	**847**	#7 AND #6 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	**2,718,488**	(TS=(adolescen* or boy* or girl* or minors or teen* or babies* or baby* or infan* or "neo nat*" or neonat* or newborn* or "post matur*" or postmatur* or "pre matur*" or prematur* or "post nat*" or postnat* or "pre term*" or preterm* or child* or kid or kids or preschool* or "school age*" or schoolchild* or toddler* or ELBW* or "elementary school*" or "grade school*" or gradeschool* or "high school*" or highschool* or kindergar* or "nursery school*" or "primary school*" or "secondary school*" or "low birth weight*" or paediatric* or pediatric* or PICU* or NICU* or (small* NEAR/2 "gestational age") or VLBW*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 6	**4,475**	#5 OR #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	**2,122**	#3 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 4	**3,020**	#2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	**240,482**	(TS=("four vessel angiograph*" or "single photon emission computed tomography" or "single photon emission ct" or spect or "digital subtraction angiograph*" or "Xenon

		computed tomography" or "xenon ct" or "magnetic resonance angiography" or "magnetic resonance perfusion" or "mr perfusion" or "computed tomography angiography" or "ct angiography" or "computed tomography perfusion" or "ct perfusion" or "transcranial doppler" or "ancillary test*" or ((brain or cerebral) NEAR/1 perfusion) or electroencephalography or eeg or "evoked potentials" or "evoked response")) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	**3,284,384**	(TS=(sensitiv* or specificity or accurac* or (predictive NEAR/3 value*) or (true NEAR/1 positive*) or (false NEAR/1 positive*) or (false NEAR/1 negative*) or (true NEAR/1 negative*) or "diagnos* determination of death" or ((diagnos* or determination) NEAR/2 death) or (observer NEAR/1 variation*) or (roc NEAR/1 curve*) or (likelihood NEAR/3 ratio*) or "differential diagnosis" or "diagnostic error*" or misdiagnos*)) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	**22,767**	(TS=("cerebral death" or "absence of neuro*" or "cerebr* circulatory arrest" or braindea* or ((brain* or neurol*) NEAR/3 (dead* or death* or deceas* or arrest* or cease* or cessation* or unarous* or "un arous*" or absen* or unresuscit*)) or ((coma* or stupor) NEAR/2 (irreversibl* or depasse* or unrespons* or "un respons*" or unresuscit*)) or ((unarous* or "un arous*") NEAR/2 (unrespons* or "un-respons*")) or "comatose patient*")) *AND* **LANGUAGE:** (English OR French) *Indexes=SCI-EXPANDED Timespan=All years*

eAppendix 5 Guideline development methodology

Guideline panel composition

This clinical practice guideline has been made possible through a financial contribution from Health Canada through the Organ Donation and Transplantation Collaborative and was developed in collaboration between Canadian Critical Care Society, Canadian Blood Services, and the Canadian Medical Association. The guideline development panel includes critical care nurses and physicians (adult and pediatric), radiologists, neurologists, neurointensivists, anesthetists, ethicists, lawyers, patient family and public partners and methodologists with expertise in guideline development using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology[1]. By design, the guideline panel included geographic diversity from all provinces (except Prince Edward Island).

We divided panel members into seven Working Groups: Definition of Death, Death Determination by Neurologic Criteria, Ancillary Testing, Whole Brain v Brainstem Death, Death Determination by Circulatory Criteria, Legal and Ethical Considerations, and Stakeholder Engagement.

Management of competing interests

All panel members were required to complete a disclosure of any potential direct or indirect competing interests form prior to their involvement in the project. Disclosure forms were collected again at project completion, prior to publication. Declarations were reviewed by members of the Steering Committee. Several panel members have professional roles in organ donation administration, affiliations with governmental not-for-profit entities, or have received funding for scientific research. However, no panel member was judged to have a relevant competing interest.

Question development

The panel derived and prioritized clinical questions to be addressed as part of the guideline. The derivation of relevant questions was facilitated by review of previously published documents. Prioritization was done ad-hoc with input from all panel members.

We divided questions into one of three general categories: actionable PICO (patients, intervention, comparator, outcomes) questions, good practice statements and foundational medical principles. Actionable PICOs were subjected to the comprehensive GRADE approach,[2] while good practice statements were recommendations that are not appropriate for formal ratings of quality of evidence[3]. The foundational medical principles (M. Weiss, Foundational Medical Principles, in submission) constitute a novel category of clinical guidance that were developed for this guideline to address a specific need. Unlike actionable PICO questions and good practice statements, foundational medical principles reflect stakeholders' collective subscription to principles that form the underpinnings for the medical, legal, and ethical frameworks of death determination in Canada. Given the concern for over-use, we sought to apply these principles sparingly and strictly for practices that met the qualifications. Ultimately, we have included 5 foundational medical principles as part of this guideline effort. Panel members also identified 14 actionable PICO questions (9 for death determination by neurologic criteria, 2 for ancillary testing, and 3 for death determination by circulatory criteria), as well as several good practice statements.

Literature search:

Panel members rated outcomes of interest based on perceived importance to patients for clinical decision-making on a scale of 1 (not important) to 9 (critically important). Working with an information specialist and health librarian, we conducted systematic reviews of the literature to seek studies examining each of the 14 PICO questions. For the neurologic and circulatory questions, between April 18 and August 21, 2021, we searched MEDLINE Ovid, EMBASE Ovid, Cochrane Central Register of Controlled

Trials and Science Citation Index Expanded via Web of Science from inception to present. For the ancillary testing questions, searches were conducted according to the PRESS Peer guidelines on September 18, 2021, and updated February 5, 2022, in the databases above (excluding Science Citation Index), and in CINAHL Ebsco.

We included all studies regardless of design, except for the ancillary testing questions, for which case reports were excluded. We limited our search to human trials published in English or French. We also reviewed the reference lists of eligible studies and inquired with panel members to ensure that no studies were missed. If we did not find any direct data, we did a rapid search of any relevant indirect data. This involved Pubmed searches using keywords and Boolian search terms.

Data collection and analysis:

For each PICO question, two investigators (panel members or methods support team) screened titles and abstracts and subsequently full-text manuscripts independently and in duplicate using Covidence® and InsightScope® software. Similarly, multiple investigators performed data extraction independently and in duplicate for each included study. We were only able to conduct a meta-analysis of the data for the ancillary testing PICO questions. We provided a narrative summary of the results for the other PICOs questions. We generated an evidence profile for each of the PICO questions[4]. Where necessary, additional evidence profiles were created to summarize the literature specific to the subgroup populations being considered. Following GRADE methodology, certainty in each outcome was rated as high, moderate, low or very low[5]. Data from randomized control trials started as high certainty and data from observational studies started as low certainty evidence. We subsequently downgraded certainty by one or two level for concerns related to individual study risk of bias, inconsistency, indirectness, imprecision or publication bias.

Formulation of recommendations:

The panel developed recommendations on a series of video conferences using the GRADE Evidence-to-Decision framework which considers the certainty in the evidence, the balance between desirable and undesirable effects, patient values and preferences, resource use, health equity, acceptability, and feasibility[6]. We designated recommendations as strong (using the phrasing “we recommend”) or weak (using the phrasing “we suggest”)[7]. Table 1 describes the implications of the strength of a recommendation. The final wording of each recommendation was reviewed and approved by panel members.

Good practice statements and foundational medical principles were drafted and then circulated to and discussed by panel members during a series of video conferences to achieve consensus on the phrasing and underlying rationale.

Manuscript Preparation:

After generating the recommendations, the panel divided into writing groups focusing on each of the PICO questions. Editing and feedback were coordinated by the guideline executive and accomplished through electronic communication. The final wording of all recommendations and narratives was approved by all panel members.

Table 1: Implications of strong and weak recommendations for different users of guidelines

	Strong Recommendation	Weak Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

References:

1. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, onso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
2. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ. 2008;336(7652):1049-51.
3. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. Journal of clinical epidemiology. 2016;80:3-7.
4. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.
5. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-6.
6. Li SA, Alexander PE, Reljic T, Cuker A, Nieuwlaat R, Wiercioch W, et al. Evidence to Decision framework provides a structured "roadmap" for making GRADE guidelines recommendations. Journal of clinical epidemiology. 2018;104:103-12.
7. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. Bmj. 2004;328(7454):1490.

eAppendix 6 Spiritual care professionals discussion report: impacts and implementation of a brain-based definition of death

Acknowledgement and Thanks

A wide range of spiritual care professionals from across the country took part in the series of discussion groups outlined below to provide their insights on a specific set of discussion questions related to the project. Our thanks to all those who participated for taking time to engage in discussion with us and for providing a wealth of personal stories, professional reflection, and strategic input/advice.

Background

Canadian Blood Services, the Canadian Critical Care Society, and the Canadian Medical Association have partnered to deliver an updated clinical practice guideline for death determination in Canada. Funded by Health Canada, the clinical practice guideline will include: a medical, brain-based definition of death that will clarify that all biomedical death is related to the loss of brain function; evidence-based and expert-informed criteria (circulatory and neurologic) for determining death; and knowledge translation tools for health care professionals, patient families, and the public.

As part of this work, a mixture of qualitative research and stakeholder engagement methods are being used to better understand the interface between public, cultural, spiritual, and/or religious understandings of death, and the professional, scientific, and medical determination of death. The objectives of this exploration are:

1. To describe the current understanding and perception of how death is understood, defined, and determined in Canada among the public and health care professionals.
2. To describe the impressions and perspectives of Canadians with respect to a brain-based definition of death.
3. To explore the acceptability of a brain-based definition of death, including in the context of organ donation.
4. To identify strategies to inform the public and health care professionals about the definition and determination of death.
5. To engage with spiritual care professionals in Canada to understand religious and spiritual understandings and supporting families and caregivers as patients are declared deceased.

Particularly on this fifth point of religious and spiritual understandings and supporting families and caregivers as patients are determined dead, the project team engaged hospital based spiritual health and care leaders across the country in a series of discussion groups in mid-January. The wealth of perspectives they provided are captured below.

Methodology

The project team worked in collaboration with The Canadian Association for Spiritual Care (CASC), and supplemented this with direct organizational outreach, to extend a broad invitation to participate in this engagement. In total, 27 spiritual care professionals across 10 provinces and territories agreed to participate and six facilitated small group discussions were held by videoconference. Discussion questions were provided in advance, and sessions ranged from 60-90 minutes.

What We Heard

Our discussion with spiritual care professionals was organized around three main discussion questions focused on the following elements:

1. Past Experience(s)
2. Professional Perspective
3. Knowledge Translation (KT) Advice

While the primary focus of discussion questions was on the work of hospital based spiritual care, particularly in the context of the ICU, discussion participants drew on a range of past work across a variety of settings to provide insights on the dynamics of death determination/declaration and advice about possible KT approaches. Input from all six discussion groups is summarized below in clusters for each of the three major sections.

This summary attempts to represent the full breadth of perspectives we heard and so in some places contrasting perspectives appear in the same section. In general, the comments are not captured verbatim, but rather summarized by the facilitator. One or more notable or frequent perspectives is highlighted in each cluster. Verbatim quotes when included (non-attributed) “appear in italics”.

Past Experience

Most participants had immediate reflections on past experience which touched on the application of a neurological death determination. Experiences varied widely and illustrated a variety of insights relating to advice for understanding the complexity of that situation. Examples that were shared included:

An emergency department care team withdrew life support after ongoing CPR did not revive a patient, but the family had an understanding of brainwaves [or lack thereof] determining death and didn’t see that status being tested/confirmed.

> *“I was in that family conference and the doctor was saying “nope his heart stopped and these are the criteria…” but within [the daughter’s] understanding, her cultural understanding, because [the patient] still had brain waves he was not dead even though his heart stopped beating”*

A family from a Muslim background that identified brain activity as the determinant of death as they understood it and rejected a declaration of death while any brain activity was present.

A Pediatric Patient in ICU. Upon arrival the spiritual care professional was told by a nurse on the care team that the patient was 'already declared' and the withdrawal of life support seemed pre-determined. The patient had a complex family and large numbers were in attendance. There was disagreement within the family (loved ones) about the situation of death. The family elected for organ donation and organs were being sustained, leading to confusion among family members.

A young adult with significant brain damage and a peripherally involved clinician who advocated to the family that they should 'wait for a miracle'.

A family who outright refused to entertain discussion of advance care planning even though their loved one's death was already expected by the care team who tried to lead the family to begin acknowledging that possibility.

A father who had a 'brain event' and was clearly declining. The family had a preliminary discussion with the care team about waiting for another family member to arrive to say goodbye. A newly arrived clinician worked to accelerate the process contrary to the family's wishes.

A man in his early 30s, in hospital for some time and then ended up in ICU. Two successful resuscitations during a relatively long stay where for a while there was hope for recovery at the beginning which failed over time. The care team tried to begin communicating the inevitability of his death. He was taken off his organ support, but higher brain function and breath and heartbeat continued, while he received artificial nutrition and hydration. His single mother (who was frail) was sure of a miraculous recovery, rejecting the end of care with certain involuntary movement being interpreted as signs of recovery. The care team expressed agony of feeling they were doing harm.

Personal experience with a family member unresponsive on life support. Observing that it was very difficult for the spouse and recognizing the desire (as another family member) to have more information to support the loved one.

Modern major hospital experience is contrasted with time in the military which often doesn't have the same equipment to support organs and as a result doesn't face the same ambiguity regarding death.

Being at the bedside of many residents as they pass away and recognizing that knowledge can be so helpful in assisting the family and loved ones to understand and accept the situation, as well as 'walking beside' the family and even exploring disagreements between them.

In the trauma neuro ICU, most patients suffer sudden and severe onset. Some stay a short time and some stay a long time. When a loved one is in a coma throughout, and families are in shock, closure is particularly difficult.

A young professional woman, hit by a streetcar, stay of 3-4 weeks in the hospital in a coma. There was an appropriate clinical time to wait and see how the brain recovers (or doesn't). During that time, she suffered a ruptured blood vessel leading to immediate brain death. The family struggled to see the difference between her prior state and her 'death'.

Seeing the team in the ICU successfully engage with a family who is expressing a religious objection to declaration of death when they have communicated early on with compassion and clarity.

Professional Perspective and Interpretation

Participants offered a variety of reflections regarding "what's really going on" in situations of tension or disconnect between loved ones or families understanding of death/dying and the clinical care team's perspective and accountability. Input clustered around five concepts:

1) Complex dynamics of death in healthcare
2) Acknowledging the health and wellbeing needs of loved ones including grieving and ritual
3) Religious Expression
4) Pluralism
5) Accommodation

1) Complex dynamics of death in healthcare

Have had the experience of challenge that went as far as the legal system but have also worked with a team that allowed space for closure/goodbye. Don't see significant patterns across patients' age/tradition/route to neurological death.

Recognizing the 'death phobic' culture and/or taboo about death and dying that avoids considering the natural course of death.

There is a need for acknowledging the inevitable course of nature

This challenge is inevitable and not about the definition or information provided.

There is always going to be tension and stress between loved ones and care providers

---

Understanding the pressures of the system for resources (human and material)

Acknowledging the requirements of organ donation add complexity with respect to family understanding and processing of death.

Modern stress on the system is putting pressure on the ability to build relationship between care team and patient's families before this moment of challenge.

Medical teams rooted in clinical perspective can be read as cold.

The most positive experiences can be those that involve clinicians who do not understand death as a failure of their abilities or work.

Clinical team's communication and walking together or sitting in the space with the family makes a significant difference.

Families may accept a dominant position of clinicians or the health system but will still be supported by an empathetic support of their human experience. [see "Acknowledging the health and wellbeing needs of loved ones including grieving and ritual" below]

The significant importance of good and authentic communication by the care team which does not rely on their personal world view or perspective. [see “pluralism” below]

It is difficult to build that relationship with families and clinicians in big organizations with a revolving cast of staff, but that does get more stable in ICU

Tensions lie earlier than the moment of death and the progression towards death.

One of the biggest sources of ‘disconnect’ is the pivot from lifesaving, or sustaining activity for a time, and the clinical team’s move to declaring death.

Understanding and sensitivity about the impact of technology and the authority and power vested in ‘modern medicine’ and encouraging acknowledgement of the pivot to hastening an acceptance of death.

Beginning the conversation earlier in the process of intervention to acknowledge the challenge of a patient’s status rather than offering hopeful words if not realistic which can ramp up the attachment of family rather than processing the reality.

There may be time on a medicine unit to acknowledge that the trajectory is uncertain, not just assure loved ones that ‘everything will be alright’.

Paying attention to the edge cases where regardless of the criteria, there will always be a case on the boundary zone.

There will always be a grey zone at the boundary of any definition of death.

2) Acknowledging the health and wellbeing needs of loved ones including grieving and ritual

Acknowledging the meaning of the moment regardless of cultural/religious/spiritual perspective.

Understanding the stages of grief (whether that is understood in a spiritual/religious context, or not).

> *“The early involvement of spiritual care professionals and ongoing involvement in the decision process for families will make a difference - facilitating and offering anticipatory grief support as the messages are slowly being delivered: facilitating the processing of the shock and denial; pain and guilt; anger and bargaining; depression and hopefully leading to the acceptance of the inevitable.”*

Understanding the importance of ritual and the processing and facilitating death.

Ritual and early involvement of spiritual care helps process and accept death when medicine ends.

There needs to be attention to the emotional and spiritual needs of family members.

Spiritual care is about meaning, purpose, and identity not just religious tradition.

Recognizing that the loved one's frame of mind and thinking can be dramatically impacted by the peril of a loved one.

The outward perspective of a patient being 'peaceful' may be alluring to family in distress.

Individuals may not be making a rational or theological decision.

Concerns for the comfort of a loved ones who are dying.

Provocative experiences of death challenge the ability to make peace but heighten the need for it.

Denial about imminent death is a real thing.

Organ donation request immediately following the message of death can be too much to bear.

Brain death is often sudden compared to other forms of death and may involve guilt among loved ones in not moving faster or doing more.

Sometimes the tension is not between the family and care team, but between family members.

The importance of understanding family systems theory dynamics

Engaging in spiritual care before the process of determining death is advisable.

The clinical team explains the medical facts, the spiritual care professional's role is to sit with the family.

Being able to work as a translator between the 'medical system' and the family creating trust and empathy.

Spiritual care should always be able to bring value and is separate and different than social work.

Spiritual care does not have a monopoly on compassion in the care team, but does have a competency of making space for the heartache.

Highlighting the value of, and importance of resourcing, spiritual care.

There is an art and science to making it a 'smooth' process.

Added complexity in the definition of death does not help process.

Understanding differing expectations between the clinical team and the family who surround a patient is important to avoid conflict.

Spiritual care professionals need strong relationship with the care team to help them understand the disconnect in their thinking with what they see loved ones doing/saying and their world view.

Sometimes the root of any disconnect can be just communication as something is unintentionally lost in translation and spiritual care can help process and understand information. Focus on ensuring that all family have the same information and interaction with the care team.

Care teams may be (but should not) make decisions without considering the perspectives or wishes of family and need to do a better job communicating and including family.

Palliative care has a lot to teach us (see Care for the Dying) about what to ask and what to try and understand.

3) Religious Expression

If the discussion is about miraculous intervention, bringing in a trusted faith advisor, to process the place of medicine (if at all) then the specific definition or tests for determination is relevant

For those waiting for a miracle, the conversation to engage at the 'end' of the process is much more difficult than when the opportunity is presented at the beginning.

Approaching a family's understandings of hope and miraculous intervention is the competency of spiritual care and can make a significant difference in the psychosocial health of family.

Considering the comparison to the idea of regrowing a limb (or rather never expecting, or praying for it to regrow). While this has never been mentioned in a critical care situation, it may be used in situations approaching palliative care where the relationship with a loved one is particularly strong.

A religious understanding can be genuine, but it is never the only thing going on intellectually for loved ones (interpersonal, psychological, other factors).

Faith can be a vehicle for expressing the history of the relationship of interpersonal issues.

Can be in any religious tradition.

Congregational clergy of various faiths may not be well versed in the determination of or definition of death.

Religious leaders can help a family give themselves 'permission' to let go.

4) Pluralism

Understanding issues of trust in the system for individuals who do not start from that position.

The importance of humility in the face of a complex situation and the reality that the dominant western medicine model is not the only understanding that individuals treated in the Canadian medical system may hold.

Acknowledging the disconnection and mistrust born of colonial action or other exercises of dominance.

Consider the acknowledgment that while this might be 'the systems' definition which the system must work with, it is not a directive.

5) Accommodation

Understanding the grief, ritual, and personal experience of the situation.

Spiritual care professionals work to create the space for the human experience.

Providing the space and resources to support the human experience of the loved ones and families, but also staff who work in the system but may hold personal spiritual perspectives at odds with clinical standards.

Common practice to prolong care to allow that space.

Families need to be given a bit of time to absorb their reality before being able to make decisions about removal of support, organ/skin/tissue donation, etc.

The nature of the death influences that willingness of the care team to allow a transitory period.

Care teams providing the 'time' by further intervening can actually make the situation harder/more difficult.

Policy language should be clear that we have the benefit of technology which can keep a patient who is brain-dead alive for many years; but that's not the purpose of the artificial life support; the purpose should be to give time to the body to regain it's own natural ways of sustaining life or in the event that's not possible, to give time to loved ones time to prepare their goodbyes.

Medical care teams sometimes offer intervention but with the advice that it wouldn't be fruitful.

The value of understanding the framing of the offer of support as walking with the family, rather than putting off the impact of the recognition of death for their benefit.

Being firm and clear, but empathetic and human.

Don't underestimate the value of some time to process.

Give clinical staff permission to allow time/space for loved ones.

Understanding clinicians may provide a buffer period of time after signaling that situation, but before anything is determined, to allow for reconciliation and ritual.

It's possible to get creative, example of using zoom to bring a lama's blessing from Tibet to satisfy a cultural/ritual closure need on a timescale that the system could accept.

Understanding the impact on clinicians of variable practice in response to family pressure.

Clinical care team may continue to provide care beyond their own judgement for fear of litigation.

Perspective of concern for the suffering of a patient or motivation of what's in the best interests of the patient.

Understanding the balance between making space and not prolonging suffering.

Spiritual care also supports the care team as they are challenged in difficult passing situations.

Knowledge Translation Advice

Participants offered advice on knowledge translation and educational resources for three major audiences: 1) Loved ones and families, 2) Clinical teams, and 3) Spiritual care professional peers. Participants also offered suggestions for additional learning for the project team as it considers the implementation of the new standard. Finally, participants reviewed and provided feedback on the 90 second definition of death video produced by the project team.

Loved Ones and Families

Huge value around education about the definition, and acknowledgement that application of the definition does not prevent a spiritual understanding or the arrival of a miracle.

Tools that help families understand the 'futility' of future or further intervention, rather than the application of a 'definition'.

A guide which can be reviewed to help prime family for a discussion and recognition of death.

Resource that provides reflective questions for family and loved ones.

We need to be careful not to overload loved ones with information.

Understanding the value of advance care planning in these situations to provide direction and clarity.

Clinical Teams

The material that would be helpful would be at the disposal of care teams including spiritual care

Asking about "the desire for support" rather than "if a family is religious", with the expectation that many who do not identify as religious will still benefit from spiritual care expertise.

Family and loved ones who may not consider themselves religious still need sense making and reconciling.

Understanding the decompensation impacting loved ones and families in the days leading up to a death determination.

Focus on clarity of the language and thoughtful communication that humanizes the experience and provides the foundation for constructive dialogue.

Encourage genuine conversations and avoiding the 'too gentle' approach.

The balance of supporting the family/loved ones without providing any false hope

> *"Clinicians should consider taking palliative care courses too so that they can learn the language - how to communicate to family when the odds of survival appear to be slim."*

Emotional sensitivity/competence is critical for clinicians, how can that be encouraged?

> *"I've been thinking about what it would be like to have the team (physicians, nurses, SW) stay in the room while spiritual care works - in the same way we are very often present*

while 'they' interact with patients and family - to witness and stand with - everyone involved."

Guidance for clinicians to ensure the involvement of spiritual care professionals.

Historically there are grand rounds on compassion and/or death and dying, but it has been on hold for some time because of Covid.

Enlist medical educators to influence the training of critical care teams and the next generation of clinicians since their approach and manner is so significant in the tone.

Spiritual Care Professionals

The sophistication of the situation requires a skilled discernment which is difficult to 'write into a book'.

The language used in prayer is just as important as the language used by clinicians.

Looking at the realities of generationally specific outlooks/understandings.

This is a great element for a CASC unit for training and the video [below] would support that.

The local CASC units could offer a webinar to those already in practice.

Project Team

Consider positioning material along the likely trajectory(ies) of that journey towards a declaration of death.

Advice to review the Netflix show Extremis (nominated for an academy award).

90 Second Definition of Death Video Feedback

Video only goes so far… lived experience and expertise in communicating on this subject is key.

The invisibility of brain death is such a challenge to make it 'real' for families and loved ones.

It doesn't replace the hard conversation or make the support requirements less.

The video is too coldly clinical and does not acknowledge 'the humanity' of an individual.

Information is not the solution. It isn't a question of just finding the right way to explain it so families 'agree' or 'make the right decision'.

Pay attention to the language and cultural nuances. Currently is does not anticipate plural audiences.

The video is great.

Very concise, but also very informative.

The language provides a vocabulary for professionals and staff to use with patients.

A good tool for teams dealing with brain-death.

It couldn't be shown to the family at the bedside in that moment, but it may have a place earlier on that might support understanding, but not sure if that would be productive. We don't want to heighten anxiety for those heading into this trajectory.

Thinking about the video as a PSA to work to shift public perspective before any particular family is confronted with the trauma of the situation.

Liked the way it lays out the neurological 'trump' in the situation, but it is contrary to the social cultural perspective about heart and lungs/breathing.

The video is certainly informative for spiritual care professionals to equip them.

Participants

Cecilia	Moore	Holy Family Long Term Care Home	Vancouver	BC
David	Maginley	Nova Scotia Health	Halifax	NS
Dorothy	Schick	Saskatchewan Health Authority		SK
Doug	Koop	HSC Winnipeg	Winnipeg	MB
Emiline	Pena	St. Paul's Hospital	Saskatoon	SK
Fritz	Clarke	Queensway Carleton Hospital	Ottawa	ON
Geoffrey	Haber	Baycrest	Toronto	ON
Helen	Chan Bennett	University of Alberta Hospital CAF, 15 Field Ambulance - Reserve Force	Edmonton	AB
Joel	Aguirre	Unity Health	Toronto	ON
Kara	Braun	Kingston General Hospital	Kingston	ON
Karen L.	Norris	University of Alberta Hospital	Edmonton	AB
Kathy	Neily	Queen Elizabeth Hospital	Charlottetown	PEI
Leslie	Clark	St Boniface Hospital	Winnipeg	MB
Lydia	Collin	University Christian Ministries	Langley	BC
Mark W.	Buell	Queen Elizabeth Hospital	Charlottetown	PEI
Marnie	Roper	Cowichan District Hospital	Duncan	BC
Moe	Weaver	Mount Sinai Hospital	Toronto	ON
Oceana	Hall	Our Place Society	Victoria	BC
Pam	Dridger	Moncton Hospital	Moncton	NB
Simon	Malonda	St. Joseph's Health Centre	Guelph	ON
Taylor	Walsh	Queen Elizabeth Hospital, Cancer Treatment Center	Charlottetown	PEI
Victoria	Shepard	St. Mary's General Hospital	Kitchener	ON

Observers

John	Hayward	The Canadian Association for Spiritual Care (CASC)	Toronto	ON
Laura	Hornby	University of Ottawa (project team)	Ottawa	ON
Lindsay	Wilson	Canadian Blood Services (project team)	Toronto	ON

Facilitator

Andrew	MacLeod	Canadian Blood Services (project team)	Toronto	ON

eAppendix 7 Evidence summaries and recommendation rationales: death determination by circulatory critiera

Monitoring Devices

PICO Question:

In all patients who are potential organ donors undergoing death determination by circulatory criteria, should alternate means of measuring circulation (palpable pulse, ECG, point of care echocardiography, doppler ultrasound, cerebral oximetry) versus continuous arterial line monitoring be used for confirmation of cessation of circulation?

Reviewers:

Core Group: Abdullah Malik, Laura Hornby, Anna-Lisa Nguyen, Sonny Dhanani, Mypinder Sekhon, Joann Kawchuk, Chip Doig, Jennifer Ann Klowak

Citation Review Only: Nedaa Aldairi, Conall Francoeur, Supun Kotteduwa Jayawarden, Ryan Sandarage, Belinda Yee

Literature Search:

Citations Screened: 5137

Citations Included: 11 (+1 unpublished study, +8 for subgroup considerations)

Recommendation(s):

We recommend continuous arterial line monitoring be used to confirm permanent cessation of circulation for patients who are potential organ donors undergoing DCC (Strong recommendation, moderate certainty in evidence).

We suggest continuous electrocardiogram monitoring be used to confirm permanent cessation of circulation in situations where the use of an arterial line is not possible for patients who are potential organ donors undergoing DCC (Weak recommendation, moderate certainty in evidence).

Evidence Summary:

We found no studies designed specifically to compare use of arterial line to noninvasive measures for determining death in patients who were organ donors after death determination by circulatory criteria (DCD) donors. We found some studies that reported on the use of arterial line and non-invasive monitoring in DCD donors and also indirect evidence regarding the use of non-invasive monitoring in the area of resuscitative medicine.

For the detection of pulse, we identified one randomized controlled trial (RCT), which compared the ability of lay people and ambulance personnel, at varying stages of their training, to use palpable pulse assessment to detect pulselessness[1] and an observational study[2] that compared the efficiency of cardiac ultrasound, Doppler ultrasound, and manual pulse palpation methods to check for a pulse in cardiac arrest patients. Measures of diagnostic accuracy for pulse by palpation in both studies had error rates above 5%. For detection of pulsatile flow by Doppler ultrasonography, in addition to the aforementioned observational study[2], we also found one pilot RCT (n=20 patients, n=3 assessors)[3] and one small trial (n= 23 patients, n=46 assessors)[4] that compared recorded videos of two-dimensional and/or colour Doppler ultrasound to arterial line measurements in patients undergoing cardiopulmonary bypass. Findings were that two-dimensional ultrasound was sensitive and specific for

detecting pulsatile flow but at relatively high mean arterial pressures (MAP) of 62mmHg (49–74 (33–82)). Colour Doppler detected pulsatile flow earlier and at lower MAP (56mmHg (52–73 (43–83)) compared to two-dimensional ultrasonography but judged by the study authors as not reliable. The intraclass correlation coefficient for two-dimensional ultrasound was 0.86 (95%CI 0.63–0.96) and 0.32 (95%CI 0.01 to 0.71) for colour Doppler.

For electrocardiogram (ECG), we found two cohort studies; a pilot study[5] (n=30) and the follow-up full study[6] (n=631) that reported on patients with vital sign monitoring (invasive arterial line and ECG) who were dying in the intensive care unit (ICU) after withdrawal of life sustaining measures (WLSM). Both studies reported that ECG activity commonly continued following the permanent cessation of circulation as assessed by the loss of invasive arterial pulse pressure. The full study, which included patients who were DCD donors as well as those who weren't, reported that the final QRS occurred at a median of 3 minutes and 35 seconds after the final arterial pulse (range, 0 seconds to 83 minutes 28 seconds)[6]. In a subgroup of this cohort who had DCD attempted (n=37), ECG became isoelectric within 2 seconds of the final pulse in 11% of patients, within 5 minutes in 49% of patients, and in 6% of patients, ECG activity had not become isoelectric within 30 minutes of the final arterial pulse[7].

Near-infrared spectroscopy (NIRS) allows for continuous non-invasive monitoring of cerebral oxygenation. We considered it's potential to be used a surrogate measure of circulation. We found evidence from one small observational study (n=6) that used NIRS to measure regional cerebral oxygen saturation (rSO2) in ICU patients after WLSM[8]. The study reported a correlation with MAP, but a broad range of values at the time of death, indicating that there is no clear cut-off rSO2 value for death[8]. Given that the evidence for the use of NIRS in our population of interest was sparse, we also considered as indirect evidence the findings from two observational studies of brain dead (n= 20 healthy and 20 brain dead patients)[9] and brain injured patients (hypoxic ischemic brain injury (HIBI) patients following cardiac arrest, n=10) [10] that compared NIRS to invasive monitoring. Both cohort studies concluded that NIRS should not be used as a noninvasive surrogate to measure cerebral oximetry in brain dead or brain injured patients because of lack of agreement with measures from invasive monitoring devices.

While we were unable to find any studies that directly compared point of care (POC) echocardiography to arterial line in our population of interest, we included one observational study that compared POC echocardiography to manual pulse palpation which concluded that POC echocardiography may allow earlier pulse detection[2]. We also included two systematic reviews (n=1695 and 2091 patients)[11, 12] that assessed POC echocardiography for prognostication during CPR, with differing conclusions on its utility.

Subgroup Considerations:

We considered the subgroup populations of pediatric/neonatal, medical assistance in dying (MAiD) and uncontrolled DCD donors. No studies directly addressed our question in these populations of interest. We did find 3 observational studies (total n=364 assessors and n=73 infants and children)[13-15] that compared palpable pulse to arterial line measurements but not for death determination. As for adults, the findings from these studies in infants and children demonstrated that overdiagnosis of absent pulse was likely if palpation alone was used for detection of arterial pulsatility. Errors are frequently committed even by experienced pediatric ICU physicians (sensitivity of 1.00 and specificity of 0.82; 18% of time when pulse present, diagnosed pulseless)[14]. The findings for ECG versus arterial line in pediatrics are also in agreement with those in adults. In the pilot study[5] mentioned above, 3/4 pediatric subjects had cessation of arterial blood pressure activity that preceded the isoelectric ECG by 11:11, 27:42, 36:29 mm:ss, respectively. Of these, two had ECG that continued up to the end of the monitoring period. Unpublished pediatric data (n=6)[7] from the large cohort study[6], reported that for 2 patients, ECG and arterial blood pressure stopped together while 4/6 subjects had cessation of arterial line pulse pressure

that preceded the isoelectric ECG by 6:29 to 50:26 mm:ss. We did not find any direct or indirect evidence for any of the noninvasive measures for the MAiD or uncontrolled DCD subgroup populations.

Justification/Rationale

Evidence demonstrates that to minimize the risks of both false positive (determining someone dead who is alive) and false negative rates (determining someone is not dead who is dead) for death determination by circulatory criteria, use of a well-functioning arterial line is required. We don't recommend any non-invasive monitoring devices for this purpose, but we suggest that ECG may be considered in exceptional circumstances only, as described below. Arterial line monitoring is an objective measure that is easily interpreted and commonly used in the ICU setting. Since ECG activity persists in some patients whose circulation has permanently ceased, when arterial line monitoring is used, no other confirmation of cessation of circulation, such as electrical asystole, is required. Auscultation or palpation should not be used to assess lack of circulation but could be applied to verify that an observed flat arterial line waveform corresponds with the clinical state.

The panel agreed that although use of arterial line monitoring is strongly favoured, there may be certain exceptional circumstances where ECG monitoring for absent cardiac electrical activity as a surrogate for absent circulation could be considered. This includes technical reasons (e.g. inability to obtain a calibrated and reliable arterial line), refusal by surrogate decision makers for pediatric or neonatal cases or refusal by potential donors in the case of MAiD. Asystole on ECG may be as good as, or even better, at identifying cessation of the circulation as an arterial line; there is moderate certainty in evidence that ECG monitoring carries a low risk of false positives (determining someone dead who is alive) but high risk of false negatives (determining someone is not dead who is dead) for death determination but the high risk of false negatives is only transient and becomes 100% specific and sensitive with time. Although outcomes for organ donation were not judged by the panel to be critical or important for this clinical question, we acknowledge that use of ECG monitoring for death determination by circulatory criteria may unnecessarily prolong the time to determine death, since ECG activity has been shown to persist for longer than 30 minutes after the arrest of pulsatile activity measured by arterial line monitoring. This risk and its potential consequences, along with the risks of arterial line placement, should be shared with patients and/or surrogate decision makers so that they can make informed choices in these contexts.

Implementation Considerations:

No significant implementation considerations were identified. Arterial line and ECG monitoring are commonly used methods for monitoring cardiocirculatory function. Clinicians must ensure that monitoring devices are properly scaled, and arterial lines are properly placed, functioning, levelled and zeroed.

References:

1. Dick WF, Eberle B, Wisser G, Schneider T. The carotid pulse check revisited: what if there is no pulse? Crit Care Med. 2000;28(11 Suppl):N183-5.
2. Zengin S, Gumusboga H, Sabak M, Eren SH, Altunbas G, Al B. Comparison of manual pulse palpation, cardiac ultrasonography and Doppler ultrasonography to check the pulse in cardiopulmonary arrest patients. Resuscitation. 2018;133:59-64.
3. Germanoska B, Coady M, Ng S, Fermanis G, Miller M. The reliability of carotid ultrasound in determining the return of pulsatile flow: A pilot study. Ultrasound. 2018;26(2):118-26.
4. Sanchez S, Miller M, Asha S. Assessing the validity of two-dimensional carotid ultrasound to detect the presence and absence of a pulse. Resuscitation. 2020;157:67-73.

5. Dhanani S, Hornby L, Ward R, Baker A, Dodek P, Chamber-Evans J, et al. Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: a multicenter prospective observational study. Crit Care Med. 2014;42(11):2358-69.
6. Dhanani S, Hornby L, van Beinum A, Scales NB, Hogue M, Baker A, et al. Resumption of Cardiac Activity after Withdrawal of Life-Sustaining Measures. N Engl J Med. 2021;384(4):345-52.
7. Scales N. Personal communication. February 2022.
8. Genbrugge C, Eertmans W, Jans F, Boer W, Dens J, De Deyne C. Regional cerebral saturation monitoring during withdrawal of life support until death. Resuscitation. 2017;121:147-50.
9. Caccioppola A, Carbonara M, Macrì M, Longhi L, Magnoni S, Ortolano F, et al. Ultrasound-tagged near-infrared spectroscopy does not disclose absent cerebral circulation in brain-dead adults. Br J Anaesth. 2018;121(3):588-94.
10. Hoiland RL, Sekhon MS, Cardim D, Wood MD, Gooderham P, Foster D, et al. Lack of agreement between optimal mean arterial pressure determination using pressure reactivity index versus cerebral oximetry index in hypoxic ischemic brain injury after cardiac arrest. Resuscitation. 2020;152:184-91.
11. Tsou PY, Kurbedin J, Chen YS, Chou EH, Lee MG, Lee MC, et al. Accuracy of point-of-care focused echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A systematic review and meta-analysis. Resuscitation. 2017;114:92-9.
12. Reynolds JC, Issa MS, T CN, Drennan IR, Berg KM, O'Neil BJ, et al. Prognostication with point-of-care echocardiography during cardiac arrest: A systematic review. Resuscitation. 2020;152:56-68.
13. Tibballs J, Russell P. Reliability of pulse palpation by healthcare personnel to diagnose paediatric cardiac arrest. Resuscitation. 2009;80(1):61-4.
14. Tibballs J, Weeranatna C. The influence of time on the accuracy of healthcare personnel to diagnose paediatric cardiac arrest by pulse palpation. Resuscitation. 2010;81(6):671-5.
15. Sarti A, Savron F, Ronfani L, Pelizzo G, Barbi E. Comparison of three sites to check the pulse and count heart rate in hypotensive infants. Paediatr Anaesth. 2006;16(4):394-8.
16. Jacq G, Gritti K, Carré C, Fleury N, Lang A, Courau-Courtois J, et al. Modalities of Invasive Arterial Pressure Monitoring in Critically Ill Patients: A Prospective Observational Study. Medicine (Baltimore). 2015;94(39):e1557.
17. Saugel B, Kouz K, Meidert AS, Schulte-Uentrop L, Romagnoli S. How to measure blood pressure using an arterial catheter: a systematic 5-step approach. Crit Care. 2020;24(1):172.

Monitoring Devices

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead by manual pulse detection who is not yet dead (false positives)									
2[1,2]	randomised trials[a]	not serious	not serious	serious[b]	not serious	none	No studies were found directly addressing the use of palpable pulse for this PICO question. Assessment of detectable pulses in low flow states (but not donation) has been studied in the context of informing resuscitation guidelines. 1 RCT included n=206 ambulance personnel and lay people and who assessed pulse at different phases of patient surgery, including moments with systolic pressures >80 or during full bypass support (no pulse pressure) in n=16 patients on cardiopulmonary bypass. 45% did not detect a carotid pulse when one was present (as monitored by an arterial line). Fully trained medical personnel (n=9) demonstrated a specificity of 89% for the manual diagnoses of pulselessness. One observational study (Zengin 2018; n= 2 physicians and 40 cardiac arrest patients undergoing CPR) reported false positive rates as 5.3% for manual pulse assessment at the first minute of CPR, 3.5% at minute 15, and 0% at the end of CPR.	⨁⨁⨁◯ Moderate	CRITICAL
Missing someone who is dead by manual palpable pulse detection (false negatives)									
2[1,2]	randomised trials[a]	not serious	not serious	serious[b]	not serious	none	1 RCT included n=206 ambulance personnel and lay people and who assessed pulse at different phases of patient surgery, including moments with systolic pressures >80 or during full bypass support (no pulse pressure) in n=16 patients on cardiopulmonary bypass. 10% (all lay people) did not correctly identify pulselessness. Sensitivity was not assessed in the fully trained group. One observational study (Zengin 2018; n= 2 physicians and 40 cardiac arrest patients undergoing CPR) reported false negative rates as 100% for manual pulse assessment at the first minute of CPR, 28% at minute 15, and 0% at the end of CPR.	⨁⨁⨁◯ Moderate	IMPORTANT

Declaring someone dead by POCUS pulse detection who is not yet dead (false positives)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2[3,4]	randomised trials[a]	serious[c]	not serious	serious[c]	serious[d]	none	1 pilot RCT (Germanoska 2018 n= 3 physicians and n=20 pts.) reported that 2D ultrasound was reliable in detecting the return of pulsatile flow. Mean arterial pressure where ultrasound flow occurred for two-dimensional ultrasound was 62mmHg (49–74 (33–82)) and 56mmHg (52–73 (43–83)) for colour Doppler Colour Doppler detected pulsatile flow earlier and at lower MAP but was not reliable. One observational study (Sanchez 2020) examined portable ultrasound that was used to record four 10-s videos the common carotid artery, three aimed for a pulse in high (>90 mmHg), medium (70-90 mmHg) and low (<70 mmHg) systolic blood pressure (SBP) ranges, and a pulseless video was recorded on cardiopulmonary bypass. Critical care physicians viewed the videos and were asked to nominate within 10 s if a pulse was present. True pulse-status was determined via the arterial-line waveform. Forty-six physicians reviewed a subset of 24 videos. Overall specificity was 0.90 (95% CI 0.86-0.93).	⊕◯◯◯ Very Low	CRITICAL
Missing someone who is dead by POCUS pulse detection (false negative)									
1[4]	observational studies	serious[c]	not serious	very serious[d]	not serious	none	1 observational study (Sanchez 2020) examined portable ultrasound that was used to record four 10-s videos the common carotid artery, three aimed for a pulse in high (>90 mmHg), medium (70-90 mmHg) and low (<70 mmHg) systolic blood pressure (SBP) ranges, and a pulseless video was recorded on cardiopulmonary bypass. Critical care physicians viewed the videos and were asked to nominate within 10 s if a pulse was present. True pulse-status was determined via the arterial-line waveform. Forty-six physicians reviewed a subset of 24 videos. Overall sensitivity was 0.91 (95% confidence interval 0.89-0.93). Sensitivity was highest in the high-SBP group (Mdn=120 mmHg) (0.96, 95% CI 0.93-0.98) and lowest in the low-SBP (Mdn=69 mmHg) group (0.83, 95% CI 0.78-0.87).	⊕◯◯◯ Very low	IMPORTANT
Declaring someone dead by isoelectric ECG who is not dead (false positive)									
2[5,6]	observational studies	not serious	not serious	not serious	not serious	strong association	2 Cohort studies (Dhanani 2021, Dhanani 2014) reported that circulation always ceased with or prior to electrical asystole.	⊕⊕⊕◯ Moderate	CRITICAL
Missing someone who is dead using isoelectric ECG (false negatives)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2[5,6]	observational studies	not serious	not serious	not serious	not serious	strong association	Cohort studies have demonstrated that if an isoelectric ECG is required to determine death, it would result in a significant number of false negatives. Dhanani 2021 reported that in 19% of 480 patients cessation of ECG coincided within 2 seconds with the last arterial pulse of at least 5 mmHg. The median time between the final arterial pulse and final ECG activity after the last arterial pulse was observed for more than 30 minutes in 7% and until the end of recording in 5%. Unpublished data in a subgroup of this cohort who were potential DCD donors (DCD attempted) demonstrated that in 11% ECG stopped within 2 seconds of arterial blood pressure, 49% within 5 minutes, and in 6%, ECG activity had not stopped within 30 minutes. Dhanani 2014 reported that in 10% of 30 patients (26 adults, 4 children), arterial blood pressure and ECG stopped at the same time. In 10% ECG continued up to the end of the 30 minute monitoring period.	⨁⨁⨁◯ Moderate	IMPORTANT
Declaring someone dead by cerebral NIRS who is not yet dead (false positives)									
1[7]	observational studies	not serious	not serious	not serious	very serious[e]	none	One study (Genbrugge 2017, pilot study, n= 6, age 53-83yrs) measured regional cerebral oxygen saturation (rSO2) by NIRS during the process of dying after WLSM in the ICU patients and compared it to invasively measured mean arterial pressure (MAP) The authors reported: 1. a continuous and patient specific decrease in rSO2 was observed in all patients with a simultaneous decrease in MAP; 2. rSO2 and MAP during the last hour before death were positively correlated, (r between 0.722–0.968; p < 0.01) (Fig. 3); **but the absolute rSO2 value at the moment death had a broad range, indicating that there is no clear cut-off rSO2 value for death.**	⨁◯◯◯ Very low	CRITICAL
Missing someone who is dead by cerebral NIRS to determine arrest of circulation (false negative)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
3[7,8,9]	observational studies	not serious	not serious	serious[f]	serious[g]	none	Genbrugge 2017 (see summary in false positive outcome). Caccioppola 2018, reported a small observational study (n= 20 healthy and 20 brain dead patients). In n=11 cases where cerebral was demonstrated to be absent by invasive monitoring, ultrasound-tagged near-infrared spectroscopy (UT-NIRS) demonstrated positive cerebral blood flow. The authors concluded that UT-NIRS needs more research in order to have validity. Hoiland 2020 reported on a small (n= 10) cohort of hypoxic ischemic brain injury (HIBI) patients following cardiac arrest. Their results demonstrated that determination of optimal mean arterial pressure by NIRS (a non-invasive surrogate) lacks agreement with optimal mean arterial pressure derived from pressure reactivity index	⨁◯◯◯ Very low	IMPORTANT

Declaring someone dead by echocardiography to determine cardiac motion who is not yet dead (false positives)

21[2,10,11,g]	observational studies	not serious	serious[i]	serious[j]	not serious	none	Indirect evidence from 1 observational study Zengin 2018 demonstrated that cardiac ultrasonography allowed a more accurate detection of pulse than manual pulse palpation and pulse by Doppler. Indirect evidence also from 2 SRs, Tsou 2017 5 studies, n= 1695 and Reynolds 2020 15 studies, n=2091; Tsou 2017 reported that by meta-analysis, spontaneous cardiac movement (SCM) detected by focused echocardiography had a pooled sensitivity (0.95, 95%CI: 0.72-0.99) in predicting return of spontaneous circulation (ROSC) during cardiac arrest, with a positive likelihood ratio of 4.8 (95% CI: 2.5-9.4). Reynolds 2020 reported that meta-analysis was not possible due to risk of bias, and therefore evidence was very low certainty so that no sonographic finding had sufficient and/or consistent sensitivity for any clinical outcome to be used as sole criterion to terminate resuscitation	⨁◯◯◯ Very low	CRITICAL

Missing someone who is dead by echocardiography to determine cardiac motion (false negative)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
21[2,10,11,g]	observational studies	not serious	serious[i]	serious[j]	not serious	none	Indirect evidence from 2 SRs, Tsou 2017 5 studies, n= 1695 and Reynolds 2020 15 studies, n=2091; Tsou 2017 reported that by meta-analysis, spontaneous cardiac movement (SCM) detected by focused echocardiography had a pooled specificity (0.80, 95%CI: 0.63-0.91) in predicting return of spontaneous circulation (ROSC) during cardiac arrest, with a negative likelihood ratio of 0.06 (95%CI: 0.01-0.39). Reynolds 2020 reported that meta-analysis was not possible due to risk of bias, and therefore evidence was very low certainty so that no sonographic finding had sufficient and/or consistent sensitivity for any clinical outcome to be used as sole criterion to terminate resuscitation	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval

Explanations

a. I study was small RCT one was observational
b. Assessors were lay people and ambulance personnel at varying stages of their training assess palpable pulses and asked to assess pulse or no pulse in less 60 seconds
c. Study included a convenience sample
d. Study compared 2D and colour Doppler in n=20 pts, age > 18 yrs. Each reviewer (n=3) watched the videos independently and recorded the timestamp at which they considered pulsatile flow to be first present in the carotid artery. These were compared to invasive ABP.
e. Low sample size, pilot study
f. Study by Caccioppola was in brain dead pts; Hoiland was HIBI pts
g. small sample size
h. 20 Studies were within 2 RCTs
i. Conflicting findings for 2 SRs
j. Studies were performed to assess prognostic value of POC readings for termination of resuscitation

References

1.Dick, W. F., Eberle, B., Wisser, G., Schneider, T.. The carotid pulse check revisited: what if there is no pulse?. Crit Care Med; Nov 2000.
2.Zengin, S., Gumusboga, H., Sabak, M., Eren, S. H., Altunbas, G., Al, B.. Comparison of manual pulse palpation, cardiac ultrasonography and Doppler ultrasonography to check the pulse in cardiopulmonary arrest patients. Resuscitation; 12 2018.
3.Germanoska, B., Coady, M., Ng, S., Fermanis, G., Miller, M.. The reliability of carotid ultrasound in determining the return of pulsatile flow: A pilot study. Ultrasound; May 2018.
4.Sanchez, S., Miller, M., Asha, S.. Assessing the validity of two-dimensional carotid ultrasound to detect the presence and absence of a pulse. Resuscitation; 12 2020.
5.Dhanani, S., Hornby, L., van Beinum, A., Scales, N. B., Hogue, M., Baker, A., Beed, S., Boyd, J. G., Chandler, J. A., Chasse, M., D'Aragon, F., Dezfulian, C., Doig, C. J., Duska, F., Friedrich, J. O., Gardiner, D., Gofton, T., Harvey, D., Herry, C., Isac, G., Kramer, A. H., Kutsogiannis, D. J., Maslove, D. M., Meade, M., Mehta, S., Munshi, L., Norton, L., Pagliarello, G., Ramsay, T., Rusinova, K., Scales, D., Schmidt, M., Seely, A., Shahin, J., Slessarev, M., So, D., Talbot, H., van Mook, Wnka, Waldauf, P., Weiss, M., Wind, J. T., Shemie, S. D., Canadian Critical Care Trials, Group, Canadian, Donation, Transplantation Research, Program. Resumption of Cardiac Activity after Withdrawal of Life-Sustaining Measures. New England Journal of Medicine; 01 28 2021.
6.Dhanani, S., Hornby, L., Ward, R., Baker, A., Dodek, P., Chamber-Evans, J., Fowler, R., Friedrich, J. O., Gow, R. M., Kutsogiannis, D. J., McIntyre, L., Momoli, F., Morin, K., Ramsay, T., Scales, D., Writer, H., Yildirim, S., Young, B., Shemie, S., Canadian Critical Care Trials, Group, in collaboration with the Bertram Loeb, Chair, Research Consortium in, Organ, Tissue, Donation. Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: a multicenter prospective observational study. Critical Care Medicine; Nov 2014.
7.Genbrugge, C., Eertmans, W., Jans, F., Boer, W., Dens, J., De Deyne, C.. Regional cerebral saturation monitoring during withdrawal of life support until death. Resuscitation; 12 2017.
8.Caccioppola, A., Carbonara, M., Macrì, M., Longhi, L., Magnoni, S., Ortolano, F., Triulzi, F., Zanier, E. R., Zoerle, T., Stocchetti, N.. Ultrasound-tagged near-infrared spectroscopy does not disclose absent cerebral circulation in brain-dead adults. Br J Anaesth; Sep 2018.
9.Hoiland, R. L., Sekhon, M. S., Cardim, D., Wood, M. D., Gooderham, P., Foster, D., Griesdale, D. E.. Lack of agreement between optimal mean arterial pressure determination using pressure reactivity index versus cerebral oximetry index in hypoxic ischemic brain injury after cardiac arrest. Resuscitation; Jul 2020.
10.Tsou, P. Y., Kurbedin, J., Chen, Y. S., Chou, E. H., Lee, M. G., Lee, M. C., Ma, M. H., Chen, S. C., Lee, C. C.. Accuracy of point-of-care focused echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A systematic review and meta-analysis. Resuscitation; 05 2017.

11.Reynolds, J. C., Issa, M. S., T, C.,Nicholson, Drennan, I. R., Berg, K. M., O'Neil, B. J., Welsford, M., Advanced Life Support Task Force of the International Liaison Committee on, Resuscitation. Prognostication with point-of-care echocardiography during cardiac arrest: A systematic review. Resuscitation; 07 2020.

Arterial Pulse Pressure

PICO Question:

In all patients who are potential organ donors undergoing death determination by circulatory criteria, should an arterial pulse pressure of more than 0 mmHg (i.e. 5, 10, 20, 40) vs an arterial pulse pressure of 0 mmHg be used for confirmation of cessation of circulation?

Reviewers:

L. Hornby, K. Dawe, M. Weiss, C. Lanos, K. Wollny, S.L. Ganesan, T. Gofton

Literature Search:

Citations Screened: 3289

Citations Included: 4 (+1 unpublished study, +3 for subgroup considerations)

Recommendation:

We recommend that an arterial pulse pressure of less than or equal to 5 mmHg and within the error of measurement of clinical monitoring equipment be used to confirm permanent cessation of circulation for patients with an arterial line who are potential organ donors undergoing DCC (Strong recommendation, very low certainty in evidence).

Evidence Summary:

We found no studies designed to compare use of different arterial pulse pressure thresholds for confirmation of cessation of circulation in the context of organ donation after death determination by circulatory criteria (DCD) or otherwise. Given the lack of direct evidence, we sought indirect evidence assessing cerebral activity in relation to pulse pressure near or at the time of circulatory arrest; this is most commonly reported after withdrawal of life sustaining measures (WLSM). Following WLSM there is generally a progressive hypoxemia and sustained decreases in systemic perfusion with a corresponding loss of cerebral perfusion.

A recent international multi-centered prospective observational study investigated the incidence and timing of resumptions of cardiac electrical and pulsatile activity in 631 adults after WLSM[1]. This study defined circulatory arrest as a pulse pressure of less than 5 mmHg for at least 60 seconds as detected using an indwelling arterial cannula. They reported that resumptions of cardiac activity occurred in 14% of patients[1]. A small subgroup of these 631 adults (n=8) underwent concurrent continuous EEG monitoring to measure cerebral electrical activity at the time of circulatory arrest and to determine the arterial pulse pressure with EEG activity < 2 microvolts in amplitude following WLSM (Gofton et al. 2021, submitted). The authors reported that EEG became isoelectric a median of 78 seconds (Q1=387s before circulatory arrest, Q3=111s after circulatory arrest) before circulatory arrest. In 3/8 patients there was potential artifact in the EEG signal. The authors used quantitative EEG analysis to demonstrate that for those 3 patients, EEG activity subsided by the time of circulatory arrest with no significant change in EEG power in the final minute before, first minute after or 5 minutes after circulatory arrest. In the 8 adult patients, pulse pressures and mean arterial pressures were averaged for 30 seconds before and 30 seconds after isoelectric EEG. The median pulse pressure at the time of isoelectric EEG was 8.2 mmHg (Q1=5.3, Q3=25), while the median mean arterial pressure at the time of isoelectric EEG was 28.7 mmHg (Q1=22.1, Q3=35.4). These data suggest that at arterial pulse pressures greater than 5 mmHg there remains the potential for persistent cerebral electrical activity.

In addition, we found 4 studies (1 observational[2], n=19 adults; 3 case studies/series[3-5], total n=6 adults) that did not report arterial pressures associated with isoelectric EEG but that reported on timing of isoelectric EEG compared to arrest of circulation (at asystole, assumption is that pulse pressure is 0mmHg). In these studies, isoelectric EEG was reported at up to 80 mins prior to and 2 minutes after asystole in 24/25 patients. It is important to note that not all reported cases were under conditions of progressive loss of cerebral blood flow and some of these reported cases were under conditions of acute interruption of cerebral blood flow associated with sudden cardiac arrest. A small case series[5] reported that 1/4 patients studied had single delta wave bursts that persisted following the cessation of both the cardiac rhythm and arterial blood pressure. These delta bursts were of unclear etiology and the authors were uncertain if they were cerebrally originating or rather artefact, but artefact was favoured.

Specific subgroups were considered including pediatrics, neonates, uncontrolled DCD, the presence of circulatory assist devices/ECMO and medical assistance in dying. There is no direct evidence to support maximum arterial pulse pressure thresholds for determining circulatory arrest in any of these populations. One publication described and used a definition of pulselessness in pediatrics as follows: pulse pressure less than 10 mm Hg and systolic blood pressure less than 50 mm Hg (≥ 1 year) or less than 40 mm Hg (< 1 year)[6]. This definition was based on previous reports in the literature[7, 8]. When considering uncontrolled DCD, a single case report measuring cerebral blood flow during cardiopulmonary resuscitation for PEA arrest documented a cerebral blood flow velocity of 51 cm/second at the same time as peak systolic arterial blood pressure was 33 mmHg[9]. This suggests that there may be preserved cerebral blood flow even at very low systolic arterial pressures. Another publication reported a comprehensive literature review that included 4 prior publications reporting loss of EEG activity at 10-30 seconds during intraoperative asystole and in the presence of general anesthesia[10]. Two more publications included in the review documented loss of EEG activity 10-15 seconds after ventricular fibrillation cardiac arrest[10].

Justification/Rationale

In the context of organ donation, specifically donation after death by circulatory criteria, the accuracy and timing of death determination are paramount to ensure that the “dead donor rule” is not violated, but that organ retrieval proceeds at the earliest opportunity. Unfortunately, the overall certainty in the evidence for the minimum pulse pressure required to accurately measure cessation of circulation is very low. There is no direct evidence to address this important question. Given the lack of direct evidence, we assessed indirect evidence in the literature. We focused on the indirect evidence which reported on brain perfusion as it relates to arterial pulse pressure during cardiopulmonary resuscitation and at the end of life, two contexts that are similar to those of controlled and uncontrolled DCD. We agreed that a pulse pressure of <5 mmHg, rather than an arterial pulse pressure=0, is recommended because the lower threshold for accurate detection of arterial pulse pressure using clinical monitoring systems is not well established at very low pulse pressures[1]. Further, we considered the findings of recent research that an arterial pulse pressure <5 mmHg maintained for 1 minute is not associated with resumptions of circulatory function beyond the recommended observation period of 5 minutes. Death determination by circulatory criteria at pulse pressures greater than 5 mmHg carries the risk of declaring death in a person with persistent brain activity.

Implementation Considerations:

Important considerations for implementation of this recommendation include the requirement for a functioning, indwelling arterial cannula for monitoring arterial pulse pressure and properly scaled blood pressure monitor. The health care providers determining death should be competent in appropriately interpreting arterial pressure waveforms obtained from indwelling arterial cannula and using the monitoring equipment. If the arterial pulse pressure falls below 5 mmHg for a period of time, but

subsequently increases above 5 mmHg then the 5-minute observation period should be restarted. Restarting the observation period may be required more than once.

References:

1. Dhanani S, Hornby L, van Beinum A, Scales NB, Hogue M, Baker A, et al. Resumption of Cardiac Activity after Withdrawal of Life-Sustaining Measures. N Engl J Med. 2021;384(4):345-52.
2. Matory AL, Alkhachroum A, Chiu WT, Eliseyev A, Doyle K, Rohaut B, et al. Electrocerebral Signature of Cardiac Death. Neurocrit Care. 2021;28:28.
3. Stecker MM, Escherich A, Patterson T, Bavaria JE, Cheung AT. Effects of acute hypoxemia/ischemia on EEG and evoked responses at normothermia and hypothermia in humans. Med Sci Monit. 2002;8(4):CR223-8.
4. Hughes JR, Uppal H. The EEG changes during cardiac arrest: a case report. Clin Electroencephalogr. 1998;29(1):16-8.
5. Norton L, Gibson RM, Gofton T, Benson C, Dhanani S, Shemie SD, et al. Electroencephalographic Recordings During Withdrawal of Life-Sustaining Therapy Until 30 Minutes After Declaration of Death. Can J Neurol Sci. 2017;44(2):139-45.
6. Morgan RW, Reeder RW, Meert KL, Telford R, Yates AR, Berger JT, et al. Survival and Hemodynamics During Pediatric Cardiopulmonary Resuscitation for Bradycardia and Poor Perfusion Versus Pulseless Cardiac Arrest. Crit Care Med. 2020;48(6):881-9.
7. Morgan RW, Landis WP, Marquez A, Graham K, Roberts AL, Lauridsen KG, et al. Hemodynamic effects of chest compression interruptions during pediatric in-hospital cardiopulmonary resuscitation. Resuscitation. 2019;139:1-8.
8. Tibballs J, Russell P. Reliability of pulse palpation by healthcare personnel to diagnose paediatric cardiac arrest. Resuscitation. 2009;80(1):61-4.
9. de Wilde RBP, Helmerhorst HJF, van Westerloo DJ. Cerebral blood flow velocity during chest compressions in cardiac arrest. Netherlands Journal of Critical Care. 2017;25(4):137-9.
10. Pana R, Hornby L, Shemie SD, Dhanani S, Teitelbaum J. Time to loss of brain function and activity during circulatory arrest. Journal of critical care. 2016;34:77-83.

Arterial Pulse Pressure

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not yet dead, pulse pressure value of more than 0 mmHg is associated with brain function, (false positives) (assessed with: arterial line and EEG)									
5[1,2,3,4,a]	observational studies	serious[a]	not serious	not serious	serious[b]	none	No direct evidence was found for this question. Indirect evidence in the context of WLSM (i.e. progressive loss of flow: progressive or sustained decline in systemic perfusion or hypoxia before circulatory arrest) includes one small (n=8 adult) observational study that reported the pulse pressures (measured with invasive arterial line) associated in time with loss of EEG (i.e. EEG wave amplitude less than 2 microvolts) during WLSM and death determination (Gofton et al. 2021, submitted, substudy of Dhanani et al. 2021). EEG stopped a median of -78s (Q1=-387, Q3=111) before circulatory arrest. However, in 3/8 there was potential artifact and quantitative EEG analysis demonstrated that for those 3 patients EEG subsided by the time of circulatory arrest with no significant change in EEG power in the final minute before, first minute after or 5 minutes after circulatory arrest. In the 8 patients, pulse pressures and mean arterial pressures were averaged for 30 s before and 30 s after the EEG was below 2 microvolts. The median pulse pressure at the time of EEG cessation was 8.2 mmHg (Q1=5.3, Q3=25), while the median mean arterial pressure at the time of EEG cessation was 28.7 mmHg (Q1=22.1, Q3=35.4). We also found 4 studies (1 observational, n=19 adults; 3 case studies/series, total n=6 adults) that reported on timing of isoelectric EEG compared to arrest of circulation. In all studies but one (n=1/25), EEG was reported to stop from 80 mins prior to 2 mins after asystole. Norton et al. 2017 reported that 1/4 patients had single delta wave bursts that persisted following the cessation of both the cardiac rhythm and arterial blood pressure. These delta bursts were of unclear etiology, uncertain if cerebrally originating *vs* artefact, but artefact was favoured.	⨁◯◯◯ Very low	CRITICAL
Missing someone dead who is dead, pulse pressure value of more than 0 mmHg not associated with brain function, (false negative)									
5[1,2,3,4,a]	observational studies	serious[a]	not serious	not serious	serious[b]	none	In the included studies, there are patients who lose brain function and pulse pressures much higher than 0 mmHg, well prior to circulatory arrest so there will be false negatives if 0 mmHg is required to indicate arrest of circulation.	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval

Explanations

a. Most direct study (Gofton 2022) is not yet published

b. very low sample size

References

1.Stecker, M. M., Escherich, A., Patterson, T., Bavaria, J. E., Cheung, A. T.. Effects of acute hypoxemia/ischemia on EEG and evoked responses at normothermia and hypothermia in humans. Med Sci Monit; Apr 2002.

2.Hughes, J. R., Uppal, H.. The EEG changes during cardiac arrest: a case report. Clin Electroencephalogr; Jan 1998.

3.Norton, L., Gibson, R. M., Gofton, T., Benson, C., Dhanani, S., Shemie, S. D., Hornby, L., Ward, R., Young, G. B.. Electroencephalographic Recordings During Withdrawal of Life-Sustaining Therapy Until 30 Minutes After Declaration of Death. Can J Neurol Sci; Mar 2017.

4.Matory, A. L., Alkhachroum, A., Chiu, W. T., Eliseyev, A., Doyle, K., Rohaut, B., Egbebike, J. A., Velazquez, A. G., Der-Nigoghossian, C., Paniker, L., Prager, K. M., Agarwal, S., Roh, D., Park, S., Claassen, J.. Electrocerebral Signature of Cardiac Death. Neurocritical Care; Jun 28 2021.

Observation Period

PICO Question:

In all patients who are potential organ donors undergoing death determination by circulatory criteria, should a 5-minute hands-off time vs a shorter or longer period of hands-off time be used for confirmation of cessation of circulation?

Reviewers:

Shemie, J; Zorko, DJ; Hornby, L; Kongkiattikul, L; Malik, A; Matheson, S; Sandarage, R; Singh, G; Wollny, K; Dhanani S

Literature Search:

Citations Screened: 3741

Citations Included: 12

Recommendations:

We recommend a minimum of 5 minutes of observation time be used to confirm permanent cessation of circulation for patients who are potential organ donors undergoing controlled donation after DCC (Strong recommendation, moderate certainty in evidence).

We recommend a minimum of 10 minutes of observation time be used to confirm permanent cessation of circulation for patients who are potential organ donors undergoing uncontrolled donation after DCC (Strong recommendation, low certainty in evidence).

Evidence Summary:

We found six studies (total n=1037) that described 23 clinically reported and confirmed events of resumptions in arterial pulsatile activity, blood pressure, electrical activity, and/or breathing in adults undergoing death determination following withdrawal of life sustaining measures[1-6]. Three studies (total n=722) were prospective observational studies[2, 3, 5] and the remaining three studies were retrospective observational studies[1, 4, 6]. All reported resumptions in cardiac or respiratory activity were transient and no patients with resumption(s) survived. All resumptions occurred within five minutes following arrest of circulation, but in six patients, resumptions occurred after two minutes of arrest of circulation. Five studies[1, 3-6] included DCD donors (total n=412) and reported 16 events of transient resumptions following arrest of circulation. None of the studies included patients supported by extracorporeal membrane oxygenation or other cardio-circulatory assist devices (pacemaker, ventricular assist devices, etc.).

The largest observational study included both DCD and non-DCD patients (n=631)[3]. In this study, the calculated incidence of clinically reported resumption of circulation, cardiac activity, and/or respiratory movement was 1% (95% CI 0-2%). However, based on retrospective analysis of ECG and blood pressure waveforms (n=480), the authors also reported a calculated incidence of resumption of cardiac electrical and pulsatile activity of 14% (95% CI, 11-17%), inclusive of resumptions identified at bedside. For this analysis, resumption of cardiac electrical and pulsatile activity was conservatively defined as a return of arterial pulse pressure of at least 5 mm Hg corresponding to at least one QRS complex, after a period of pulse pressure of less than 5 mm Hg for at least 60 seconds, as detected by indwelling arterial cannula. The longest time between arrest and resumption of cardiac activity was 4 minutes 20 seconds.

Subgroup Considerations

Uncontrolled DCD: No studies were found that reported on events of resumptions in pulsatile activity, ECG, blood pressure or breathing in adults following arrests of circulation in uncontrolled DCD but many studies have been published associated with the termination of resuscitation, both in and out of hospital which is a similar context to that of uncontrolled DCD. A prospective, observational study[7] reported 5 autoresuscitation events in 840 out of hospital cardiac arrest patients who had resuscitation attempts terminated on site. The time between arrest and autoresuscitation was 3 minutes in 3 cases and 6 minutes and 8 minutes in the two others; none of the patients survived. There were two protocol deviations in the study: in the patient with autoresuscitation at 6 minutes, the ventilation bag was not immediately disconnected from the intubation tube when CPR ceased; in the patient with autoresuscitation at 8 minutes, a noradrenaline infusion initiated before cardiac arrest was not discontinued when CPR stopped. Previous systematic reviews have found more than 60 case reports of autoresuscitation in adults monitored following termination of resuscitation with the longest reported to be 10 minutes. In addition, there are 3 case reports[8-10] of 4 children who experienced autoresuscitation after resuscitation was terminated. The autoresuscitation times were reported to be within 30 seconds, within 1 minute, 2 minutes and 6 minutes. All of the children in these reports died except the 18-month-old with the 6-minute event who survived[10].

Pediatrics: We found limited direct evidence pertaining to observation time in pediatric DCD. Five studies (total n=21) reported on five total events of resumptions in arterial pulsatile activity, blood pressure, electrical activity and/or breathing in children with arrests of circulation. Two studies (n=8) [5] and (n=4)[2] reported that no autoresuscitation events occurred in the included pediatric patients. The subsequent study[3] enrolled seven pediatric patients (of which complete data was collected on six; none were DCD donors; all died), demonstrating that two patients had transient resumptions of pulsatile activity following arrest of circulation at 1 minute 23 seconds and 1 minute 53 seconds, respectively (Personal correspondence, Dhanani). One case report[11] of two pediatric patients receiving end-of-life care described autoresuscitation events with durations of 14 minutes and "several minutes." One of the patients survived and was discharged from PICU. Another case report[12] described a pediatric DCD donor with a transient resumption of circulation that occurred >2 minutes but <5 minutes after cessation of pulsatile activity, lasting approximately 20 minutes.

Neonates and Medical Assistance in Dying (MAID): No specific evidence was found pertaining to these subgroups.

Justification/Rationale

Avoiding false positives (i.e. declaring someone dead who is not yet) dead is an important cornerstone of death declaration and assures a trustworthy process, especially in the case of DCD donation. The current evidence pertaining to the context of withdrawal of life sustaining measures, including a large international, multicentered observational study, demonstrates that a 5-minute observation time was associated with no false positives, even amongst controlled DCD donors.

In the context of uncontrolled DCD, evidence suggests that the number of false positives may be significant if the time of the observation period is shorter that 10 minutes. While considering the potential importance of missing false positives to patients, families and clinicians, the panel strongly felt that a shorter period of observation time (< 5minutes for controlled DCD and < 10 minutes for uncontrolled DCD) was associated with important uncertainty, even in light of the current evidence demonstrating that resumptions of cardiac activity are transient. There is no available evidence to suggest that a longer observation period would result in more certainty of death declaration in this population. In consideration of the impact on current practice of extending the observation period to gain more certainty in death declaration, the panel felt that 5-minutes for controlled DCD and 10 minutes for uncontrolled DCD is the optimal approach while acknowledging that little data exists to

inform a longer observation period. These recommendations also accounted for the acceptability of this practice as all Canadian centers are currently using 5 minutes of observation time for controlled DCD and select centres that offer uncontrolled DCD are using 10 minutes observation time. Given this body of indirect evidence the panel felt that a separate specific recommendation of longer period (at least 10 minutes) of observation time is warranted for the subgroup of patients undergoing uncontrolled DCD.

Implementation Considerations:

The panel felt that there were negligible implementation considerations associated with these recommendations as they do not represent a change to Canadian practice and as such, there are negligible financial cost or resource requirements.

References

1. Cook DA, Widdicombe N. Audit of ten years of donation after circulatory death experience in Queensland: observations of agonal physiology following withdrawal of cardiorespiratory support. Anaesth Intensive Care. 2018;46(4):400-3.
2. Dhanani S, Hornby L, Ward R, Baker A, Dodek P, Chamber-Evans J, et al. Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: a multicenter prospective observational study. Crit Care Med. 2014;42(11):2358-69.
3. Dhanani S, Hornby L, van Beinum A, Scales NB, Hogue M, Baker A, et al. Resumption of Cardiac Activity after Withdrawal of Life-Sustaining Measures. N Engl J Med. 2021;384(4):345-52.
4. Koo CW, Helmick RA, Van Frank K, Gilley K, Eason JD. Incidence of autoresusCITATION in donation after cardiac death donors. American Journal of Transplantation. 2019;19 (Supplement 3):478-9.
5. 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(1):158-61.
6. Yong SA, D'Souza S, Philpot S, Pilcher DV. The Alfred Hospital experience of resumption of cardiac activity after withdrawal of life-sustaining therapy. Anaesth Intensive Care. 2016;44(5):605-6.
7. Kuisma M, Salo A, Puolakka J, Nurmi J, Kirves H, Vayrynen T, et al. Delayed return of spontaneous circulation (the Lazarus phenomenon) after cessation of out-of-hospital cardiopulmonary resuscitation. Resuscitation. 2017;118:107-11.
8. Cummings BM, Noviski N. Autoresuscitation in a child: The young Lazarus. Resuscitation. 2011;82(1):134.
9. Duff JP, Joffe AR, Sevcik W, deCaen A. Autoresuscitation after pediatric cardiac arrest: is hyperventilation a cause? Pediatr Emerg Care. 2011;27(3):208-9.
10. Mullen S, Roberts Z, Tuthill D, Owens L, Te Water Naude J, Maguire S. Lazarus Syndrome - Challenges Created by Pediatric Autoresuscitation. Pediatr Emerg Care. 2021;37(4):e210-e1.
11. Steinhorn D, Calligan AL. Lazarus syndrome in pediatric hospice care: Does it occur andwhat home hospice providers should know? Pediatrics. 2021;147 (3):538-9.
12. Zier JL, Newman NA. Unassisted Return of Spontaneous Circulation Following Withdrawal of Life-Sustaining Therapy During Donation After Circulatory Determination of Death in a Child. Crit Care Med. 2021;06:06.

Observation Period – Controlled Donation After Death Determination by Circulatory Criteria

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not yet dead, i.e. resumption of circulation or pulsatile activity outside of 5 minutes of observation time (false positives) (assessed with: arterial line and ECG)									
6[1,2,3,4,5,6]	observational studies	not serious	not serious	not serious	not serious	strong association	Six studies (total n=1037) described 23 clinically reported and confirmed events of resumptions in pulsatile activity and/or ECG and/or blood pressure and/or breathing in adults following arrests of circulation after WLSM. However, these resumptions were all transient and none of these patients survived. All resumptions followed arrests that lasted <5mins (longest=4 mins20s); in 6 patients the arrests lasted >2mins. Three studies (Dhanani 2014, Dhanani 2021, Sheth 2012; total n=722) were prospective observational studies and the remaining 4 were retrospective. Five studies (Dhanani 2021, Sheth 2012, Cook 2018, Koo 2019 (Abstract only), Yong 2016) included DCD (n=420 total) donors and reported 16 events of transient resumptions following arrests of circulation (longest=3 mins).	⨁⨁⨁◯ Moderate	CRITICAL
Missing someone who is dead, i.e. no resumption of circulation or pulsatile activity prior to end of 5 minutes of observation time (false negatives) (assessed with: arterial line and ECG)									
6[1,2,3,4,5,6]	observational studies	not serious	not serious	not serious	not serious	strong association	In the included studies the majority of pts did not have any resumptions of circulation or pulsatile activity or ECG or breathing (reported incidences ranged from 0-14%) so in the majority of patients, confirmation of permanent cessation of circulation occurred well before the 5 minutes of observation time.	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval

References

1.Cook, D. A., Widdicombe, N.. Audit of ten years of donation after circulatory death experience in Queensland: observations of agonal physiology following withdrawal of cardiorespiratory support. Anaesthesia & Intensive Care; 07 2018.

2.Dhanani, S., Hornby, L., van Beinum, A., Scales, N. B., Hogue, M., Baker, A., Beed, S., Boyd, J. G., Chandler, J. A., Chasse, M., D'Aragon, F., Dezfulian, C., Doig, C. J., Duska, F., Friedrich, J. O., Gardiner, D., Gofton, T., Harvey, D., Herry, C., Isac, G., Kramer, A. H., Kutsogiannis, D. J., Maslove, D. M., Meade, M., Mehta, S., Munshi, L., Norton, L., Pagliarello, G., Ramsay, T., Rusinova, K., Scales, D., Schmidt, M., Seely, A., Shahin, J., Slessarev, M., So, D., Talbot, H., van Mook, Wnka, Waldauf, P., Weiss, M., Wind, J. T., Shemie, S. D., Canadian Critical Care Trials, Group, Canadian, Donation, Transplantation Research, Program. Resumption of Cardiac Activity after Withdrawal of Life-Sustaining Measures. New England Journal of Medicine; 01 28 2021.

3.Koo, C. W., Helmick, R. A., Van Frank, K., Gilley, K., Eason, J. D.. Incidence of autoresusCITATION in donation after cardiac death donors. American Journal of Transplantation; April 2019.

4.Dhanani, S., Hornby, L., Ward, R., Baker, A., Dodek, P., Chamber-Evans, J., Fowler, R., Friedrich, J. O., Gow, R. M., Kutsogiannis, D. J., McIntyre, L., Momoli, F., Morin, K., Ramsay, T., Scales, D., Writer, H., Yildirim, S., Young, B., Shemie, S., Canadian Critical Care Trials, Group, in collaboration with the Bertram Loeb, Chair, Research Consortium in, Organ, Tissue, Donation. Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: a multicenter prospective observational study. Critical Care Medicine; Nov 2014.

5.Sheth, K. N., Nutter, T., Stein, D. M., Scalea, T. M., Bernat, J. L.. Autoresuscitation after asystole in patients being considered for organ donation. Critical Care Medicine; Jan 2012.

6.Yong, S. A., D'Souza, S., Philpot, S., Pilcher, D. V.. The Alfred Hospital experience of resumption of cardiac activity after withdrawal of life-sustaining therapy. Anaesthesia & Intensive Care; 09 2016.

Observation Period – Uncontrolled Donation After Death Determination by Circulatory Criteria

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not yet dead for uncontrolled DCD i.e. resumption of circulation or pulsatile activity outside of 5 minutes of observation time (false positives) (assessed with: ECG, Pulse, non-invasive BP)									
1[1]	observational studies	not serious	not serious	not serious[a]	not serious	none	No studies were found that reported on autoresuscitation in the context of adult uncontrolled DCD but many studies have been published in the context of termination of resuscitation, both in and out of hospital. A prospective observational study by Kuisma 2017 reported 5 autoresuscitation events in 840 out of hospital cardiac arrest patients who had resuscitation attempts terminated on site. The time of three of the autoresuscitation events was at 3 minutes, one was at 6 minutes and one at 8 minutes. None of the patients survived. Several reviews have been published on this topic, including two systematic reviews (Hornby 2010 and Hornby 2018) and a scoping review (Gordon 2020). These reviews include more than 60 case reports in adults with the longest reported AR event at 10 minutes, with patient recovery (Adanali 2014).	⨁⨁◯◯ Low	CRITICAL
Missing someone who is dead, i.e. no resumption of circulation or pulsatile activity prior to end of 5 minutes of observation time (false negatives) (assessed with: ECG, Pulse, non-invasive BP)									
1[1]	observational studies	not serious	not serious	not serious[a]	not serious	none	In the Kuisma study the majority of pts did not experience any autoresuscitation events and the reported incidence was 5.95/1000 (95% CI 2.10-14.30) in field-terminated CPR attempts. There were two protocol deviations in the study, in case 2 (AR at 6 minutes), the ventilation bag was not immediately disconnected from the intubation tube when CPR ceased; in case 5 (AR at 8 minutes), a noradrenaline in fusion initiated before cardiac arrest was not discontinued when CPR stopped. Therefore, in the majority of patients, confirmation of permanent cessation of circulation occurred prior to the 5-minute observation time.	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval

Explanations

a. Cohort was OHCA patients whose resuscitation was terminated on site and did not include any uncontrolled DCD patients

References

1.Kuisma, M., Salo, A., Puolakka, J., Nurmi, J., Kirves, H., Vayrynen, T., Boyd, J.. Delayed return of spontaneous circulation (the Lazarus phenomenon) after cessation of out-of-hospital cardiopulmonary resuscitation. Resuscitation; 09 2017.

eAppendix 8 Managing pharmacological confounders in death determination by neurologic criteria

This clinical practice guideline recommends that pharmacologic conditions that may confound the clinical assessment or mimic the symptoms and signs of death determination by neurologic criteria (DNC) be excluded prior to commencing an assessment of neurologic function. Pharmacologic confounders typically refer to therapeutic or neuroprotective sedatives (e.g., benzodiazepines, propofol, barbiturates) and opioids administered to patients during resuscitative efforts and after admission to hospital.(1) However, drugs taken in an overdose setting can also reversibly mimic DNC, but causative agents are often different from those administered in critical care settings (i.e., opiate overdose, venomous toxins, baclofen, toxic alcohols, antidepressants and anti-epileptics).(2) In both scenarios the effects of these drugs can mimic signs of DNC such as absence of consciousness and loss of brainstem reflexes. In most cases, as the effects of these drugs wear off, the underlying neurological function can be assessed without these potential confounders.

Knowing how long to wait for the effects of these drugs to wear off is often a challenge. Being able to measure serum concentrations of these drugs would effectively solve this problem but therapeutic drug monitoring is not available for most drugs. Train of four monitoring can be useful for paralytics and urine and blood toxicology screening can be useful in mixed or unknown/suspected overdoses but do not provide quantitative levels of drugs. Although it may not always be necessary to wait until the offending drugs and their active metabolites are completely eliminated from the body, prudent guidance from these and other guidelines suggest waiting at least 5 elimination half-lives before clinical evaluation.(3) Waiting 5 elimination half-lives from the last administered dose means that almost 97% of the drug has been cleared by the body.

Estimates of drug half-life can be found in on-line drug information databases, however, there are two things to consider when using this information. Firstly, many sedatives and opioids have active metabolites, and in some cases, the active metabolites have longer half-lives than their parent drug. For example, the half-life of diazepam in its product monograph is up to 48 hours but its active metabolite, N-desmethyldiazepam has a half-life of up to 100 hours. Secondly, the pharmacokinetic parameters found in drug databases often come from studies of healthy volunteers rather than critically ill patients or patients with toxicologic exposures. This is an important distinction as the pharmacokinetics of most drugs are significantly different in critically ill patients when compared to less sick individuals due to treatment, patient, disease and environmental factors.(4, 5) The greatest predictors of half-life are drug volume of distribution and drug clearance. There are many variables in the ICU that affect drug distribution and clearance in critically ill patients, some of which are related to the patient and their disease/injury and others that are related to interventions made by care providers in these settings (Table 1).

Table 1: Examples of Patient and Clinical Variables that can Influence Sedative and Opioid Half-Life

Variables that Prolong Half-Life	Mechanism	Variables that Shorten Half-Life	Mechanism
Liver/kidney dysfunction	↓Cl; ↑Vd	Hyperdynamic states, vasopressor infusions	↑Cl
Advanced age/frailty	↓Cl	Brain injury, trauma, burns	↑Cl
Aggressive fluid resuscitation/overload	↑Vd	Hypoproteinemia (↓protein binding)	↑Cl
Obesity	↑Vd (especially for lipophilic drugs)	Aggressive diuresis or renal replacement therapy	↑Cl, ↓Vd
ECMO, cardiopulmonary bypass	↑Vd	Surgical drainage	↓Vd
Prolonged infusions of sedatives/opioids	↑Vd, ↓Cl	Augmented renal clearance	↑Cl, ↓Vd
Systemic inflammation/leaky capillaries	↑Vd		

The reality is that in most patients several of these variables exist simultaneously both prolonging and shortening effective drug half-lives and the balance of these variables can be difficult to predict. It is not unreasonable to envision a patient in a hyperdynamic state due to a brain injury who develops hypoalbuminemia and undergoes aggressive diuresis (variables that shorten drug half-life) but also has a kidney dysfunction, advanced age, prolonged infusions of sedatives and fluid overload (variables that prolong half-life). The impact of each one of these variables on drug half-life are difficult to predict at the bedside particularly when these variables fluctuate over time (i.e., patients receive aggressive fluid resuscitation upon admission but then undergo aggressive diuresis or dialysis in the later course of their care. There is some evidence with respect to the duration of continuously infused sedatives and opioids and their impact on drug half-life. Given that most of these drugs are lipophyllic to facilitate penetration across the blood-brain barrier, prolonged infusions (i.e., longer than 48-72 hours) are associated with longer half-lives when compared to shorter infusions or non-critically ill patients.(6) For example, after prolonged infusions of propofol, midazolam their respective half-lives approximately double. Even short acting agents like remifentanil and sufentanyl exhibit a doubling of their half-lives after prolonged infusions. Similarly, after prolonged infusions, the clearance of morphine drops by 90% and the volume of distribution for lorazepam quadruples as metabolites accumulate in adipose tissue.

The net effect of these variables is hard to predict. Prudent advice to the clinician, in the absence of being able to measure drug levels directly, would be to be conservative and err on the side of waiting longer. Consider the reported half-lives of the drugs in question and then consider variables that might lengthen or shorten that half-life (i.e., end organ dysfunction, obesity, duration of continuous infusions etc.). It is important to remember in toxicology settings that clinical pharmacokinetics are not the same as toxicokinetics and that toxicology literature and databases are better suited to find starting points for estimates of half-life. If you predict that the half-life is prolonged, consider your estimation

conservatively using multiples of reported half-lives. Ultimately, under circumstance where the confounding effect of drugs cannot be reliably eliminated, ancillary testing may be necessary.

References

1. Busl KM, Greer DM. Pitfalls in the diagnosis of brain death. Neurocrit Care. 2009;11(2):276-87.
2. Murphy L, Wolfer H, Hendrickson RG. Toxicologic Confounders of Brain Death Determination: A Narrative Review. Neurocrit Care. 2021;34(3):1072-89.
3. Greer DM, Shemie SD, Lewis A, Torrance S, Varelas P, Goldenberg FD, et al. Determination of Brain Death/Death by Neurologic Criteria: The World Brain Death Project. JAMA. 2020;324(11):1078-97.
4. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin. 2006;22(2):255-71, vi.
5. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. Chest. 2012;141(5):1327-36.
6. Tse AHW, Ling L, Lee A, Joynt GM. Altered Pharmacokinetics in Prolonged Infusions of Sedatives and Analgesics Among Adult Critically Ill Patients: A Systematic Review. Clin Ther. 2018;40(9):1598-615 e2.

eAppendix 9 Clinical asessment for death determination by neurologic criteria

Death determination by neurologic criteria (DNC) is primarily a clinical assessment that requires all of the following:

- absence of consciousness demonstrated by a lack of arousal and awareness in response to external stimuli, *and*
- absence of brainstem function as demonstrated by cranial nerve testing, *and*
- absence of the capacity to breathe demonstrated by formal apnea testing

The following prerequisites must be met prior to conducting a valid clinical assessment for death determination by neurologic criteria:

- There must be an established cause of devastating brain injury severe enough to cause death
- Potential confounders of an accurate clinical assessment have been considered and excluded

Clinical Assessment Procedures (Adapted from the World Brain Death Project[1])

Procedures are the same for adults, pediatrics, newborns, and in patients requiring extracorporeal membrane oxygenation (ECMO).

1. Absence of Consciousness and Brainstem Function

Test	**Response consistent with DNC / Considerations**
Pupillary Reflexes *We suggest using either quantitative pupillometry or routine clinical pupil assessment in death determination by neurologic criteria. (Weak recommendation, low certainty in evidence)* Shine a bright light into each of the person's eyes, looking for pupillary constriction and measuring the diameter of the pupils. Pupillometer also be used.	There should be absence of ipsilateral and contralateral pupillary response, with pupils fixed in a midsize or dilated position (≈4-6 mm), in both eyes. Considerations: Constricted pupils are not consistent with DNC and suggest the possibility of drug intoxication or locked-in syndrome. Pupils can be any shape (round, oval, irregular). Corneal trauma or prior ophthalmic surgery may influence pupillary reactivity and preclude adequate evaluation, necessitating ancillary testing. Ocular instillation of drugs may artificially produce transiently nonreactive pupils. In the setting of anophthalmia or inability to see the pupils, ancillary testing is recommended.
Vestibulo-Ocular Reflexes (VOR): Examine the auditory canal for patency and an intact tympanic membrane. Elevate the head to 30° to place the horizontal semicircular canals in the correct vertical position. Irrigate with at least 30mL of ice water for at least 60 seconds using a syringe or a syringe attached	Detection of any extraocular movements is not compatible with death. Considerations: Ensure the integrity of the tympanic membrane. Presence of a ruptured tympanic membrane does not negate the clinical testing but may risk introducing infections in the ear. A fracture of the base of the skull or petrous temporal bone may obliterate the

Test	Response consistent with DNC / Considerations
to a catheter placed inside the canal. Test both sides separately, with a 5-minute interval between to allow the endolymph temperature to equilibrate. *We recommend against the addition of oculocephalic reflex testing to vestibulo-ocular reflex testing as part of the clinical assessment for death determination by neurologic criteria. (Strong recommendation, moderate certainty in evidence).*	response on the side of the fracture, and ancillary testing is recommended in this instance. Severe orbital or scleral edema or chemosis may affect the free motion of the globes, and ancillary testing is recommended in this instance. In the setting of anophthalmia, ancillary testing is recommended.
Corneal Reflex Touch the cornea of both eyes with a cotton swab on a stick at the external border of the iris, applying light pressure and observing for any eyelid movement.	There should be no eyelid movement in response to bilateral corneal stimulation with a cotton swab at the external border of the iris, applying light pressure and observing for any eyelid movement. Considerations: Care should be taken to avoid damaging the cornea. In the setting of anophthalmia, severe orbital edema, prior corneal transplantation, or scleral edema or chemosis, ancillary testing should be performed.
Motor Responses Apply deep pressure to all of the following: 1. the condyles at the level of the temporomandibular joints 2. the supraorbital notch bilaterally 3. the sternal notch 4. all 4 extremities both proximally and distally	Noxious stimuli should not produce grimacing, facial muscle movement, or a motor response of the limbs other than spinally mediated reflexes. Noxious stimuli above the foramen magnum should not produce any movement in the face or body. Noxious stimuli below the foramen magnum should not produce any movement in the face but may elicit spinally mediated peripheral motor reflexes. Considerations: The clinical differentiation of spinal from brain-mediated motor responses requires expertise. Consultation with an experienced practitioner is recommended if the origin of a response is unclear. Alternatively, if interpretation is unclear, ancillary testing is recommended.
Gag and Cough Reflexes Gag reflex: stimulate the posterior pharyngeal wall bilaterally with a tongue depressor or suction catheter. Cough reflex: stimulate the tracheobronchial wall to the level of the carina with deep endotracheal placement of a suction catheter.	There should be absence of gag and cough. Considerations: The efferent limb for the cough reflex includes the phrenic nerve, which may be injured in persons with high cervical cord injuries, so ancillary testing is recommended in this setting.

Test	Response consistent with DNC / Considerations
Sucking and Rooting Reflexes (for newborns only) Sucking: placing a nipple, clean finger, or pacifier inside the baby's mouth. Rooting: The corner of the baby's mouth is stroked or touched.	The baby should place their lips around the item and then rhythmically squeeze it between their tongue and palate. The baby will turn his or her head and open his or her mouth to follow and root in the direction of the stroking.

2. Apnea Testing

The apnea test should be conducted last, after the rest of the clinical assessment is completed and found to be consistent with death. Ventilator requirements, pulmonary status and hemodynamic stability should be assessed before apnea testing to determine whether a person is likely to tolerate the evaluation.

Before commencing the apnea test:

- the person should be preoxygenated with 100% O_2 for at least 10 minutes,
- minute ventilation should be adjusted to establish normocarbia ($PaCO_2$ of 35-45 mmHg) prior to apnea testing, confirmed by arterial blood gas testing prior to apnea testing.

GRADEd Recommendations for Apnea Testing

1. *We suggest using either positive pressure (continuous positive airway pressure) or passive oxygenation when performing the apnea test for death determination by neurologic criteria. (Weak recommendation, low certainty in evidence).*
    - Application of positive airway pressure with the use of CPAP/PEEP (continuous positive airway pressure/positive end-expiratory pressure) may prevent derecruitment and decrease the risk of cardiopulmonary instability, so 100% oxygen can be delivered to the lungs (i) via CPAP on the mechanical ventilator or (ii) via a resuscitation bag with a functioning PEEP valve.
    - Oxygen can also be delivered via the oxygen insufflation method via placement of a tracheal cannula.
2. *We suggest using exogenously administered CO_2, for patients who are undergoing apnea testing as a part of death determination by neurologic criteria and who have a high pre-test probability for cardio-respiratory instability that could prevent successful completion of the apnea test or who fail to complete the apnea test due to cardio-respiratory instability. (Weak recommendation, low certainty in evidence).*
3. *We suggest using a $PaCO_2$ threshold of greater than or equal to 60 mmHg (and ≥ 20 mmHg above baseline) performing the apnea test for death determination by neurologic criteria. (Weak recommendation, very low certainty in evidence)*

Arterial blood gas should be tested 10 minutes after commencing apnea testing.

- If point-of-care testing is available and the patient is stable, they can be kept off the ventilator with repeated arterial blood gas sampling every 2 to 3 minutes until it is determined that the

$PaCO_2$ is at least 60 mmHg (and ≥20 mmHg above any known chronic baseline $PaCO_2$ in persons with pre-existing hypercapnia).

- If point-of-care testing is not available, the patient should be reconnected to the ventilator when the arterial blood gas is sent at 10 minutes.

While non-invasive capnography may guide the duration of apneic observation, the arterial $PaCO_2$ should be used to confirm adequate elevation of CO_2 during apnea testing.

Apnea test targets during testing should have a pH ≤ 7.28 and $PaCO_2$ of at least 60 mmHg (8.0 kPa) unless a patient has pre-existing hypercapnia, in which case it should be at least ≥ 20 mmHg (2.7 kPa) above their baseline $PaCO_2$, if known.

If the apnea test is inconclusive (does not reach $PaCO_2$ goals) but the patient was stable during testing from pulmonary and hemodynamic standpoints, the test may be repeated after re-establishing preoxygenation, normocapnia, a normal pH, and extending the test by several minutes, using the same technique and parameters as above.

The apnea test should be aborted if:

- spontaneous respirations are witnessed during apnea testing,
- systolic blood pressure becomes lower than 100 mmHg or mean arterial pressure becomes lower than 60 mmHg despite titration of fluids/inotropes/vasopressors,
- there is sustained oxygen desaturation below 85%,
- an unstable arrhythmia occurs.

If the apnea test was aborted because of cardiorespiratory instability, an arterial blood gas can be sent for testing. If the $PaCO_2$ target is met, the apnea test can be considered consistent with DNC.

If the apnea test has been aborted because spontaneous respirations are witnessed during testing, apnea testing can be repeated after 24 hours if the clinical assessment remains consistent with DNC.

If the apnea test is aborted and cannot be repeated safely, it is suggested that either ancillary testing be performed, or apnea testing be attempted after pre-apnea recruitment maneuvers, induction of hypercarbia with CO_2 or carbogen before disconnecting from the ventilator or utilizing CPAP to maintain oxygenation.

Apnea Testing for Patients Requiring ECMO

Apnea testing is part of DNC for patients receiving veno-venous or veno-arterial ECMO, unless contraindicated due to cardiopulmonary instability.

In patients receiving veno-arterial ECMO for circulatory and respiratory support, extracorporeal blood flow is maintained during the clinical assessment and apnea test in order to prevent hemodynamic instability and maintain a mean arterial pressure of at least 60 mmHg in adults and age-appropriate targets in pediatrics.

Veno-arterial ECMO flow rates may be increased to support the mean arterial pressure if required before or during testing.

Prior to apnea testing, a period of preoxygenation should be provided for all persons receiving ECMO by administering 100% inspired oxygen via the mechanical ventilator and increasing the O_2 in the membrane lung from the ECMO machine to 100%.

Apnea testing in persons receiving ECMO can be conducted by:

a. 100% oxygen to the lungs via CPAP on the mechanical ventilator, a resuscitation bag with a functioning PEEP valve, or oxygen flow via a tracheal cannula.
b. It is recognized that some patients may not be mechanically ventilated during ECMO and suspected DNC. Under these conditions, while an apnea test can still be conducted, maintaining oxygenation during the apnea test may be challenging due to the inability to deliver oxygen to the lower airway. Oxygenation will depend on providing 100% oxygen in the sweep gas. If oxygenation cannot be maintained appropriately, the test will need to be aborted and ancillary testing will be required.

In cases of veno-arterial ECMO with intrinsic cardiac output, blood gases should be measured simultaneously from the distal arterial line and post oxygenator ECMO circuit. The apnea tests targets for both sampling sites should be pH ≤ 7.28 and $PaCO_2$ of at least 60 mmHg (and ≥ 20 mmHg above the patient's baseline $PaCO_2$ for persons with preexisting hypercapnia).

Oxygen in the membrane lung should be maintained at 100% throughout the duration of the testing, by titrating the sweep gas flow rate to 0.5-1.0L/min while maintaining oxygenation.

Spontaneous breathing should be assessed while targeting traditional apnea test targets via serial blood gases (as described in apnea test section above), keeping in mind that achieving a pH ≤ 7.28 and $PaCO_2$ of at least 60 mmHg (and ≥ 20 mmHg above the patient's baseline $PaCO_2$ for patients with preexisting hypercapnia) may take longer than in a person without ECMO support.

Terminate the test immediately if there are spontaneous respiratory movements or the person becomes unstable.

If the apnea test cannot be safely conducted or completed, an ancillary investigation is necessary for DNC in patients greater than 2 months.

References

1. Greer DM, Shemie SD, Lewis A, Torrance S, Varelas P, Goldenberg FD, et al. Determination of Brain Death/Death by Neurologic Criteria: The World Brain Death Project. Jama. 2020;324(11):1078-97.

eAppendix 10 Evidence summaries and recommendation rationales: death determination by neurologic criteria

Clinical Assessment after Return of Spontaneous Circulation Post-Cardiac Arrest

PICO Question:

In all patients without imaging evidence of devastating brain injury but otherwise appearing to meet neurologic criteria for death determination, once known confounders have been excluded, does delaying the clinical assessment for death determination compared to immediate performance of the clinical assessment for death determination improve the accuracy of death determination by neurologic criteria?

Subgroups for consideration:

1. Patients who are post therapeutic hypothermia
2. Specific group post cardiac arrest

Reviewers:

J. Teitelbaum, M. Leeies, J. Singh, K. Hornby, A. Zaloum, G. Boyd

Literature Search:

Citations Screened: 1118

Articles originally retained are analyzed within the systematic review

Citations Included: 1 systematic review of indirect evidence

Recommendation:

We suggest delaying the clinical assessment for at least 48 hours from the time of return of spontaneous circulation post-cardiac arrest for patients with hypoxic-ischemic injury who do not have imaging evidence consistent with devastating brain injury undergoing DNC (Weak recommendation, low certainty in evidence).

Evidence Summary:

We found no direct evidence to address our question and therefore included indirect evidence from a systematic review of predictors of poor neurologic outcome in comatose survivors of cardiac arrest[1]. In the review, poor prognosis is defined as death, vegetative state, or severe disability (Cerebral Performance Category score 3-5) at hospital discharge/1 month or later, in comatose adult survivors from cardiac arrest. Ninety-four studies were included in the systematic review. The large majority of studies (72%) reported that targeted temperature management (TTM) was used in 100% of patients; TTM was used in 17.5-94% of patients in 22 of included studies, one study did not use TTM and this information was not available for three of the studies. Therefore, results in patients undergoing TTM could not be differentiated from those who did not. Articles evaluated for the systematic review included children as well as adults. A total of 30 studies looked at clinical criteria of poor prognosis.

Nineteen studies in the review reported on standard pupillary light reflex (s-PLR). Immediately following return of spontaneous circulation (ROSC), bilaterally absent s-PLR demonstrated high sensitivity but low specificity (high false positive rate) for prediction of poor neurological outcome. These findings were consistent for patients assessed at the time of return to normothermia as well. However, by 48 hours from ROSC, some studies reported a 0% false positive rate for s-PLR. This rate became consistent when

measured 4 days post ROSC, with sensitivities from 17.9-35.7%. Eleven studies reported on corneal reflex. A 0% false positive rate was achieved at 36-72 hours from ROSC in some studies and became consistent after 4 days from ROSC (23.1% to 40.5% sensitivities). Two studies included the combination of s-PLR and corneal reflex, and findings suggest that a 0% false positive rate is achieved at 4-5 days after ROSC. In four studies that reported on the combined absence of gag and cough, a 0% false positive rate occurred, starting from 48 hours after ROSC. However, precision was low due to the small number of studies. In summary, it appears that s-PLR or corneal reflex are very specific indices of poor neurological outcome. However, false positive rates of 6–7% were found at 72 hours from ROSC. The false positive rates of 0% are at day 4 from ROSC. Absence of motor response any time after ROSC has high sensitivity, but low specificity for predicting poor neurological outcome.

For the subgroup of pediatrics, in addition to the above findings, we considered one other article of indirect evidence that evaluated prognosis specifically for brain death as a secondary outcome measure in 35 children treated with therapeutic hypothermia after cardiac arrest[2]. The authors reported that by 24 hours post normothermia, absent motor and pupil responses were highly predictive of unfavorable outcome (PCPC 4,5,6) (PPV 100% and $p<0.03$ for all categories), while at earlier times the predictive value was lower.

Justification/Rationale

Although this question could apply to any devastating neurologic injury such as traumatic brain injury, massive ischemic stroke or intracerebral hemorrhage, imaging in these cases almost always confirms the etiology of the clinical picture, especially if there is evidence of cerebral edema, mass effect and herniation. However, in patients with hypoxic-ischemic injury after cardiac arrest, where the imaging may not reflect the damage done especially in the first 24 to 48 hours after the event, there may be uncertainty with respect to whether the loss of brainstem reflexes is permanent. There is evidence in this group that brainstem reflexes can return in the first 24 hours post ROSC[1] and cerebral edema with or without herniation cannot be equated with death by neurologic criteria. Our recommendation, therefore, is aimed most specifically at this group of patients, where initial imaging lacks evidence of a devastating permanent brain injury and where this imaging will not necessarily be repeated. This group of patients are at a greater risk of a false positive death determination and thus the interval between the devastating event and the time when death determination by neurologic criteria can confidently be performed is of major importance. The only evidence found to address our question and support our recommendation is indirect, as it supports time intervals for poor prognosis rather than for death but based on this evidence and taking a conservative approach to ensuring permanence of the loss of brainstem reflexes, we suggest delaying the clinical assessment for death determination by neurologic criteria for at least 48 hours from the time of return of circulation post-cardiac arrest.

Implementation Considerations:

Prior to performing the clinical assessment for death determination by neurologic criteria factors that may confound, or make the clinical assessment ambiguous in interpretation, must have been screened and excluded. Commonly this will take at least 24 hours from the time of the injury. Delaying the death determination by neurologic criteria for 48 hours from cardiac arrest would therefore represent a maximum of an additional 24 hours. This delay may result in a small increase in costs related to the longer stay in ICU and may also lead to an increase in hemodynamic instability of the patient, requiring an increase in care. It is possible as well that substitute decisions makers/family members would consider the additional delay unacceptable. It is also possible that physicians may wish to shorten the delay by performing repeat imaging to confirm the extent of the presumed hypoxemic ischemic brain injury or conduct ancillary testing or more specialized imaging if indicated.

References

1. Sandroni C, D'Arrigo S, Cacciola S, Hoedemaekers CWE, Kamps MJA, Oddo M, et al. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med. 2020;46(10):1803-51.

2. Abend NS, Topjian AA, Kessler SK, Gutierrez-Colina AM, Berg RA, Nadkarni V, et al. Outcome prediction by motor and pupillary responses in children treated with therapeutic hypothermia after cardiac arrest. Pediatr Crit Care Med. 2012;13(1):32-8.

Clinical Assessment after Return of Spontaneous Circulation Post-Cardiac Arrest

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead by neurological criteria who is not (false positive)									
1[1]	observational studies	not serious	not serious	not serious	not serious	none	Although there are limitations in the included studies (all assessed poor neuro outcome following cardiac arrest), the Sandroni 2020 systematic review, Table 1, page 1804, reported the following based on 30 studies: *Standard pupillary reflex or corneal reflex are very specific indices of poor neurological outcome, but false positive predictions may occur with a rate up to 6–7% even at 72 h from ROSC. Lowest FPR (0%) is achieved after day 4 from ROSC…Absence of motor response any time after ROSC is highly sensitive but not a specific index of poor neurological outcome.*	⨁⨁◯◯ Low	CRITICAL
Missing someone who is dead by neurological criteria (false negative)									
							Not specifically discussed in the studies captured for this question, however, indirect evidence would suggest that waiting longer should lead to less false negatives. Some patients will progress during the waiting period to brain death, including those that would not initially meet criteria.	-	CRITICAL

CI: confidence interval

References

1.Sandroni, C., D'Arrigo, S., Cacciola, S., Hoedemaekers, C. W. E., Kamps, M. J. A., Oddo, M., Taccone, F. S., Di Rocco, A., Meijer, F. J. A., Westhall, E., Antonelli, M., Soar, J., Nolan, J. P., Cronberg, T.. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Medicine; 10 2020.

Core Body Temperature

PICO Question:

In patients being considered for neurological determination of death, does ensuring a core body temperature of 36 °C as compared to 34°C improve the accuracy of the neurological determination of death?

Reviewers:

J. Singh, A. Baker, K. Soliman

Literature Search:

Citations Screened: 1007

Citations Included: 0

Recommendation(s):

We suggest ensuring a core body temperature of greater than or equal to 36°C for patients undergoing DNC (Weak recommendation, very low certainty in evidence).

Evidence Summary:

We found no studies that directly compared temperature at time of death determination by neurologic criteria (DNC). We found that much of the published literature on the impact of temperature on the neurologic evaluation is in the context of therapeutic hypothermia or targeted temperature management (TTM) after cardiac arrest. It is challenging to draw useful inferences from these data because none of these studies evaluated DNC as an outcome and application of therapeutic hypothermia is usually associated with concurrent administration of sedative medications that may also confound DNC. Furthermore, extrapolation of temperature on prognostication of non-fatal neurological outcomes after TTM with induced hypothermia may not be generalizable to our target population valid due to the dynamic nature of cooling and re-warming and the superimposed hypoxic/ischemic insult.

We found some informative indirect and ancillary evidence. Depression of cerebral metabolism and function by hypothermia is well-established from physiologic experiments and animal studies, but there are no data to indicate a specific threshold temperature that precludes confounding of the clinical determination for death by neurologic criteria. We found neurophysiologic studies demonstrating that electroencephalographic silence occurs only at very low temperatures (below 20°C).[1] One neurophysiology study of 109 patients with hypothermic circulatory arrest during surgery found that the mean core temperature when electroencephalographic (EEG) silence appeared was 20.6°C, and the highest temperature associated with EEG silence being 27.2°C. Likewise, the mean core temperatures associated with disappearance of somatosensory evoked potentials were 24.7°C and 20.1°C respectively.[1] It should be noted in this study patients received induction of anesthesia which may have raised the temperature threshold for electrophysiological silence by incrementally suppressing cortical activity. Another study found that the cortically generated component of somatosensory evoked potentials was consistently recordable at a core temperature above 26°C, and disappeared after

decreasing the temperature down to 20°C. [2] These same authors studied brainstem auditory evoked potentials during induced hypothermia for cardiac surgery and found that the components were present in all patients at temperatures above 23°C and absent below 20°C.[3]

These indirect data would suggest that decreased brain temperature by itself is unlikely to mimic death by neurologic criteria in the healthy brain except at very low temperatures (less than 30°C). However, it is well-recognized that brain function is passively dependent on temperature, and cognitive dysfunction has been observed with temperature exposure and mild fluctuations in core body temperature[4, 5]. It is thus possible that mild to moderate hypothermia might incrementally depress the function of an injured brain below the threshold for clinical detection.

Justification/Rationale

Addressing or eliminating potential confounders to the clinical assessment is a foundational criterion of the determination of DNC. Temperature, specifically hypothermia, may affect the clinical DNC determination via depression of brain metabolism and function, or indirectly through the accumulation of confounding drugs from temperature-related changes in pharmacokinetics. These effects are potentially additive such that mild hypothermia and a sub-therapeutic level of sedative may together effectively abolish clinical responses, so elimination of all possible confounders and restoration of normothermia is recommended. Given the importance and implications of death determination, and the high emphasis on avoiding false-positive determination (i.e. declaring someone dead who is not yet dead) we recommend a cautious and conservative approach to temperature considerations in death determination by neurologic criteria.

Given the potential for the evaluation for coma and absence of brainstem function to be impacted by hypothermia, patients suspected to be dead by neurologic criteria should not be hypothermic at the time of the determination. Patients with a clinical evaluation suggestive of DNC and a brain injury consistent in extent and severity to cause death should be warmed to normothermia. In jurisdictions where multiple independent evaluations are required, physicians should be aware that loss of thermoregulation due to loss of brain function may result in significant changes in body temperature between evaluations as patients become poikilothermic and verify the patient's temperature prior to each evaluation.

Given this rationale and lack of definitive evidence, we make a conditional recommendation that a temperature of greater than or equal to 36°C is achieved prior to death determination by neurological criteria. We acknowledge the lack of comparative data indicating superiority of one temperature threshold over another. Future studies may provide clarity in this regard and inform future revised recommendations. We also recognize that this is a change from the recommendations of 34°C in previous death determination guideline[6] and from some other jurisdictions, and our recommendation is not meant to invalidate determinations made at temperature as low as 34°C. We selected normothermia (36°C) as the suggested temperature threshold out of an abundance of caution, given the aforementioned theoretical potential for incremental confounding at lower temperatures, and the risks of warming to normothermia are few. Warming to normothermia also reduces the risk of potential drug confounding from temperature-related alterations in pharmacokinetics, although it should be noted that drug accumulation what may have occurred during a period of hypothermia may still be present for some time after achieving normothermia until drug is eliminated from the body.

Finally, our recommended temperature is also consistent with recommendations from the recent international World Brain Death Project, and thus supports consistency in criteria across jurisdictions, and creates a consistent standard of clinical practice in the determination of DNC.

In cases of prehospital environmental exposure or induced hypothermia for neuroprotection at ≤ 34°C, waiting 24 hours after return to normothermia is advised[7].

Implementation Considerations:

The panel felt that there were negligible implementation considerations associated with warming to normothermia (36°C).

References:

1. Stecker MM, Cheung AT, Pochettino A, Kent GP, Patterson T, Weiss SJ, et al. Deep hypothermic circulatory arrest: I. Effects of cooling on electroencephalogram and evoked potentials. Ann Thorac Surg. 2001;71(1):14-21.
2. Markand ON, Warren C, Mallik GS, King RD, Brown JW, Mahomed Y. Effects of hypothermia on short latency somatosensory evoked potentials in humans. Electroencephalogr Clin Neurophysiol. 1990;77(6):416-24.
3. Markand ON, Lee BI, Warren C, Stoelting RK, King RD, Brown JW, et al. Effects of hypothermia on brainstem auditory evoked potentials in humans. Ann Neurol. 1987;22(4):507-13.
4. Taylor L, Watkins SL, Marshall H, Dascombe BJ, Foster J. The Impact of Different Environmental Conditions on Cognitive Function: A Focused Review. Frontiers in Physiology. 2016;6:1-12.
5. Walter EJ, Carraretto M. The neurological and cognitive consequences of hyperthermia. Crit Care. 2016;20(1):199-.
6. Shemie SD, Doig C, Dickens B, Byrne P, Wheelock B, Rocker G, et al. Severe brain injury to neurological determination of death: Canadian forum recommendations. CMAJ. 2006;174(6):S1-13
7. Greer DM, Shemie SD, Lewis A, Torrance S, Varelas P, Goldenberg FD, et al. Determination of Brain Death/Death by Neurologic Criteria: The World Brain Death Project. Jama. 2020;324(11):1078-97.

Pupillary Assessment

PICO Question:

In patients who appear to meet criteria for neurological determination of death, does use of pupillometry compared with routine clinical pupil assessment improve the accuracy of neurological determination of death?

Reviewers:

K.Soliman, A. LeBlanc

Literature Search:

Citations Screened: 996

Citations Included: 9

Recommendation:

We suggest using either quantitative pupillometry or routine clinical pupil assessment for patients undergoing DNC (Weak recommendation, low certainty in evidence).

Evidence Summary (including subgroup considerations, if relevant):

We found nine studies (n=424) that compared manual pupil examination to quantitative pupillometry[1-9]. The nine studies were of varied size and methodological quality. Seven prospective observational studies primarily looking at brain injured patients found discordance between the manual examination and quantitative pupillometry regarding size and reactivity[2, 4-9]. Manual exam either under or over-estimated pupil size compared to the quantitative pupillometry. In general, agreement was better with larger pupils as compared to smaller pupils. In one study, quantitative pupillometry found 44% discordance with absent light reactivity by manual exam[6]. Only one small study (n=7) published over 25 years ago included patients determined dead by neurological criteria, and it confirmed 100% concordance between manual exam and quantitative pupillometry[2].

The two remaining included studies were a case series that described quantitative pupillometry discordance with manual absent light reflex exam[3] and a case report where a prolonged light reflex caused quantitative pupillometry to miss a reactive pupil by manual exam[1].

Justification/Rationale

Pupillary examination is a cornerstone of the clinical assessment for death determination by neurologic criteria and it is critically important not to miss a reactive pupil. Although of varied quality, the current evidence points to improved accuracy with quantitative pupillometry relative to routine clinical assessment for pupillary response of the brain injured patient. In patients undergoing death determination by neurologic criteria, the pre-test probability is high, and this potential improved accuracy is not apparent in the only direct evidence we found[2] nor by clinical experience of the panel.

The panel also identified that most clinicians outside neurosurgical centers would not have access to quantitative pupillometry for death determination by neurologic criteria. This led to the recommendation of suggesting use of either quantitative pupillometry or clinical pupil exam in death determination by neurologic criteria.

Implementation Considerations:

The panel felt there would be negligible implementation considerations in suggesting either method of pupillary response for the clinical assessment. Centers using either method would continue to do so.

References:

1. Kramer CL, Rabinstein AA, Wijdicks EF, Hocker SE. Neurologist versus machine: is the pupillometer better than the naked eye in detecting pupillary reactivity. Neurocrit Care. 2014;21(2):309-11.
2. Larson MD, Muhiudeen I. Pupillometric analysis of the 'absent light reflex'. Arch Neurol. 1995;52(4):369-72.
3. Papangelou A, Zink EK, Chang WW, Frattalone A, Gergen D, Gottschalk A, et al. Automated Pupillometry and Detection of Clinical Transtentorial Brain Herniation: A Case Series. Mil Med. 2018;183(1-2):e113-e21.
4. Couret D, Boumaza D, Grisotto C, Triglia T, Pellegrini L, Ocquidant P, et al. Reliability of standard pupillometry practice in neurocritical care: an observational, double-blinded study. Crit Care. 2016;20:99.
5. Meeker M, Du R, Bacchetti P, Privitera CM, Larson MD, Holland MC, et al. Pupil examination: validity and clinical utility of an automated pupillometer. J Neurosci Nurs. 2005;37(1):34-40.
6. Olsen MH, Jensen HR, Ebdrup SR, Topp NH, Strange DG, Moller K, et al. Automated pupillometry and the FOUR score - what is the diagnostic benefit in neurointensive care? Acta Neurochir (Wien). 2020;162(7):1639-45.
7. Olson DM, Stutzman S, Saju C, Wilson M, Zhao W, Aiyagari V. Interrater Reliability of Pupillary Assessments. Neurocrit Care. 2016;24(2):251-7.
8. Park JG, Moon CT, Park DS, Song SW. Clinical Utility of an Automated Pupillometer in Patients with Acute Brain Lesion. J. 2015;58(4):363-7.
9. Smith J, Flower O, Tracey A, Johnson P. A comparison of manual pupil examination versus an automated pupillometer in a specialised neurosciences intensive care unit. Aust Crit Care. 2020;33(2):162-6.

Pupillary Assessment

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not (false positive)									
3[1,2,3]	observational studies	not serious	not serious	not serious	not serious	none	A number of case reports and case series were found where manual assessment of pupils found non-reactive whereas quantitative pupillometry found reactivity. However, the frequency of this occurence is hard to quantify based on the study types.	⨁⨁◯◯ Low	CRITICAL
Missing someone who is dead (false negative)									
7[1,4,5,6,7,8,9]	observational studies	not serious	not serious	not serious	not serious	none	Included studies were of variable size and methodological quality. In almost all cases, intervention was the NeuroLight device as compared to manual exam. Agreement between the techniques was not great, and almost universally the manual exam either under or over-estimated pupil size compared to the quantitative pupillometry. In general, agreement was better with larger pupils, as compared to smaller pupils.	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval

References

1.Larson, M. D., Muhiudeen, I.. Pupillometric analysis of the 'absent light reflex'. Arch Neurol; Apr 1995.

2.Papangelou, A., Zink, E. K., Chang, W. W., Frattalone, A., Gergen, D., Gottschalk, A., Geocadin, R. G.. Automated Pupillometry and Detection of Clinical Transtentorial Brain Herniation: A Case Series. Military Medicine; 01 01 2018.

3.Kramer, C. L., Rabinstein, A. A., Wijdicks, E. F., Hocker, S. E.. Neurologist versus machine: is the pupillometer better than the naked eye in detecting pupillary reactivity. Neurocritical Care; Oct 2014.

4.Olsen, M. H., Jensen, H. R., Ebdrup, S. R., Topp, N. H., Strange, D. G., Moller, K., Kondziella, D.. Automated pupillometry and the FOUR score - what is the diagnostic benefit in neurointensive care?. Acta Neurochirurgica; 07 2020.

5.Smith, J., Flower, O., Tracey, A., Johnson, P.. A comparison of manual pupil examination versus an automated pupillometer in a specialised neurosciences intensive care unit. Australian Critical Care; 03 2020.

6.Couret, D., Boumaza, D., Grisotto, C., Triglia, T., Pellegrini, L., Ocquidant, P., Bruder, N. J., Velly, L. J.. Reliability of standard pupillometry practice in neurocritical care: an observational, double-blinded study. Critical Care (London, England); Mar 13 2016.

7.Olson, D. M., Stutzman, S., Saju, C., Wilson, M., Zhao, W., Aiyagari, V.. Interrater Reliability of Pupillary Assessments. Neurocritical Care; Apr 2016.

8.Park, J. G., Moon, C. T., Park, D. S., Song, S. W.. Clinical Utility of an Automated Pupillometer in Patients with Acute Brain Lesion. Journal of Korean Neurosurgical Society; Oct 2015.

9.Meeker, M., Du, R., Bacchetti, P., Privitera, C. M., Larson, M. D., Holland, M. C., Manley, G.. Pupil examination: validity and clinical utility of an automated pupillometer. Journal of Neuroscience Nursing; Feb 2005.

Vestibulo-Ocular Reflex

PICO Question:

In patients who appear to meet criteria for neurological determination of death, does the combination of oculocephalic reflex (OCR) testing and vestibulo-ocular reflex (VOR, or cold-calorics testing) testing, compared to VOR alone, improve the accuracy of neurological determination of death?

Reviewers:

A. Healey, L. Lee

Literature Search:

Citations Screened: 1144

Citations Included: 4

Recommendation(s):

We recommend against the addition of oculocephalic reflex testing to vestibulo-ocular reflex testing as part of the clinical assessment for patients undergoing DNC (Strong recommendation, moderate certainty in evidence).

Evidence Summary (including subgroup considerations, if relevant):

We found four observational studies (n=210)[1-4], all published between 1957 and 1979, that addressed our question. All 4 studies described testing of the vestibulo-ocular reflex (VOR) and the oculocephalic reflex (OCR) in patients determined dead by neurologic criteria or in those with brain dysfunction or barbituate poisoning as compared to healthy or comatose patients. One study compared absence of OCR and VOR in 50 healthy controls to 60 patients with varying degrees of coma. OCR was found to be absent in all 16 pts who were determined to be dead and was also found to be absent in 30 pts with varying levels of coma who were not dead, while VOR was found to be absent in 15/16 patients determined to be dead and 10 pts who were not dead but had a varying degree of coma[1]. The second study described 30 pts in fulminant liver failure. Four patients admitted with absent VOR all died, 16 patients who lost their VOR on admission all died within 1-4 days, and 9 that retained the VOR all survived. Two of the survivors lost their OCR at some point during their coma, but they normalized during recovery[2]. The third study describes 25 patients determined dead by neurologic criteria on postmortem examination, of whom 23 had absent VOR and 2 had a minima VOR, and 17 unconscious but not dead patients, of whom 5 had normal VOR, 11 had abnormal VOR, and 1 was absent. All patients in this analysis had absent OCR[3]. The fourth study described 28 patients, 23 of whom had proven brain disease and 5 who had barbituate induced deep sleep[4]. All patients who had absent OCR and VOR, were proven post-mortem to have brainstem damage. They also reported 4 cases of barbituate poisoning and 1 case of massive subarachnoid hemorrhage who had absent OCR and VORs.

Subgroup Considerations:

The four studies that were found only included adult participants, thus there are no pediatric or neonatal specific data for this question. However, the panel had no reason to believe the recommendations would not be generalizable to these populations.

Justification/Rationale

Avoiding false positives (i.e., declaring someone dead who is not) is of utmost importance in determining criteria of neurological determination of death. However, adding diagnostic tests that do not increase accuracy does not improve protection against false positives and only takes up time and resources. Though the literature summarized here is quite historical and of low quality, the results are consistent across the four studies so the certainty in evidence was judged to be moderate. The OCR has much lower specificity than the VOR and the VOR is very sensitive for determining death by neurologic criteria. Thus, on the balance of the evidence, the panel determined that the addition of OCR testing to VOR testing risks confounding of the determination of death without improvements in sensitivity or specificity. Also, given that many patients may have a contra-indication to OCR testing (e.g., potential spinal cord injury), it's requirement would necessitate higher rates of ancillary testing if it was unable to be completed. The evidence does not support that this test improves our ability to diagnose death and as such we recommend against it.

Implementation Considerations:

The panel felt that the main consideration for implementation of this recommendation is that it requires a change in practice. Many centers currently complete both VOR and OCR testing as part of the clinical assessment for the determination of death by neurologic criteria and thus education around this recommendation will be required. A further issue discussed by the panel is related to patients for whom VOR testing cannot be completed (e.g tympanic membrane injury). The panel felt that since the evidence does not support the use of OCR testing for death determination by neurologic criteria, if testing of the VOR cannot be completed, the clinical assessment is deemed incomplete and ancillary testing is likely required.

References

1. Bedi HK, Devpura JC, Parakh SC. Value of oculocephalic reflex and cold caloric test in coma. J Assoc Physicians India. 1972;20(2):157-61.
2. Hanid MA, Silk DB, Williams R. Prognostic value of the oculovestibular reflex in fulminant hepatic failure. Br Med J. 1978;1(6119):1029.
3. Nathanson M, Bergman PS, Anderson PJ. Significance of oculocephalic and caloric responses in the unconscious patient. Neurology. 1957;7(12):829-32.
4. Hicks RG, Torda TA. The vestibulo-ocular (caloric) reflex in the diagnosis of cerebral death. Anaesth Intensive Care. 1979;7(2):169-73.

Vestibulo-Ocular Reflex

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not (false positive)									
4[1,2,3,4]	observational studies	not serious	not serious	not serious	not serious	strong association	All included cohort studies demonstrate that OCR is commonly lost in patients with coma, liver failure, or even deep sleep. Although not perfect, VOR was much more specific for neurological death. This finding was consistent across all studies.	⊕⊕⊕◯ Moderate	CRITICAL
Missing someone who is dead (false negative)									
4[1,2,3,4]	observational studies	not serious	not serious	not serious	not serious	strong association	From the included studies, OCR is sensitive but poorly specific. Therefore it is less likely to miss someone who is dead.	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval

References

1.Bedi, H. K., Devpura, J. C., Parakh, S. C.. Value of oculocephalic reflex and cold caloric test in coma. Journal of the Association of Physicians of India; Feb 1972.

2.Hanid, M. A., Silk, D. B., Williams, R.. Prognostic value of the oculovestibular reflex in fulminant hepatic failure. British Medical Journal; Apr 22 1978.

3.Nathanson, M., Bergman, P. S., Anderson, P. J.. Significance of oculocephalic and caloric responses in the unconscious patient. Neurology; 1957.

4.Hicks, R. G., Torda, T. A.. The vestibulo-ocular (caloric) reflex in the diagnosis of cerebral death. Anaesthesia & Intensive Care; May 1979.

Apnea Testing

PICO Question:

In patients who are undergoing apnea testing as part of death determination by neurologic criteria, does using a PaCO2 threshold of 60mmHg as compared to 80mmHg or 90mmHg improve the accuracy of death determination by neurologic criteria?

Reviewers:

G. Isac, A. LeBlanc, K. Soliman

Literature Search:

Citations Screened: 266

Citations Included: 0

Recommendation:

We suggest using a PaCO2 threshold of greater than or equal to 60mmHg (and ≥ 20mmHg above baseline) when performing apnea testing for patients undergoing DNC (Weak recommendation, very low certainty of evidence).

Evidence Summary:

We screened 266 citations. There were no studies that we found that directly addressed the question of whether a PaCO2 threshold of 60mmHg vs higher for the apnea test would improve the accuracy of death determination by neurologic criteria. There was no additional information to make any subgroup recommendations. Thus, the conditional recommendation was based on very low certainty of evidence and reflects the expert opinion of the panel. Our literature review did include several case reports in the infant and pediatric age groups where patients were noted to have made respiratory efforts at PaCO2 thresholds greater than 60 mmHg. The evidence in these reports was not robust enough to change the panel's recommendation but does indicate opportunity for further research in this patient population.[1-5]

Justification/Rationale:

Given the long standing and near universal acceptance for a PaCO2 threshold of greater than 60 mmHg (or >20mmHg above baseline) during the apnea test, we found no evidence to support changing the current threshold.

Implementation Considerations:

It appears that 60mmHg (or >20mmHg above baseline) has become the current agreed upon "standard of care" in Canada and internationally and is almost universally accepted as the threshold. There does not appear to be any evidence to justify changing the current pattern of practice. It is important to note that the PaCO2 thresholds above require the corresponding drop in pH <7.28. The above discussed thresholds do not apply to patients with chronic PaCO2 retention that may require a higher PaCO2 levels to stimulate respiratory efforts, >20mmHg above the patient's baseline.

References

1. Brilli RJ, Bigos D. Altered apnea threshold in a child with suspected brain death. J Child Neurol. 1995;10(3):245-6.
2. Levin SD, Whyte RK. Brain death sans frontières. N Engl J Med. 1988;318(13):852-3.

3. Okamoto K, Sugimoto T. Return of spontaneous respiration in an infant who fulfilled current criteria to determine brain death. Pediatrics. 1995;96(3 Pt 1):518-20.
4. Sosa T, Berrens Z, Conway S, Stalets EL. Apnea Threshold in Pediatric Brain Death: A Case with Variable Results Across Serial Examinations. J Pediatr Intensive Care. 2019;8(2):108-12.
5. Vardis R, Pollack MM. Increased apnea threshold in a pediatric patient with suspected brain death. Crit Care Med. 1998;26(11):1917-9.

PICO Question:

In patients who are undergoing apnea testing as part of neurological determination of death, does using any CO_2 insufflation as compared to not using CO_2 insufflation (exogenous CO_2 administration) improve the ability to complete the apnea test or influence the accuracy of neurological determination of death?

Reviewers:

G. Isac, A. LeBlanc

Literature Search:

Citations Screened: 745

Citations Included: 8

Recommendation:

We suggest using exogenously administered CO2 for patients undergoing DNC who have a high pre-test probability for cardio-respiratory instability that could prevent successful completion of the apnea test or who fail to complete the apnea test due to cardio-respiratory instability (Weak recommendation, low certainty in evidence).

Evidence Summary:

Eight studies were included in this review with certainty in evidence considered to be low due to observational study design[1-8]. In those studies that reported completion of the apnea test using augmented CO_2, all tests were completed, and all patients were determined dead by neurologic criteria[1-4, 7]. Several studies evaluated the safety of CO_2 augmentation. Most studies reported no adverse events with CO_2 augmentation[1, 2, 4, 7]. A single brief episode of desaturation during the final minute of the apnea test for one patient was reported in one study[6]. The remaining 23 participants experienced no complications. A lower rate of complications (14%) in patients undergoing apnea tests using CO_2 insufflated into the mechanical ventilation circuit compared to conventional apnea testing (23%) was also reported in one study[8]. Reduced heart rate and blood pressure variability was also reported in a cohort of patients with CO_2 augmentation compared to conventional apnea testing[2]. A clinically insignificant decrease in blood pressure with CO_2 augmented testing was reported in one study but there was no comparison group[4]. Two studies reported higher CO_2 at the end of the apnea test in patients with CO_2 augmentation[2, 3]. Concern for CO_2 overshoot led to the investigation of techniques to monitor CO_2 rise more closely during the test[3, 4, 6]. Consideration of CO_2 augmentation when CO_2 levels are slow to rise has been advocated for[5]. Additional benefits of CO_2 augmented apnea testing could include reduced hypoxemia due to the ability to continue mechanical ventilation with CO_2 exogenously administered via the mechanical ventilator or ECMO circuit[4, 5].

Theoretically, CO_2 augmentation has the potential to improve the completion of apnea testing and thereby avoid the need for ancillary testing, but this was not clearly demonstrated in the included studies. However, there is a case report of a 6-month-old patient on ECMO who was unable to complete the apnea test when t-pieced and off sweep gas flow due to hypotension and hypoxemia[9]. This patient completed an apnea test with CO_2 augmented via the ECMO circuit.

Methods/Techniques

CO_2 augmentation can be accomplished by adding CO_2 into the mechanical ventilator circuit or ECMO using a CO_2 cylinder or a carbogen mixture (97% O_2/3%CO_2). Techniques and protocols for augmenting CO_2 during apnea testing vary significantly.

Subgroup considerations

ECMO

The panel made no specific recommendation for use in ECMO although there are case reports of CO_2 augmentation for the completion of the apnea test on ECMO[7, 10, 11]and for those patients on ECMO who couldn't complete the apnea test without its use[9].

Pediatrics/neonates

The panel felt there was not enough data available to comment on this subgroup.

Justification/Rationale

The challenges (physiologic instability, incomplete tests) of achieving the required CO_2 threshold during apnea testing have led clinicians to investigate options for increasing the CO_2 more quickly or in a more controlled manner. Exogenous CO_2 administration has the potential to reduce the risk of physiologic instability and the potential for incomplete tests due to inadequate CO_2 rise and to avoid the need for ancillary testing to determine death by neurologic criteria. There were no undesirable effects of CO_2 augmentation identified in the reviewed studies. The theoretical concern of increased hemodynamic instability was not supported by the literature. The potential for CO_2 overshoot can be mitigated through careful CO_2 monitoring (End-tidal, percutaneous or frequent arterial blood gases). CO_2 augmentation does introduce additional complexity to the apnea test which does not appear to improve the test sensitivity nor specificity.

Based on the evidence in this review, exogenous augmentation of CO_2 is not justified for every patient undergoing apnea testing to determine death by neurologic criteria. However, for patients who cannot complete or are at high risk of failing to complete the apnea test, a technique utilizing exogenous CO_2 augmentation may allow for the successful completion of the apnea test, thereby avoiding the need for ancillary testing.

Implementation Considerations:

The panel identified several considerations for implementation of this recommendation. Firstly, there is no standard method/techniques/protocol for CO_2 augmentation as part of apnea testing and CO_2 augmentation can be accomplished via the mechanical ventilator or directly into an ECMO circuit. Although the required equipment is basic and commonly used, it requires specialized clinical and technical expertise. Required materials, depending on the method used, include CO_2 cylinders, flow/pressure regulators, tubing/connectors. Some centres may not have experience with exogenous CO_2 administration so that local expertise is likely to be the main barrier for implementation.

References:

1. Lang CJ. Apnea testing by artificial CO2 augmentation. Neurology. 1995;45(5):966-9.
2. Lang CJ. Blood pressure and heart rate changes during apnoea testing with or without CO2 insufflation. Intensive Care Med. 1997;23(8):903-7.
3. Lang CJ. Apnea testing guided by continuous transcutaneous monitoring of partial pressure of carbon dioxide. Crit Care Med. 1998;26(5):868-72.
4. Sharpe MD, Young GB, Harris C. The apnea test for brain death determination: an alternative approach. Neurocrit Care. 2004;1(3):363-6.
5. Harrar DB, Kukreti V, Dean NP, Berger JT, 3rd, Carpenter JL. Clinical Determination of Brain Death in Children Supported by Extracorporeal Membrane Oxygenation. Neurocrit Care. 2019;31(2):304-11.

6. Pepe J, Wolffing A, Couture M, Brautigam R, Butler K. Safety first: Carbogen and capnography use minimizes complications during apnea testing. Crit Care Med. 2014;42(12):A1489-A90.
7. Madden M, Andrews P, Rector R, Menaker J, Habashi N. Carbogen for Apnea Testing During the Brain Death Declaration Process in Subjects on Extracorporeal Membrane Oxygenation. Respir Care. 2020;65(1):75-81.
8. Melano R, Adum ME, Scarlatti A, Bazzano R, Araujo JL. Apnea test in diagnosis of brain death: comparison of two methods and analysis of complications. Transplant Proc. 2002;34(1):11-2.
9. Saritas Nakip O, Kesici S, Terzi K, Bayrakci B. Apnea test on extra corporeal membrane oxygenation; One step forward with carbon dioxide. Pediatr Crit Care Med. 2021;22 (SUPPL 1):143.
10. Andrews P, Dolly K, Madden M, Habashi N. The use of carbogen facilitates apnea testing in a patient on venous-arterial extracorporeal membrane oxygenation (VA-ECMO). Neurocrit Care. 2012;17:S125.
11. Beam WB, Scott PD, Wijdicks EFM. The Physiology of the Apnea Test for Brain Death Determination in ECMO: Arguments for Blending Carbon Dioxide. Neurocrit Care. 2019;31(3):567-72.

CO2 Insufflation

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not (false positive)									
3[1,2,3]	observational studies	not serious	not serious	not serious	not serious	none	Of the 3 studies that included a cohort of patients that had apnea tests both with CO2 insufflation and without CO2 insufflation, all had 100% congruence with or without. There was no improvements in sensitivity or specificity in apnea testing with using CO2.	⨁⨁◯◯ Low	CRITICAL
Missing someone who is dead by neurologic criteria (false negative)									
3[1,2,3]	observational studies	not serious	not serious	not serious	not serious	none	Of the 3 studies that included a cohort of patients that had apnea tests both with CO2 insufflation and without CO2 insufflation, all had 100% congruence with or without. There was no improvements in sensitivity or specificity in apnea testing with using CO2.	⨁⨁◯◯ Low	CRITICAL
Duration of apnea test									
5[1,2,3,4,5]	observational studies	not serious	serious[a]	not serious	not serious	none	3/5 studies reported a significant reduction in time to achieve CO2 targets using Carbogen, while 2/5 studies reported no change. Some of this may have been due to variation in Carbogen protocols.	⨁◯◯◯ Very low	IMPORTANT
Need to abort apnea test due to hypoxia or instability									
7[1,3,4,5,6,7,8]	observational studies	not serious	not serious	not serious	not serious	none	All included studies suggest no increased risk of hypoxia, arrythmias or other complications when using Carbogen. The Melano 2002 retrospective cohort study actually demonstrated a higher risk of complications in the group without insufflation (33% vs 14%, OR = 3.04, 95% CI 1.43 to 6.49).	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval

Explanations

a. Variation in results across studies lowers certainty in findings.

References

1.Lang, C. J.. Apnea testing by artificial CO2 augmentation. Neurology; May 1995.

2.Lang, C. J.. Apnea testing guided by continuous transcutaneous monitoring of partial pressure of carbon dioxide. Critical Care Medicine; May 1998.

3.Lang, C. J.. Blood pressure and heart rate changes during apnoea testing with or without CO2 insufflation. Intensive Care Medicine; Aug 1997.

4.Sharpe, M. D., Young, G. B., Harris, C.. The apnea test for brain death determination: an alternative approach. Neurocritical Care; 2004.

5.Harrar, D. B., Kukreti, V., Dean, N. P., Berger, J. T.,3rd, Carpenter, J. L.. Clinical Determination of Brain Death in Children Supported by Extracorporeal Membrane Oxygenation. Neurocritical Care; 10 2019.

6.Pepe, J., Wolffing, A., Couture, M., Brautigam, R., Butler, K.. Safety first: Carbogen and capnography use minimizes complications during apnea testing. Critical Care Medicine; December 2014.

7.Madden, M., Andrews, P., Rector, R., Menaker, J., Habashi, N.. Carbogen for Apnea Testing During the Brain Death Declaration Process in Subjects on Extracorporeal Membrane Oxygenation. Respiratory Care; Jan 2020.

8.Melano, R., Adum, M. E., Scarlatti, A., Bazzano, R., Araujo, J. L.. Apnea test in diagnosis of brain death: comparison of two methods and analysis of complications. Transplantation Proceedings; Feb 2002.

PICO Question:

In patients who are undergoing apnea testing as part of neurological determination of death, does using positive pressure (CPAP, PEEP) compared to passive oxygenation (continuous oxygen insufflation) improve the ability to complete the apnea test or influence the accuracy of neurological determination of death?

Reviewers:

A. Healey, L. Lee, K. Hornby

Literature Search:

Citations Screened: 523

Citations Included: 3

Recommendation:

We suggest using either positive pressure (continuous positive airway pressure) or passive oxygenation when performing the apnea test for patients undergoing DNC (Weak recommendation, low certainty in evidence).

Evidence Summary:

We found no studies that described the influence of positive pressure on the accuracy of neurological determination of death.

We found 3 studies that described clinically important outcomes around the ability to complete the apnea test. One retrospective review of patients undergoing the apnea test reported on 67 patients who under testing with continuous positive airway pressure (CPAP) and 78 patients underwent non-CPAP, passive oxygen insufflation apnea testing[1]. Another retrospective observational study performed 49 conventional apnea tests on 25 patients who were dead by neurological criteria and 77 apnea tests with CPAP (using a bag-mask device with a positive end expiratory pressure valve) in 39 patients[2]. There were no meaningful differences between the groups in duration of apnea testing or the ability to complete apnea tests. Our review also included one prospective, randomized crossover study with 20 adult patients undergoing three types of oxygenation during apnea testing – CPAP, passive oxygen insufflation, and T-piece passive oxygenation[3]. In this study, two out of 20 patients could not complete the apnea test using passive methods of oxygenation but were successful at completion of the test with CPAP. Other parameters were not clinically or statistically significantly different.

Several case reports[4-7] describe instances where clinicians applied positive pressure oxygen delivery because they did not believe they could complete the test with passive oxygenation. Two additional reports[8, 9] describe failure to complete the test with passive oxygenation and subsequent successful completion of testing with positive pressure oxygenation. There seems to be an experience of caring for patients with significant lung pathology for whom clinicians demonstrated failure of passive oxygenation or believed completion of the test would not be possible without positive pressure.

Justification/Rationale

Completion of the components of the unconfounded physical examination for death determination remains the gold standard for death determination. The ability to complete a carbon dioxide challenge to the brainstem as a component of the physical examination is a central component of the determination. Failing to complete the apnea test, an ancillary test is required, and this is accompanied by independent challenges.

There was minimal difference demonstrated in the studies available between passive and positive pressure oxygenation techniques. Given the limited evidence available, our certainty in is low and the differences probably trivial to a population of patients. However, minimal additional resources would be required to offer positive pressure, some families may be more accepting of apnea testing with ongoing positive pressure, and the likelihood of harm is exceedingly low.

It is important to mitigate failure to complete the apnea test using a variety of methods (as above). The panel made a weak recommendation based on low certainty in evidence to use positive pressure in appropriate circumstances. This should be employed in patients where clinicians are of the opinion that despite adequate preparation (pre-oxygenation, recruitment maneuver, adequate perfusion) the apnea test may not be able to be completed with passive oxygenation alone. Alternatively, some clinicians may choose only to apply positive pressure in circumstances where conventional methods of apnea testing have failed or in whom substantial oxygen requirements / lung pathology exist.

Implementation Considerations:

Non-passive modes of oxygenation during apnea testing require education for staff. These techniques may be more acceptable to families and others observing the test especially if there is no ventilator disconnection. If the ventilator remains attached, false triggering of the ventilator may also be present which may confound interpretation or require a repeat test. Family views on ventilator disconnection may vary and some may even prefer disconnection. A variety of options exist (T-piece oxygenation, continuous positive airway pressure using a ventilator or bag-mask device with valve, intermittent ventilation techniques). Typically, 10 cm H20 is used as the level of continuous pressure although this may vary based on patient characteristics. Having access to a variety of these techniques will assist clinicians in addressing the most challenging cases.

References:

1. Hubbard JL, Dirks RC, Veneman WL, Davis JW. Novel method of delivery of continuous positive airway pressure for apnea testing during brain death evaluation. Trauma surg. 2016;1(1):e000046.
2. Park J, Lee YJ, Hong KS. Proposed safe apnea test using positive end-expiratory pressure valve and short-term blood gas analysis: Observational study. Medicine (Baltimore). 2019;98(19):e15602.
3. Levesque S, Lessard MR, Nicole PC, Langevin S, LeBlanc F, Lauzier F, et al. Efficacy of a T-piece system and a continuous positive airway pressure system for apnea testing in the diagnosis of brain death. Crit Care Med. 2006;34(8):2213-6.
4. Carneiro BV, Garcia GH, Isensee LP, Besen B. Optimization of conditions for apnea testing in a hypoxemic brain dead patient. Rev. 2019;31(1):106-10.
5. Hocker S, Whalen F, Wijdicks EF. Apnea testing for brain death in severe acute respiratory distress syndrome: a possible solution. Neurocrit Care. 2014;20(2):298-300.
6. Shrestha GS, Shrestha PS, Acharya SP, Sedain G, Bhandari S, Aryal D, et al. Apnea testing with continuous positive airway pressure for the diagnosis of brain death in a patient with poor baseline oxygenation status. Indian J. 2014;18(5):331-3.
7. Ahlawat A, Carandang R, Heard SO, Muehlschlegel S. The Modified Apnea Test During Brain Death Determination: An Alternative in Patients With Hypoxia. J Intensive Care Med. 2016;31(1):66-9.
8. Westphal GA, Fernandes V, Westphal V, Fonseca JC, Silva LRD, Valiatti J. Use of CPAP as an alternative to the apnea test during the determination of brain death in hypoxemic patients. Report of two cases. Rev. 2020;32(2):319-25.

9. Wieczorek A, Gaszynski T. Boussignac CPAP system for brain death confirmation with apneic test in case of acute lung injury/adult respiratory distress syndrome - series of cases. Ther Clin Risk Manag. 2015;11:961-5.

Positive pressure (CPAP, PEEP, etc.)/Passive Oxygenation

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not (false positive)									
0							Not assessed in any of the included studies.	-	CRITICAL
Missing someone who is dead by neurologic criteria (false negative)									
0							Not assessed in any of the included studies.	-	CRITICAL
Duration of apnea test									
2[1,2]	observational studies	not serious	not serious	not serious	not serious	none	2 studies reported on comparisons of the duration of the apnea test using positive pressure as compared to passive oxygenation. One study reported longer apnea test with positive pressure ventilation, the other with passive oxygenation, neither was statistically significant.	⨁⨁◯◯ Low	IMPORTANT
Need to abort apnea test due to hypoxia or instability									
1[3]	randomised trials	not serious	not serious	very serious[a]	not serious	none	This prospective randomized crossover study of 20 adult patients for confirmation of brain death was designed to compare efficacy of 3 techniques and was not powered to estimate the incidence of their side effects. However, analysis of the 3 systems suggests that the T-piece, & CPAP are less prone to complications described below. HR & SBP remained stable during AT without any difference between the 3 techniques. IATs were stopped in 1 patient at 9 mins both with the T-piece & CPAP because of arterial hypotension <90 mm Hg, (HR & arterial oxygen saturation remained stable). With the oxygen catheter, the test was barely completed with a systolic pressure of 90 mm Hg. One prospective randomized crossover study of 20 adult patients compared CPAP to O2 catheter to T-piece for confirmation of brain death. There was no difference in PaCO2 between techniques. PaO2 decreased less with CPAP compared with the oxygen catheter or the T-piece (-22.4 +/- 76, -99.1 +/- 158, and -91.6 +/- 133 mm Hg, respectively, p < .01). n 2 patients, AT could not be completed with O2 catheter & T-piece because of desaturation.	⨁⨁◯◯ Low	IMPORTANT

Explanations

a. RCT was "designed to compare efficacy of 3 techniques and was not powered to estimate the incidence of their side effects."

References

1.Hubbard, J. L., Dirks, R. C., Veneman, W. L., Davis, J. W.. Novel method of delivery of continuous positive airway pressure for apnea testing during brain death evaluation. Trauma Surgery & Acute Care Open; 2016.

2.Park, J., Lee, Y. J., Hong, K. S.. Proposed safe apnea test using positive end-expiratory pressure valve and short-term blood gas analysis: Observational study. Medicine; May 2019.

3.Levesque, S., Lessard, M. R., Nicole, P. C., Langevin, S., LeBlanc, F., Lauzier, F., Brochu, J. G.. Efficacy of a T-piece system and a continuous positive airway pressure system for apnea testing in the diagnosis of brain death. Critical Care Medicine; Aug 2006.

Number of Clinical Assessments

PICO Question:

In patients who appear to meet criteria for neurologic death, does the addition of a second clinical assessment for death determination by neurologic criteria separated in time, compared to a single clinical assessment, improve the accuracy of death determination by neurologic criteria?

Reviewers:

J. Teitelbaum, M. Leeies, J. Arbour

Literature Search:

Citations Screened: 1147

Citations Included: 3

Recommendation:

We recommend that one complete clinical assessment is sufficient for patients one year of age or older who are undergoing DNC (Strong recommendation, moderate certainty in evidence).

We suggest two complete clinical assessments separated in time is sufficient for patients less than one year corrected gestational age who are undergoing DNC (Weak recommendation, very low certainty in evidence).

Evidence Summary:

We included three observational cohort studies from this systematic review[1-3]. One retrospective multicenter chart review of Canadian pediatric intensive care units reported that in 68/135 patients (36 weeks corrected gestational age to 17 years old) where two assessments for death determination by neurologic criteria (DNC) had been performed, there was 1 case of a discordant second assessment. The details of the case were limited by the retrospective nature of the study but there were concerns regarding potential inconsistencies in pupil size documentation[2]. A second multicentre, retrospective chart review of 1229 adult and 82 pediatric patients[3] and prospective observational study of 28 adult patients[1] both reported no discordant DNC assessments.

Despite heterogeneity in location, practice and patient populations, of 1407 patients with two DNC assessments included in these three cohort studies, there was a single case in which there were discordant DNC assessments where a first assessment was consistent with neurologic death but a later assessment was not (an 11-month old with multiple congenital malformations, inconsistencies in pupil size documentation and hydrocephalus post cardiac arrest who had spontaneous breathing efforts noted during the second DNC assessment and subsequently received withdrawal of life sustaining measures and palliative care). Therefore, the congruence between DNC assessments is extremely high over a wide variation in patients and settings.

Subgroup considerations

Newborn infants were under-represented in this sample. Given existing practice patterns and biologic rationale that open fontanelles may alter the pathophysiology of death by neurologic criteria caution is recommended in this subgroup.

Patients with decompressive craniectomies were also under-represented in this sample. Given recent concerns regarding the accuracy of the DNC assessment in this population similar caution is recommended in this subgroup

Justification/Rationale

Given the available body of evidence and values and preferences factors, our consensus was that the desirable effects of a second DNC assessment were trivial because of the very high congruence between complete DNC assessments. The undesirable effects of requiring two DNC assessments separated in time (vs. 1 DNC assessment) were, however, moderately important. We considered that unnecessary delays to the determination of neurologic death could lead to prolonged suffering for the loved ones, families, or substitute decision makers of the deceased. Similarly, this delay could lead to indignity in the care of the deceased's bodily remains where the deceased is exposed to ongoing non-therapeutic elements of critical care and a delay to culturally specific practices or ceremonies for the deceased. Additionally, we identified that a requirement for a second DNC assessment could increase health care resource utilization. Further, unnecessary delays in confirmation of the death determination by neurologic death have been associated with loss of viable organs for organ donation for those who wanted to donate.

Newborns and infants were under-represented in the published literature, however, experts noted that current practice typically consists of two clinical assessments for DNC. For newborns there may be a differing pathophysiology of neurological death where open fontanelles can potentially alter the pathway of increased intracranial pressure leading to whole brain ischemia that ultimately results in neurologic death in patients with a fixed intracranial space. For this reason, along with limited direct evidence, a lack of collective experience with DNC in this age group, and a desire to promote maximum safeguarding of the determination of death in these very young patients, the panel suggests two complete clinical assessments at a different time for newborns and infants less than one year. There is no recommended minimum time interval between clinical assessments, however, 24 hours between assessments for newborns (less than two months corrected gestational age may be advisable given the inability to use ancillary testing for DNC in this age group. The time interval may be extended according to physician judgment.

Similarly, for patients > 1 year old who have undergone decompressive complete or partial craniectomies (or have a non-closed skull for other reasons) multiple DNC clinical assessments or ancillary tests may be considered.

The purpose of the DNC assessment must also be contextualized in the patient's overall course. If organ donation following DNC is being pursued it is imperative that an accurate determination of death be conducted so as to protect the ethical and legal integrity of the deceased organ donation system where the "dead-donor rule" is sacrosanct[4] TRUOG. If there is a legal requirement for two examiners to agree on the death determination, these assessments can be done concurrently. In circumstances where a patient has suffered an un-survivable devastating brain injury, is not being considered for deceased organ donation and next steps in clinical care involve withdrawal of life-sustaining measures and palliative care there might be a differential risk/benefit profile where the same threshold for accuracy of the DNC assessment may or may not be required.

Implementation Considerations:

Implementation of standardizing clinical practice whereby only one DNC assessment is required is anticipated to have minimal barriers.

A change in practice and policy may be required in some jurisdictions where two DNC assessments separated in time are required. An effective knowledge translation approach will be needed to support this change in routine practice in relevant jurisdictions.

References:

1. Al-Shammri S, Al-Feeli M. Confirmation of brain death using brain radionuclide perfusion imaging technique. Med Princ Pract. 2004;13(5):267-72.

2. Joffe AR, Shemie SD, Farrell C, Hutchison J, McCarthy-Tamblyn L. Brain death in Canadian PICUs: demographics, timing, and irreversibility. Pediatr Crit Care Med. 2013;14(1):1-9.

3. Lustbader D, O'Hara D, Wijdicks EF, MacLean L, Tajik W, Ying A, et al. Second brain death examination may negatively affect organ donation. Neurology. 2011;76(2):119-24.

4. Truog RD, Miller FG, Halpern SD. The dead-donor rule and the future of organ donation. N Engl J Med. 2013;369(14):1287-9.

Number of Clinical Assessments

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Declaring someone dead who is not (false positive)									
3[1,2,3]	observational studies	not serious	not serious	not serious	not serious	strong association	Despite heterogeneity in location, practice and patients populations, of almost 2000 patients included in these 3 cohort studies there was a single case in which there were discrepant brain death exams between two examinations separated in time (an 11-month old with multiple congenital malformations and hydrocephalus post cardiac arrest who had a spontaneous breathing effort during the second exam and who ended up receiving WLS and palliative care). Therefore, the congruence between exams is extremely high over a wide variation in patients and settings.	⊕⊕⊕◯ Moderate	CRITICAL
Missing someone who is dead (false negative)									
3[1,2,3]	observational studies	not serious	not serious	not serious	not serious	strong association	Similar to impact from above, the high degree of congruence between the two exams across cohort studies is reassuring.	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval

References

1.Al-Shammri, S., Al-Feeli, M.. Confirmation of brain death using brain radionuclide perfusion imaging technique. Medical Principles & Practice; Sep-Oct 2004.

2.Lustbader, D., O'Hara, D., Wijdicks, E. F., MacLean, L., Tajik, W., Ying, A., Berg, E., Goldstein, M.. Second brain death examination may negatively affect organ donation. Neurology; Jan 11 2011.

3.Joffe, A. R., Shemie, S. D., Farrell, C., Hutchison, J., McCarthy-Tamblyn, L.. Brain death in Canadian PICUs: demographics, timing, and irreversibility. Pediatric Critical Care Medicine; Jan 2013.

PICO Question:

In adult patients suspected of neurological death for whom the clinical examination cannot be completed due to confounders, which ancillary test(s) should be used to diagnose death by neurologic criteria?

Reviewers:

Michaël Chassé, Joel Neves Briard, Roy Nitulescu, Émile Lemoine, Polina Titova, Shane English, Lauralyn McIntyre, Greg Knoll, Sam Shemie, Claudio Martin, Alexis F Turgeon, François Lauzier, Dean A Fergusson

Literature Search:

Citations Screened: 5164

Citations Included: 57 (+1 preliminary analyses from the INDex trial)*

* Note: For these guidelines, we restricted our work to the following ancillary tests: CT-angiography (4-point, 7-point, and 10-point scales), CT-perfusion, radionuclide imaging (99m Tc pertechnetate flow imaging, ^{99m}Tc HMPAO with SPECT imaging and ^{99m}Tc HMPAO with planar imaging, transcranial Doppler ultrasound, electroencephalography, brainstem auditory evoked potentials, four-vessel cerebral angiography, and magnetic resonance imaging with time-of-flight angiography. If there was no data from studies including comatose patients with and without DNC (both positives and negatives respectively), we used data from studies including only patients with DNC (only positives). This work is part of a larger systematic review and meta-analysis on ancillary test diagnostic accuracy for DNC [1].

Recommendation(s):

We suggest performing computed tomography-perfusion, computed tomography-angiography, transcranial doppler, or a radionuclide brain perfusion study employing a lipophilic radiopharmaceutical (with or without tomographic imaging) in adult patients who require an ancillary investigation for DNC (Weak recommendation, very low to moderate certainty in evidence).

We suggest against performing electroencephalography, brainstem auditory evoked potentials, somatosensory evoked potentials, a radionuclide brain flow only study employing a lipophobic radiopharmaceutical, four-vessel cerebral angiography, or magnetic resonance imaging in adult patients who require an ancillary investigation for DNC (Weak recommendation, very low certainty in evidence).

Evidence Summary (including subgroup considerations, if relevant):

We found a total of 57 publications addressing the question of interest, to which we added preliminary data from the recent Canadian prospective multicentric INDex trial on the diagnostic accuracy of CT-perfusion and CT-angiography for DNC. We chose to include the INDex preliminary data although it has not yet been published in a peer-reviewed journal as this trial provides the highest-quality data on CT-perfusion and CT-angiography diagnostic accuracy for DNC to date. Preliminary results were presented at the Canadian Critical Care Canada Forum in December 2021 and based on the analysis of 273 patients, with 14 patients awaiting final neuroimaging interpretation.

Studies on CT-angiography diagnostic accuracy for DNC employed a variety of radiological criteria, most frequent of which were the 4-point, the 7-point and the 10-point scales (Table 1). We found 6 studies (576 patients) of cohort and case-control methodologies investigating the accuracy of the 4-point scale [2-7]. The quality of evidence was very low for sensitivity and low for specificity. The false-negative rate (i.e. the number of tests indicating that a patient does not have DNC although they fulfill all clinical criteria for DNC) per 1000 patients tested assuming a pre-test probability of 95% was 142 (95% confidence interval: 57-313). The false-positive rate (i.e. the number of tests indicating that a patient has DNC although they do not fulfill all clinical criteria for DNC) per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-1). We found 3 studies (352 patients) of cohort and case-control methodologies investigating the accuracy of the 7-point scale [3, 5, 8]. The quality of evidence was very low for sensitivity and low for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 86 (95% confidence interval: 19-256). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-2). We found 2 studies (327 patients) of cohort methodology investigating the accuracy of the 10-point scale [3, 5]. The quality of evidence was low for sensitivity and moderate for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 105 (95% confidence interval: 19-361). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-2).

Table 1. Vessels investigated for opacification in the 4-point, 7-point and 10-point CT-angiography scales for DNC

Artery or vein	**4-point scale**	**7-point scale**	**10-point scale**
Bilateral M4 segments of the middle cerebral arteries	√	√	√
Bilateral A3 segments of the anterior cerebral arteries		√	√
Bilateral internal cerebral veins	√	√	√
Great vein of Galen		√	√
Basilar artery			√
Bilateral P2 segments of the posterior cerebral arteries			√

We found 2 studies (313 patients) of cohort methodology investigating the accuracy of CT-perfusion [3, 5]. Both studies employed visual inspection of the perfusion scans, with a matched absence of cerebral blood flow and cerebral blood volume in the entire brain considered diagnostic of DNC. The quality of evidence was moderate for sensitivity and low for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 28 (95% confidence interval: 0-114). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-8).

Radionuclide scans were classified according to the physiological process evaluated by the exam. Radionuclide studies using lipophobic radiopharmaceuticals provide evaluation of cerebral blood flow, and resemble contrast angiography tests. In contrast, radionuclide studies utilizing lipophilic radiopharmaceuticals provide evaluation of both cerebral blood flow (early phase) and parenchymal

perfusion (late phase). These perfusion studies can be imaged employing planar or tomographic (SPECT) techniques.

We found 2 studies (254 patients) of cohort methodology investigating the accuracy of ^{99m}Tc pertechnetate flow imaging [9, 10]. The quality of evidence was low for sensitivity and very low for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 9 (95% confidence interval: 0-66). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-22).

We found 2 studies (76 patients) of cohort methodology investigating the accuracy of ^{99m}Tc HMPAO perfusion with SPECT (tomographic) imaging [11, 12]. Complete absence of brain perfusion on visual inspection was considered diagnostic for DNC, including the posterior fossa and brainstem, to the extent visible. The quality of evidence was very low for sensitivity and low for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 86 (95% confidence interval: 9-342). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-1).

We found 3 studies (93 patients) of cohort methodology investigating the accuracy of ^{99m}Tc HMPAO perfusion with planar (non-tomographic) imaging [5, 13, 14]. Complete absence of brain perfusion on visual inspection was considered diagnostic for DNC. Generally anterior and lateral views are required to adequately evaluate the posterior fossa. The quality of evidence was very low for sensitivity and for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 76 (95% confidence interval: 19-275). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-2).

We found 20 studies (1108 patients) of cohort and case-control methodologies investigating the accuracy of transcranial Doppler ultrasound [2, 15-33] (diagnostic criteria are provided in Table 2). The quality of evidence was very low for sensitivity and low for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 38 (95% confidence interval: 19-76). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-1).

Table 2. Diagnostic criteria for DNC based on transcranial Doppler ultrasound in included studies

Diagnostic criteria	**Number of studies (Number of patients)**
Ultrasound pattern compatible with DNC	
Oscillatory/reverberating flow, systolic spikes or no flow*	7 (549)
Oscillatory/reverberating flow or systolic spikes	6 (287)
Only oscillatory/reverberating flow	5 (184)
Only no flow*	1 (131)
Other	1 (28)
Vessels investigated	
Common carotid arteries	1 (28)
Internal carotid arteries	5 (318)
Anterior cerebral arteries	6 (440)
Middle cerebral arteries	18 (1065)

Vertebral arteries	8 (488)
Basilar artery	9 (700)
Posterior cerebral arteries	3 (200)

* Note: for no flow to be considered compatible with DNC, at least one previous ultrasound must have demonstrated the presence of intracranial flow, thus excluding that the finding of no flow is potentially a consequence of a non-acoustic bone window.

The most frequently used transcranial Doppler ultrasound diagnostic criterion for DNC (either in combination or isolation) was oscillatory/reverberating flow (i.e. a retrograde diastolic flow in the presence of a systolic anterograde flow). Most studies also accepted systolic spikes and no flow in a patient who had documented flow in a previous ultrasound as criteria for DNC.

To gain a deeper understanding of the impact of the diagnostic criteria in transcranial Doppler ultrasound studies, we here provide details on studies with poor specificity estimates and/or large specificity imprecision. In one study with a sample size of 42 patients and a specificity of 90% (95% highest density interval: 75-98%), authors had defined oscillatory/reverberating flow and systolic spikes as patterns consistent with DNC and investigated only the middle cerebral arteries [23]. In one study with a sample size of 15 patients and a specificity of 80% (95% highest density interval: 19-98%), authors had defined oscillatory/reverberating flow and systolic spikes as patterns consistent with DNC and investigated the internal carotid arteries and vertebral arteries [29]. In one study with a sample size of 131 patients and a specificity of 91% (95% highest density interval: 58-100%), authors had defined no flow as the pattern consistent with DNC and investigated the anterior cerebral arteries, the middle cerebral arteries, the posterior cerebral arteries, the vertebral arteries, and the basilar artery. In three other studies, pooled specificity estimates were good (96-100%) but had wide highest density intervals (with a range including values $\leq$90%), probably owing to small sample sizes (25, 12 and 24 patients respectively) [24, 25, 28].

We found 5 studies (264 patients) of cohort and case-control methodologies investigating the accuracy of electroencephalography [14, 31, 34-36]. Electrocerebral silence on visual inspection was considered diagnostic for DNC. The quality of evidence was very low for sensitivity and low for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 76 (95% confidence interval: 19-199). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-1).

We found 3 studies (98 patients) of cohort methodology investigating the accuracy of brainstem auditory evoked potentials [10, 14, 37]. The quality of evidence was low for sensitivity and very low for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-28). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 10 (95% confidence interval: 0-43).

We found 21 studies (951 patients) of cohort methodology investigating the accuracy of four-vessel cerebral angiography [38-58]. Complete absence of intracranial circulation was considered diagnostic for DNC. All these studies were conducted on populations of patients with DNC, meaning that only sensitivity estimates are included. The quality of evidence was very low for sensitivity. The false-negative

rate per 1000 patients tested assuming a pre-test probability of 95% was 66 (95% confidence interval: 38-114).

We found 1 study (30 patients) of case-control methodology investigating the accuracy of magnetic resonance imaging with time-of-flight angiography [59]. The quality of evidence was very low for sensitivity and for specificity. The false-negative rate per 1000 patients tested assuming a pre-test probability of 95% was 19 (95% confidence interval: 0-180). The false-positive rate per 1000 patients tested assuming a pre-test probability of 95% was 0 (95% confidence interval: 0-12).

Justification/Rationale

The panel considered the present question to be a priority since excellent diagnostic accuracy is crucial in DNC determination. For all ancillary tests, the panel felt there were no important uncertainty or variability in how people value the main outcome. Certainty of evidence of required resources was moderate for all tests. We did not include cost-effectiveness studies, so this was not considered in development of these recommendations.

Certain ancillary tests can only be conducted (or interpreted) in larger centers in denser urban centers compared to rural institutions. Since there are important differences in rural and urban patient demographics, there could be inequities that arise based on test availability. The panel therefore felt that use of four-vessel angiography reduced health equity. Furthermore, the panel felt the following tests probably reduce health equity: CT-perfusion, radionuclide perfusion imaging, transcranial Doppler ultrasound, brainstem auditory evoked potentials, and magnetic resonance imaging. There is probably no impact for the use of CT-angiography, which is routinely available in most Canadian hospitals with intensive care units. Finally, no major impact on health equity is expected from the use of electroencephalography, which is available in most Canadian hospitals during usual business hours.

CT-angiography was considered to have moderate desirable effects and undesirable effects based on significant false negative and false positive rates. The certainty of evidence was very low to low for this ancillary test. The panel felt the balance between desirable and undesirable effects probably favors the use of CT-angiography over another ancillary test. The resource requirements for this test were judged to be moderate (negligible). Key stakeholders are likely to accept the use of this test. The panel felt this test was feasible to implement due to its availability in most Canadian hospitals with intensive care units and widespread radiologist training in CT-angiography.

CT-angiography diagnostic criteria: The 10-point scale, applied to the late acquisition phase, should be favored to diagnose DNC using CT-angiography. Unlike other commonly investigated scales, the 10-point scale studies opacification of both supratentorial and infratentorial vessels.

CT-perfusion was considered to have high desirable effects based on an acceptable false negative rate. Undesirable effects were judged to be low due to an acceptable false positive rate. The certainty of evidence was low to moderate for this ancillary test. The panel felt the balance between desirable and undesirable effects favors the use of CT-perfusion over another ancillary test. The resource requirements for this test were judged to be moderate (negligible). There is likely variability in the acceptability of this test among key stakeholders, notably due to its novelty as a test for DNC determination. The panel felt the implementation feasibility of this test is variable due to novelty of the

imaging modality. Furthermore, operator training is probably heterogeneous across Canada and may not reflect the level of expertise found in the evidence base.

CT-perfusion diagnostic criteria: Visual qualitative assessment of the processed perfusion maps should demonstrate matched decrease in cerebral blood flow and cerebral blood volume in at least 2 consecutive axial cross-sections of the brainstem to diagnose DNC using CT-perfusion. These were the criteria used in the INDex study.

Radionuclide perfusion imaging (radionuclide imaging using a lipophilic agent) with planar or SPECT imaging was considered to have high desirable effects based on an acceptable false negative rate. Undesirable effects were judged to be low due to an acceptable false positive rate. The certainty of evidence was low for this ancillary test. The panel felt the balance between desirable and undesirable effects favors the use of radionuclide perfusion imaging over another ancillary test. The resource requirements for this test were judged to be moderate (negligible). Key stakeholders are likely to accept the use of this test. The panel felt this test was feasible to implement due to its availability in most Canadian hospitals with intensive care units and widespread nuclear imaging specialist training in radionuclide imaging.

Radionuclide perfusion imaging diagnostic criteria: Absence of intracranial radionuclide uptake on planar or tomographic imaging including assessment of the posterior fossa and brainstem to the extent possible is necessary for DNC. Where flow images are also obtained during injection of the lipophilic radiopharmaceuticals, there should also be no visualization of the anterior and middle cerebral arteries.

Transcranial Doppler ultrasound was considered to have high desirable effects based on an acceptable false negative rate. Undesirable effects were judged to be low due to an acceptable false positive rate. The certainty of evidence was very low to low for this ancillary test. The panel felt the balance between desirable and undesirable effects probably favors the use of transcranial Doppler ultrasound over another ancillary test. The resource requirements for this test were judged to be low (moderate savings). There is likely variability in the acceptability of this test among key stakeholders, notably due to its reliance on operator expertise, novelty as a test for DNC determination and the heterogeneity of ultrasound diagnostic criteria for DNC found in the evidence base. Moreover, this test is not appropriate is a significant proportion (~10%) of patients with an inadequate bone window. The panel felt the implementation feasibility of this test is variable due to its limited availability in Canadian hospitals. Furthermore, operator training is probably heterogeneous across Canada and may not reflect the level of expertise found in the evidence base.

Transcranial Doppler ultrasound diagnostic criteria: Visual inspection of blood flow patterns should demonstrate oscillatory/reverberating flow (i.e. a retrograde diastolic flow in the presence of a systolic anterograde flow), systolic spikes, or no flow in a patient with documented flow in a previous transcranial Doppler ultrasound study, in the anterior (minimally the middle cerebral arteries) and the vertebrobasilar (minimally the basilar artery) circulations to diagnose DNC using transcranial Doppler ultrasound [60, 61]. A formal ultrasound exam should be performed and interpreted by an expert with formal neurosonography training. Point-of-care ultrasonography is discouraged for DNC diagnosis since studies that determined accuracy of this ancillary test were generally performed by experienced operators.

Radionuclide flow imaging (typically using a lipophobic agent) was considered to have moderate desirable effects based on a significant false negative rate. Undesirable effects were judged to be moderate due to a significant false positive rate. The certainty of evidence was very low for this ancillary test. The panel felt the balance between desirable and undesirable effects probably favors the use of another ancillary test over radionuclide angiography. The resource requirements for this test were judged to be moderate (negligible). Key stakeholders are likely to accept the use of this test. The panel felt this test was feasible to implement due to its availability in most Canadian hospitals with intensive care units and widespread nuclear imaging specialist training in radionuclide angiography.

Electroencephalography was considered to have high desirable effects based on an acceptable false negative rate. Undesirable effects were judged to be moderate due to an acceptable false positive rate but concerns on test validity in the presence of confounders to the clinical examination such as persistent intoxication and sedation. The certainty of evidence was very low to low for this ancillary test. The panel felt the balance between desirable and undesirable effects probably favors the use of another ancillary test over electroencephalography. The resource requirements for this test were judged to be low (moderate savings). Key stakeholders are likely not to accept the use of this test due to concerns of its validity in the context of confounders such as intoxication and sedation. The panel felt this test was probably feasible to implement.

Brainstem auditory evoked potentials were considered to have low desirable effects based on a high false negative rate. Undesirable effects were judged to be high due to a high false positive rate and concerns on test validity in the presence of confounders to the clinical examination such as persistent intoxication and sedation. The certainty of evidence was very low for this ancillary test. The panel felt the balance between desirable and undesirable effects probably favors the use of another ancillary test over brainstem auditory evoked potentials. The resource requirements for this test were judged to be low (moderate savings). Key stakeholders are likely not to accept the use of this test due to concerns of its validity in the context of confounders such as intoxication and sedation. The panel felt this test was probably not feasible to implement due to the lack of evoked potential neurophysiologic expertise in most Canadian hospitals.

Four vessel cerebral angiography was considered to have moderate desirable effects based on an acceptable false negative rate. Undesirable effects were judged to be high in the absence of data on test specificity. The certainty of evidence was very low for this ancillary test. The panel felt the balance between desirable and undesirable effects probably favors the use of another ancillary test over four-vessel cerebral angiography. The resource requirements for this test were judged to be moderate to high compared to alternative diagnostic tests. Key stakeholders probably accept the use of this test due to its historical role in DNC determination over the past decades. The panel felt this test was probably feasible to implement only in experienced centers.

Magnetic resonance imaging with time-of-flight angiography was considered to have moderate desirable effects based on a significant false negative rate. Undesirable effects were judged to be moderate due to a significant false positive rate. The certainty of evidence was very low for this ancillary test. The panel felt the balance between desirable and undesirable effects probably favors the use of another ancillary test over magnetic resonance imaging. The resource requirements for this test were judged to be low (moderate savings). Key stakeholders are likely not to accept the use of this test due to concerns of its validity in DNC determination. The panel felt this test was probably feasible to implement

due to its availability in most Canadian hospitals with intensive care units and widespread radiologist training in magnetic resonance imaging.

Implementation Considerations:

Systems of care may face certain challenges implementing provided recommendations. Access to expertise for the interpretation of CT-perfusion and transcranial Doppler ultrasound may be limited in many Canadian non-academic hospitals, notably outside comprehensive stroke centers where these tests are not frequently used. Appropriate training, adequate caseload and active performance monitoring are essential to ensure the level of expertise in clinical practice is representative of the expertise in the evidence base. The use of uniform diagnostic criteria is essential to maximize test reliability both within and between institutions. These considerations are true for all ancillary tests, but these may be less challenging for the other recommended tests since these are already widely used in clinical practice.

Knowledge Gaps/Research Considerations:

Further high-quality research is required to characterize the diagnostic accuracy of ancillary tests for DNC. At the present time, the evidence base is mostly comprised of studies of moderate to high risk of bias, most of which did not include a sample entirely representative of the target population. Research is encouraged to develop and validate ancillary tests that test cerebral function (without using blood flow or perfusion as a surrogate for function), without being significantly affected by intoxication or sedation. Particular attention to function assessment would be valuable. The validity of ancillary tests based on interpretation by non-experts (for instance, in community settings) is another important topic of further research. Finally, the reliability and cost-effectiveness of ancillary tests for DNC also merits further investigation.

References:

1. Chassé M, Glen P, Doyle MA, McIntyre L, English SW, Knoll G, et al. Ancillary testing for diagnosis of brain death: a protocol for a systematic review and meta-analysis. Systematic Reviews. 2013;2(100).
2. Brasil S, Bor-Seng-Shu E, de-Lima-Oliveira M, Taccone FS, Gattas G, Nunes DM, et al. Computed tomography angiography accuracy in brain death diagnosis. J Neurosurg. 2019:1-9.
3. Chassé M, Shankar J, Titova P, editors. Improving Neurological Diagnostic Death Evaluation : a prospective Canadian multicenter diagnostic test study – Preliminary results. Canadian Critical Care Forum; 2021; Canada.
4. Garrett MP, Williamson RW, Bohl MA, Bird CR, Theodore N. Computed tomography angiography as a confirmatory test for the diagnosis of brain death. J Neurosurg. 2018;128(2):639-44.
5. MacDonald D, Stewart-Perrin B, Shankar JJS. The Role of Neuroimaging in the Determination of Brain Death. J Neuroimaging. 2018;28(4):374-9.
6. Nunes DM, Maia ACM, Jr., Boni RC, da Rocha AJ. Impact of Skull Defects on the Role of CTA for Brain Death Confirmation. AJNR Am J Neuroradiol. 2019;40(7):1177-83.
7. Sawicki M, Solek-Pastuszka J, Chamier-Cieminska K, Walecka A, Bohatyrewicz R. Accuracy of Computed Tomographic Perfusion in Diagnosis of Brain Death: A Prospective Cohort Study. Med Sci Monit. 2018;24:2777-85.
8. Dupas B, Gayet-Delacroix M, Villers D, Antonioli D, Veccherini MF, Soulillou JP. Diagnosis of brain death using two-phase spiral CT. AJNR Am J Neuroradiol. 1998;19:641-7.

9. Flowers WM, Patel BR. Radionuclide angiography as a confirmatory test for brain death a review of 229 studies in 219 patients. Southern Medical Journal. 1997;90(11):1091-6.
10. Link J, Wagner W, Rohling R. Auditory evoked potentials and determinatin of brain death. Klin Wochenschr. 1988;66:62-6.
11. Facco E, Zucchetta P, Munari M, Baratto F, Behr AU, Gregianin M, et al. 99mTc-HMPAO SPECT in the diagnosis of brain death. Intensive Care Med. 1998;24:911-7.
12. Laurin NR, Driedger AA, Hurwitz GA, Mattar AG, Powe JE, Chamberlain MJ, et al. Cerebral perfusion imaging with technetium-99m HM-PAO in brain death and severe central nervous system injury. J Nucl Med. 1989;30:1627-35.
13. Mrhac L, Zakko S, Parikh Y. Brain death: The evaluation of semi-quantitative parameters and other signs in HMPAO scintigraphy. Nuclear Medicine Communications. 1995;16:1016-20.
14. Schlake HP, Bottger IG, Grotomeyer KH, Husstedt IW, Brandau W, Schober O. Determination of cerebral perfusion by means of planar brain scintigraphy and 99mTc-HMPAO in brain death, persistent vegetative state. Intensive Care Med. 1992;18:76-81.
15. Azevedo E, Teixeira J, Neves JC, Vaz R. Transcranial Doppler and Brain Death. Transplant Proc. 2000;32:2579-81.
16. Brunser AM, Lavados PM, Cárcamo DA, Hoppe A, Olavarría VV, López J, et al. Accuracy of Power Mode Transcranial Doppler in the Diagnosis of Brain Death. Journal of Medical Ultrasound. 2015;23(1):29-33.
17. Davalos A, Rodriguez-Rago A, Mate G, Molins A, Genis D, Gonzalez JL, et al. Value of the transcranial Doppler examination in the diagnosis of brain death. Med Clin (Barc). 1993;100:249-52.
18. Dominguez-Roldan JM, Murillo-Cabezas F, Munoz-Sanchez A, Santamaria-Mifsut JL, Villen-Nieto J. Changes in the Doppler waveform of intracranial arteries in patients with brain-death status. Transplant Proc. 1995;27(4):2391-2.
19. Dosemeci L, Dora B, Yilmaz M, Cengiz M, Balkan S, Ramazanoglu A. Utility of transcranial doppler ultrasonography for confirmatory diagnosis of brain death: two sides of the coin. Transplantation. 2004;77(1):71-5.
20. Feri M, Ralli L, Felici M, Vanni D, Capria V. Transcranial Doppler and brain death diagnosis. Crit Care Med. 1994;22(7):1120-6.
21. Hadani M, Bruk B, Ram Z, Knoller N, Spiegelmann R, Segal E. Application of transcranial doppler ultrasonography for the diagnosis of brain death. Intensive Care Med. 1999;25:822-8.
22. Kuo JR, Chen CF, Chio CC, Chang CH, Wang CC, Yang CM, et al. Time dependent validity in the diagnosis of brain death using transcranial Doppler sonography. J Neurol Neurosurg Psychiatry. 2006;77(5):646-9.
23. Li Y, Liu S, Xun F, Liu Z, Huang X. Use of Transcranial Doppler Ultrasound for Diagnosis of Brain Death in Patients with Severe Cerebral Injury. Med Sci Monit. 2016;22:1910-5.
24. Nebra AC, Virgos B, Santos S, Tejero C, Larraga J, Araiz JJ, et al. Clinical diagnostic of brain death and transcranial Doppler, looking for middle cerebral arteries and intracranial vertebral arteries. Agreement with scintigraphic techniques. Rev Neurol. 2001;33(10):916-20.
25. Newell DW, Grady MS, Sirotta P, Winn HR. Evaluation of brain death using transcranial Doppler. Neurosurgery. 1989;24(4):509-13.
26. Payen DM, Lamer C, Pilorget A, Moreau T, Beloucif S, Echter E. Evaluation of pulsed Doppler common carotid blood flow as a noninvasive method for brain death diagnosis a prospective study. Anesthesiology. 1990;72:222-9.
27. Petty GW, Mohr JP, Pedley TA, Tatemichi TK, Lennihan L, Duterte DI, et al. The role of transcranial Doppler in confirming brain death sensitivity, specificity, and suggestions for performance and interpretation. Neurology. 1990;40:300-3.

28. Powers AD, Graever MC, Smith RR. Transcranial Doppler ultrasonography in the determination of brain death. Neurosurgery. 1989;24(6):884-9.
29. Rosendahl TH, Muller C, Foran R, Cossman D, Carroll R, Ellison J, et al. Internal carotid and vertebral duplex scanning for the determination of brain death. The Journal of Vascular Technology. 1994;18(2):89-93.
30. Shiekh BY, Al Jihani H. Implementing transcranial Doppler as confirmatory test in brain death criteria. Pan Arab Journal of Neurosurgery. 2008;12(1):46-9.
31. Su Y, Yang Q, Liu G, Zhang Y, Ye H, Gao D, et al. Diagnosis of brain death confirmatory tests after clinical test. Chin Med J. 2014;127(7):1272-7.
32. Van Velthoven V, Calliauw L. Diagnosis of brain death. Transcranial Doppler sonography as an additional method. Acta Neurochir (Wien). 1988;95:57-60.
33. Werner C, Kochs E, Rau M, Schulte am Esch J. Transcranial Doppler sonography as a supplement in the detection of cerebral circulatory arrest. Journal of Neurosurgical Anesthesiology. 1990;2(3):159-65.
34. Cao J, Watabe D, Zhang L, editors. An EEG diagnosis system for quasi brain death based on complexity and energy analyses. 35th Annual International Conference of the IEEE EMBS; 2013.
35. Hicks RG, Torda TA. The vestibulo-ocular (caloric) reflex in the diagnosis of cerebral death. Anaesth Intensive Care. 1979;7:169-73.
36. Zhang Y, Sun B, Wu XY. Spectrum analysis of the EEG in patients with brain death. J Clin Neurol. 2008;21(3):213-5.
37. Bhattarai BK, Kaul HL, Muralidhar V, Bhatia M. An analysis of brainstem auditory evoked potentials (BAEP) in brain death and its usefulness in the diagnosis of braint death. J Anesth Clin Pharmacol. 2002;18(4):397-404.
38. Bergquist E, Bergstrom K. Angiography in cerebral death. Acta Radiologica Diagnosis. 1972;12(3):283-8.
39. Berlit P, Wetzel E. HM-PAO cerebral blood flow scintigraphy in the manifestation stage of brain death. Nervenarzt. 1992;63:101-4.
40. Braun M, Ducrocq X, Huot JC, Audibert G, Anxionnat R, Picard L. Intravenous angiography in brain death report of 140 patients. Neuroradiology. 1997;39:400-5.
41. Combes JC, Chomel A, Ricolfi F, d'Athis P, Freysz M. Reliability of computed tomographic angiography in the diagnosis of brain death. Transplant Proc. 2007;39(1):16-20.
42. Hassler W, Steinmetz H, Pirschel J. Transcranial Doppler study of intracranial circulatory arrest. J Neurosurg. 1989;71:195-201.
43. Hoffmann O, Masuhr F. Use of Observational Periods or Ancillary Tests in the Determination of Brain Death in Germany. Eur Neurol. 2015;74(1-2):11-7.
44. Jorgensen PB, Jorgensen EO, Rosenklint A. Brain death pathogenesis and diagnosis. Acta Neurol Scand. 1973;49:355-67.
45. Kramar F, Mohapl M, Benes V. Diagnosis of brain death with TCD. Anesteziologie a neodkladna pece. 2001;3:145-7.
46. Lovrencic-Huzjan A, Vukovic V, Gopcevic A, Vucic M, Kriksic V, Demarin V. Transcranial Doppler in brain death confirmation in clinical practice. Ultraschall Med. 2011;32(1):62-6.
47. Matsumura A, Meguro K, Tsurushima H, Komatsu Y, Kikuchi Y, Wada M, et al. Magnetic resonance imaging of brain death. Neurol Med Chir (Tokyo). 1996;36:166-71.
48. Munari M, Zucchetta P, Carollo C, Gallo F, De Nardin M, Marzola MC, et al. Confirmatory tests in the diagnosis of brain death: comparison between SPECT and contrast angiography. Crit Care Med. 2005;33(9):2068-73.
49. Nau R, Prange HW, Klingelhöfer J, Kukowski B, Sander D, Tchorsch R, et al. Results of four technical investigations in fifty clinically brain dead patients. Intensive Care Med. 1992;18:82-8.

50. Paolin A, Manuali A, Di Paola F, Boccaletto F, Caputo P, Zanata R, et al. Reliability in diagnosis of brain death. Intensive Care Med. 1995;21:657-62.
51. Pedicelli A, Bartocci M, Lozupone E, D'Argento F, Alexandre A, Garignano G, et al. The role of cervical color Doppler ultrasound in the diagnosis of brain death. Neuroradiology. 2019;61(2):137-45.
52. Picard L, Braun M, Anxionnat R, Claise B, Ducrocq X, Pincemaille B, et al. Venous angiography importance in the diagnosis of brain death. 125 cases. Bull Acad Natle Med. 1995;179(1):27-40.
53. Sawicki M, Solek-Pastuszka J, Jurczyk K, Skrzywanek P, Guzinski M, Czajkowski Z, et al. Original Protocol Using Computed Tomographic Angiography for Diagnosis of Brain Death: A Better Alternative to Standard Two-Phase Technique? Ann Transplant. 2015;20:449-60.
54. Soldatos T, Karakitsos D, Chatzimichail C, Papathanasiou M, Gouliamos A, Karabinis A. Transcranial doppler sonography as a confirmatory test in the diagnosis of brain death. Neuroradiology. 2009;51 Suppl 1:S71.
55. Tan WS, Wilbur AC, Jafar JJ, Spigos DG, Abejo R. Brain death use of dynamic CT and intravenous digital subtraction angiography. AJNR Am J Neuroradiol. 1987;8:123-5.
56. Van Bunnen Y, Delcour C, Wery D, Richoz B, Struyven J. Intravenous digital subtraction angiography. A criteria of brain death. Ann Radiol. 1989;32(4):279-81.
57. Vatne K, Nakstad P, Lundar T. Digital subtraction angiography (DSA) in the evaluation of brain death. A comparison of conventional cerebral angiography with intravenous and intraarterial DSA. Neuroradiology. 1985;27:155-7.
58. Wieler H, Marohl K, Kaiser KP, Klwaki P, Frossler H. Tc-99m HMPAO cerebral scintigraphy. A reliable, noninvasive method for determination of brain death. Clinical Nuclear Medicine. 1993;18(2):104-9.
59. Karantanas AH, Hadjigeorgiou GM, Paterakis K, Sfiras D, Komnos A. Contribution of MRI and MR angiography in early diagnosis of brain death. Eur Radiol. 2002;12(11):2710-6.
60. Alexandrov AV, Sloan MA, Tegeler CH, Newell DN, Lumsden A, Garami Z, et al. Practice standards for transcranial Doppler (TCD) ultrasound. Part II. Clinical indications and expected outcomes. J Neuroimaging. 2012;22(3):215-24.
61. Alexandrov AV, Sloan MA, Wong LK, Douville C, Razumovsky AY, Koroshetz WJ, et al. Practice standards for transcranial Doppler ultrasound: part I--test performance. J Neuroimaging. 2007;17(1):11-8.

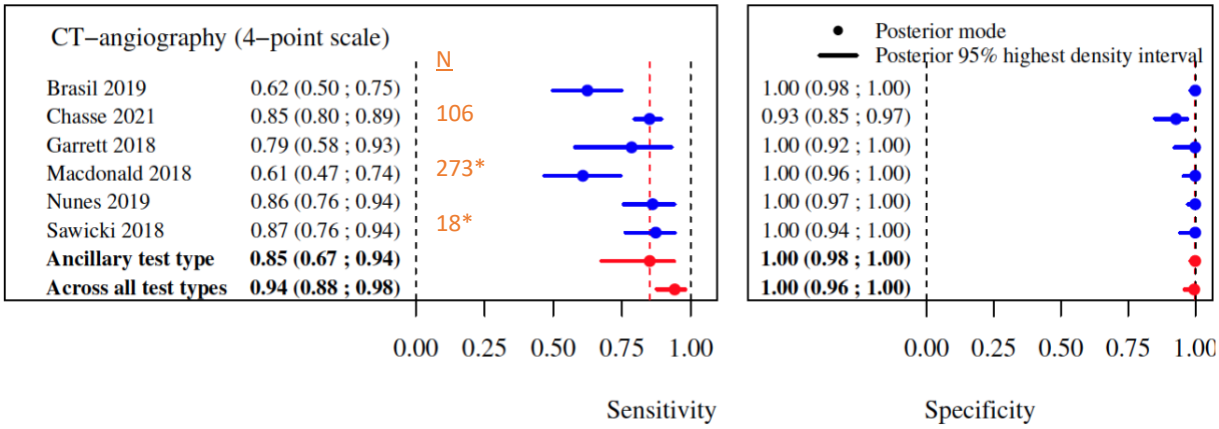
Summary Table

Ancillary test	Studies/Patients	Lay Language Outcome	Effect		Certainty of evidence
			Sensitivity/Specificity with 95% highest density interval (95% HDI)	Effect per 1000 patients assuming a pre-test probability of 95%	
Tests based on brain circulation					
Four-vessel angiography	Based on data from 951 patients in 21 studies	Not declaring someone dead although they are death	Sensitivity: 0.93 (0.88-0.96)	False negatives: 66 (38 to 114)	**Very low** (risk of bias, indirectness, inconsistency)
		Declaring someone dead although they are not dead	Specificity: Not calculated, as no studies had patients that were alive.	False positives: N/A	**N/A**
CT-angiography (4-point scale)	Based on data from 576 patients in 6 studies	Not declaring someone dead although they are death	Sensitivity: 0.85 (0.67-0.94)	False negatives: 142 (57 to 313)	**Very low** (risk of bias, indirectness, inconsistency, imprecision)
		Declaring someone dead although they are not dead	Specificity: 1.00 (0.98-1.00)	False positives: 0 (0 to 1)	**Low** (risk of bias, indirectness)
CT-angiography (7-point scale)	Based on data from 352 patients in 3 studies	Not declaring someone dead although they are death	Sensitivity: 0.91 (0.73-0.98)	False negatives: 86 (19 to 256)	**Very low** (risk of bias, indirectness, inconsistency, imprecision)
		Declaring someone dead although they are not dead	Specificity: 1.00 (0.95-1.00)	False positives: 0 (0 to 2)	**Low** (risk of bias, indirectness)
CT-angiography (10-point scale)	Based on data from 327 patients in 2 studies	Not declaring someone dead although they are death	Sensitivity: 0.89 (0.62-0.98)	False negatives: 105 (19 to 361)	**Low** (inconsistency, imprecision)
		Declaring someone dead although they are not dead	Specificity: 1.00 (0.95-1.00)	False positives: 0 (0 to 2)	**Moderate** (inconsistency)
MRI with time-of-flight angiography	Based on data from 30 patients in 1 study	Not declaring someone dead although they are death	Sensitivity: 0.98 (0.81-1.00)	False negatives: 19 (0 to 180)	**Very low** (risk of bias, indirectness, imprecision)
		Declaring someone dead although they are not dead	Specificity: 1.00 (0.76-1.00)	False positives: 0 (0 to 12)	**Very low** (risk of bias, indirectness, imprecision)
99m Tc pertechnetate angiography	Based on data from 254 patients in 2 studies	Not declaring someone dead although they are death	Sensitivity: 0.99 (0.93-1.00)	False negatives: 9 (0 to 66)	**Low** (risk of bias, indirectness)
		Declaring someone dead although they are not dead	Specificity: 0.99 (0.55-1.00)	False positives: 0 (0 to 22)	**Very low** (risk of bias, indirectness, inconsistency, imprecision)
Transcranial Doppler ultrasound	Based on data from 1108 patients in 20 studies	Not declaring someone dead although they are death	Sensitivity: 0.96 (0.92-0.98)	False negatives: 38 (19 to 76)	**Very low** (risk of bias, indirectness, inconsistency)
		Declaring someone dead although they are not dead	Specificity: 0.99 (0.97-1.00)	False positives: 0 (0 to 1)	**Low** (risk of bias, indirectness)

Ancillary test	Studies/Patients	Lay Language Outcome	Effect		Certainty of evidence
			Sensitivity/Specificity with 95% highest density interval (95% HDI)	Effect per 1000 patients assuming a pre-test probability of 95%	
Tests based on brain perfusion					
CT-perfusion	Based on data from 313 patients in 2 studies	Not declaring someone dead although they are death	Sensitivity: 0.97 (0.88-1.00)	False negatives: 28 (0 to 114)	**Moderate** (inconsistency)
		Declaring someone dead although they are not dead	Specificity: 0.99 (0.84-1.00)	False positives: 0 (0 to 8)	**Moderate** (inconsistency, imprecision)
99m Tc HMPAO with SPECT	Based on data from 76 patients in 2 studies	Not declaring someone dead although they are death	Sensitivity: 0.91 (0.64-0.99)	False negatives: 86 (9 to 342)	**Very low** (risk of bias, inconsistency, imprecision)
		Declaring someone dead although they are not dead	Specificity: 1.00 (0.97-1.00)	False positives: 0 (0 to 1)	**Low** (risk of bias, imprecision)
99m Tc HMPAO without SPECT	Based on data from 93 patients in 3 studies	Not declaring someone dead although they are death	Sensitivity: 0.92 (0.71-0.98)	False negatives: 76 (19 to 275)	**Very low** (risk of bias, indirectness, inconsistency, imprecision)
		Declaring someone dead although they are not dead	Specificity: 1.00 (0.96-1.00)	False positives: 0 (0 to 2)	**Very low** (risk of bias, indirectness, imprecision)
Tests based on neurophysiological function					
Electroencephalography	Based on data from 264 patients in 5 studies	Not declaring someone dead although they are death	Sensitivity: 0.92 (0.79-0.98)	False negatives: 76 (19 to 199)	**Very low** (risk of bias, indirectness, inconsistency, imprecision)
		Declaring someone dead although they are not dead	Specificity: 1.00 (0.97-1.00)	False positives: 0 (0 to 1)	**Low** (risk of bias, indirectness)
Brainstem auditory evoked potentials	Based on data from 98 patients in 3 studies	Not declaring someone dead although they are death	Sensitivity: 1.00 (0.97-1.00)	False negatives: 0 (0 to 28)	**Low** (risk of bias, indirectness)
		Declaring someone dead although they are not dead	Specificity: 0.80 (0.13-0.99)	False positives: 10 (0 to 43)	**Very low** (risk of bias, indirectness, inconsistency, imprecision)

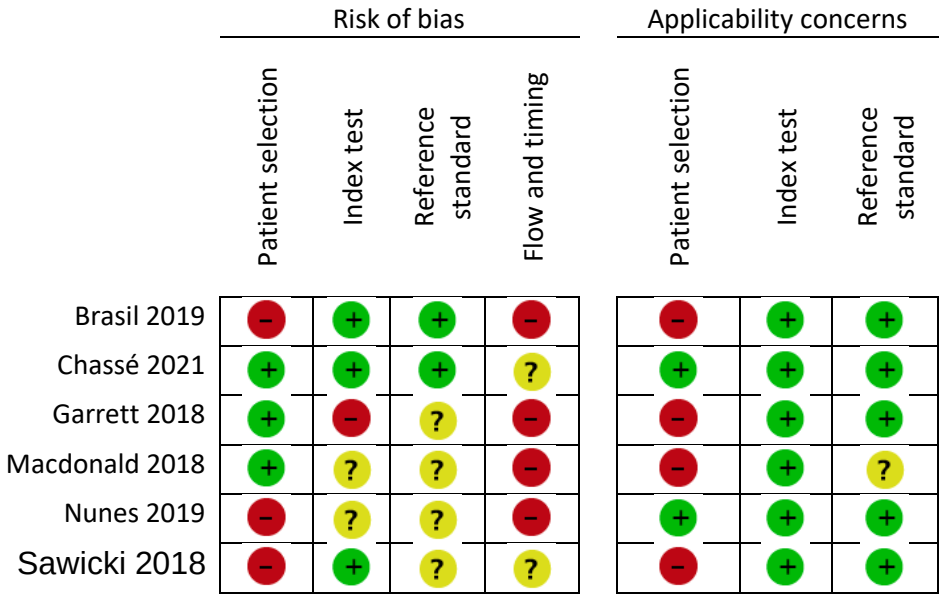
CT-angiography (4-point scale)

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



CT-angiography (4-point scale)

Sensitivity	0.85 (95% CI: 0.67 to 0.94)
Specificity	1.00 (95% CI: 0.98 to 1.00)

Prevalences	50%	90%	95%

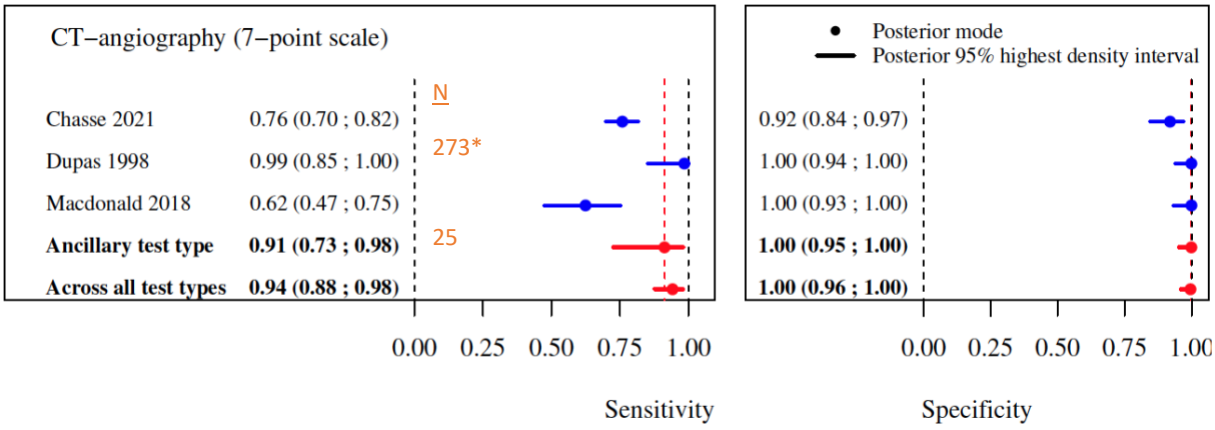
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	6 studies 576 patients [1-6]	cohort (3) & case-control (3) type studies	serious[a]	serious[b]	serious[c]	serious[d]	Total number of patients with DNC ("dead"): 413	425 (335 to 470)	765 (603 to 846)	808 (637 to 893)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)							Total TP: 325 Total FN: 88	75 (30 to 165)	135 (54 to 297)	142 (57 to 313)	
True negatives (patients without death by neurologic criteria)	6 studies 576 patients [1-6]	cohort (3) & case-control (3) type studies	serious[a]	serious[b]	not serious	not serious	Total number of patients without DNC ("not dead"): 163	500 (490 to 500)	100 (98 to 100)	50 (49 to 50)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having death by neurologic criteria)							Total TN: 156 Total FP: 7	0 (0 to 10)	0 (0 to 2)	0 (0 to 1)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns in many studies regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.
d. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

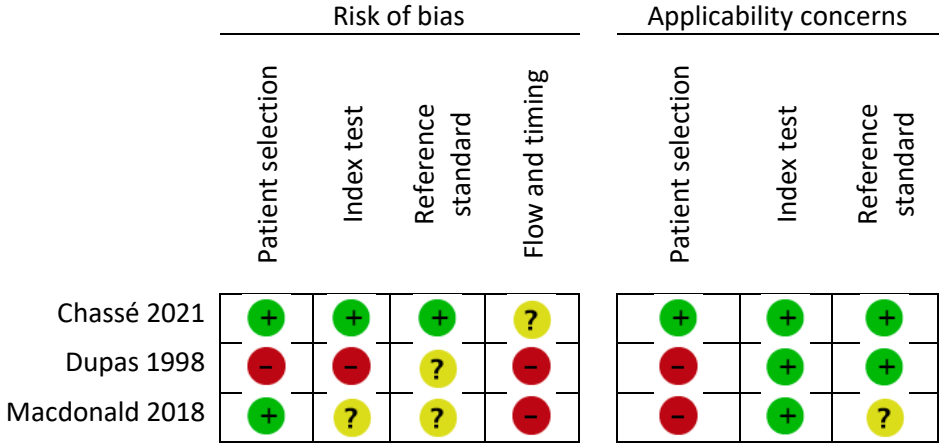
CT-angiography (7-point scale)

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



CT-angiography (7-point scale)

Sensitivity	0.91 (95% CI: 0.73 to 0.98)
Specificity	1.00 (95% CI: 0.95 to 1.00)

Prevalences	50%	90%	95%

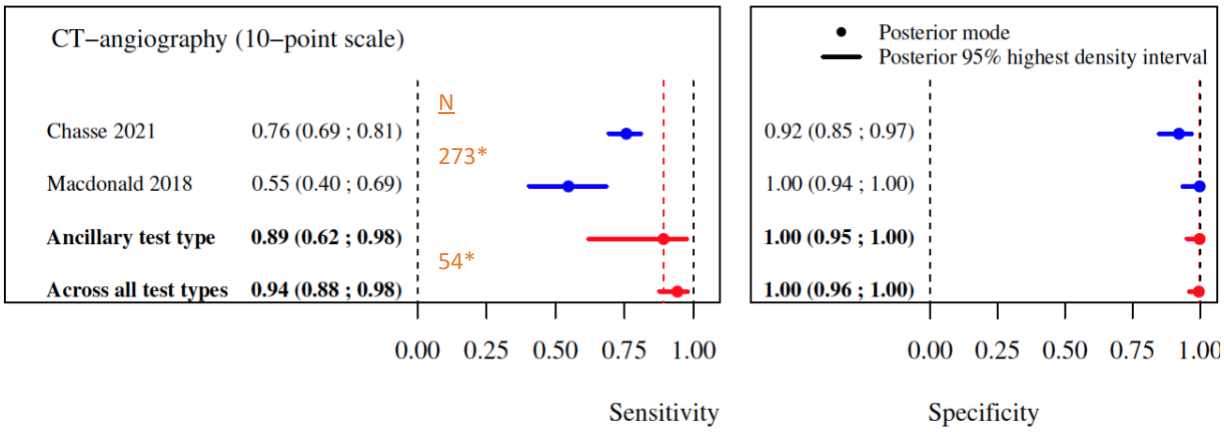
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	3 studies 352 patients [2, 4, 7]	cohort (2) & case-control (1) type studies	serious[a]	serious[b]	serious[c]	serious[d]	Total number of patients with DNC ("dead"): 259 Total TP: 192 Total FN: 67	455 (365 to 490)	819 (657 to 882)	864 (694 to 931)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								45 (10 to 135)	81 (18 to 243)	86 (19 to 256)	
True negatives (patients without death by neurologic criteria)	3 studies 352 patients [2, 4, 7]	cohort (2) & case-control (1) type studies	serious[a]	serious[b]	not serious	not serious	Total number of patients without DNC ("not dead"): 93 Total TN: 86 Total FP: 7	500 (475 to 500)	100 (95 to 100)	50 (48 to 50)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having death by neurologic criteria)								0 (0 to 25)	0 (0 to 5)	0 (0 to 2)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns in many studies regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.
d. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

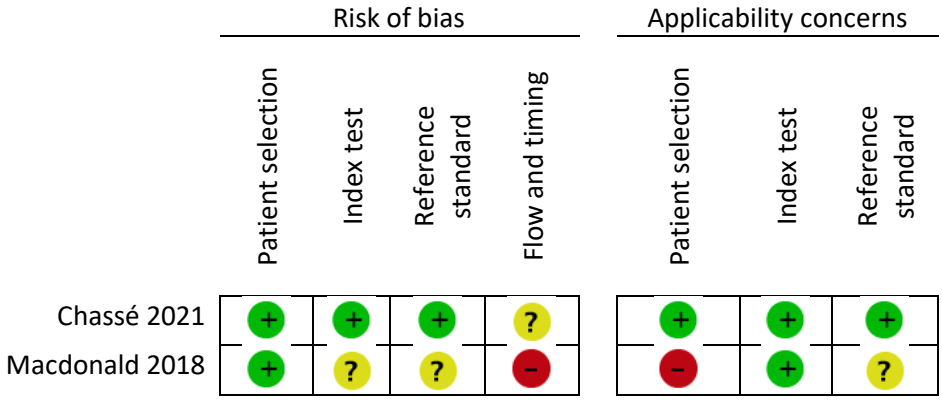
CT-angiography (10-point scale)

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



CT-angiography (10-point scale)

Sensitivity	0.89 (95% CI: 0.62 to 0.98)
Specificity	1.00 (95% CI: 0.95 to 1.00)

Prevalences	50%	90%	95%

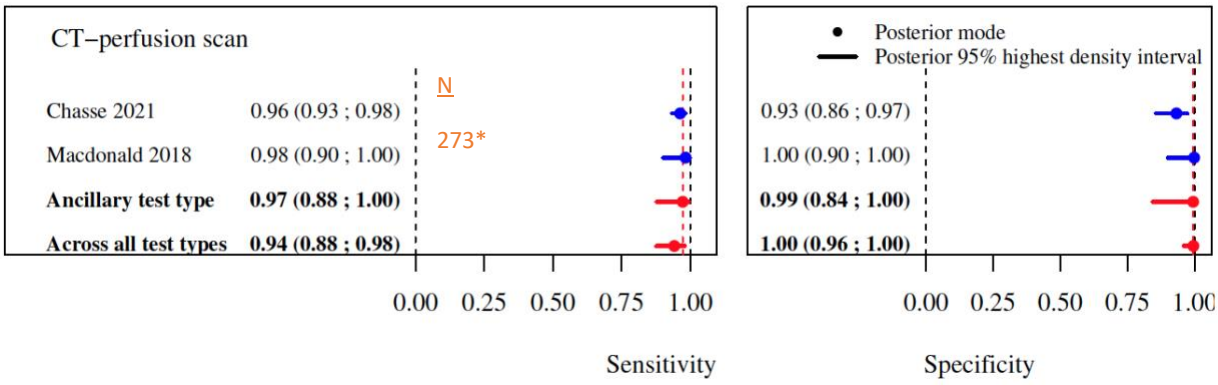
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	2 studies 327 patients [2, 4]	cross-sectional (cohort type accuracy study)	not serious	not serious	serious[b]	serious[d]	Total number of patients with DNC ("dead"): 245 Total TP: 174 Total FN: 71	445 (310 to 490)	801 (558 to 882)	845 (589 to 931)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								55 (10 to 190)	99 (18 to 342)	105 (19 to 361)	
True negatives (patients without death by neurologic criteria)	2 studies 327 patients [2, 4]	cross-sectional (cohort type accuracy study)	not serious	not serious	serious[c]	not serious	Total number of patients without DNC ("not dead"): 82 Total TN: 75 Total FP: 7	500 (475 to 500)	100 (95 to 100)	50 (48 to 50)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having death by neurologic criteria)								0 (0 to 25)	0 (0 to 5)	0 (0 to 2)	

Explanations

a. We rated down for indirectness since there were concerns regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
b. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.
c. We rated down for inconsistency since results from the high methodological quality study have not been replicated.
d. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

CT-perfusion

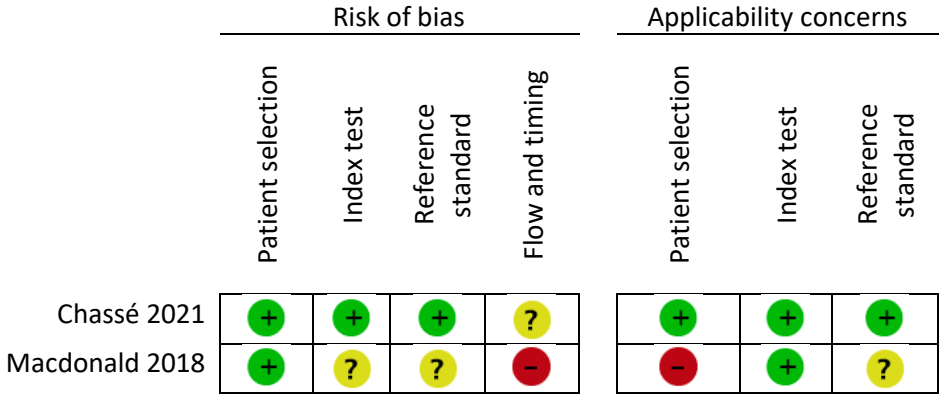
Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Results are based on the “whole-brain” criterion.

Risk of bias (QUADAS-2)



CT-perfusion

Sensitivity	0.97 (95% CI: 0.88 to 1.00)
Specificity	0.99 (95% CI: 0.84 to 1.00)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	2 studies 313 patients [2, 4]	cross-sectional (cohort type accuracy study)	not serious	not serious	serious[a]	not serious	Total number of patients with DNC ("dead"): 231 Total TP: 222 Total FN: 9	485 (440 to 500)	873 (792 to 900)	922 (836 to 950)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having death by neurologic criteria)								15 (0 to 60)	27 (0 to 108)	28 (0 to 114)	
True negatives (patients without death by neurologic criteria)	2 studies 313 patients [2, 4]	cross-sectional (cohort type accuracy study)	not serious	not serious	serious[a]	serious[b]	Total number of patients without DNC ("not dead"): 82 Total TN: 76 Total FP: 6 *	495 (420 to 500)	99 (84 to 100)	50 (42 to 50)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having death by neurologic criteria)								5 (0 to 80)	1 (0 to 16)	0 (0 to 8)	

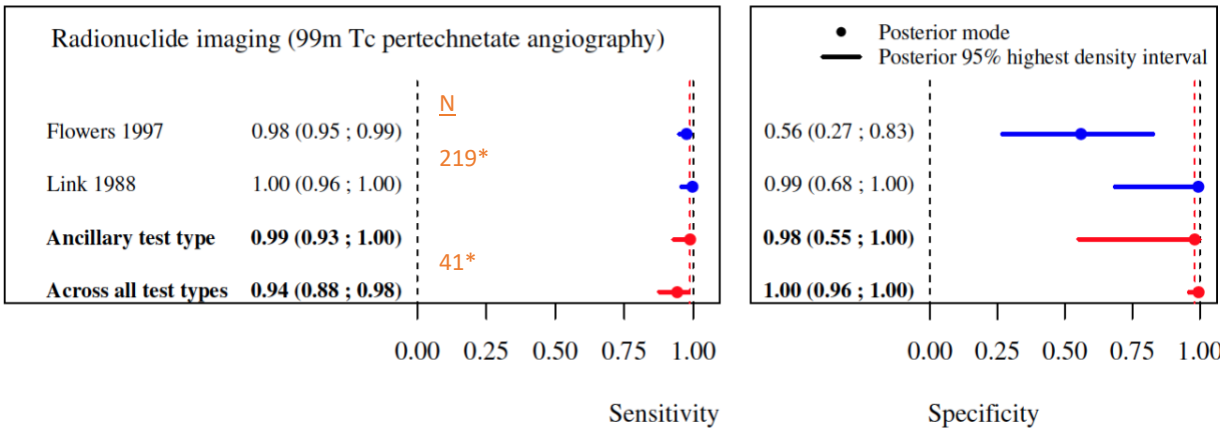
Explanations

a. We rated down for inconsistency since results from the study with high methodological quality have not been replicated.
b. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

** Exploratory findings in the 6 FP in Chassé 2021: 1 with contralateral miosis with cold water, 2 atypical movements, 1 potential auto-trigger?, 1 cough, 1 breathing at apnea test on t-tube*

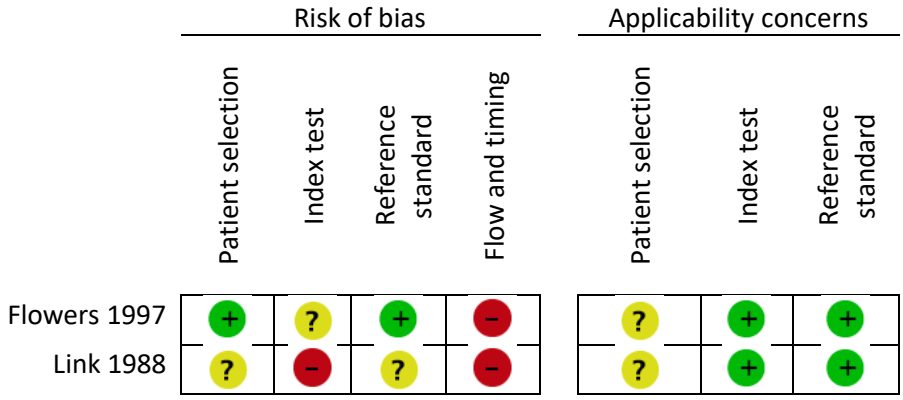
Radionuclide imaging (99m Tc pertechnetate angiography)

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Radionuclide imaging (99m Tc pertechnetate angiography)

Sensitivity	0.99 (95% CI: 0.93 to 1.00)
Specificity	0.99 (95% CI: 0.55 to 1.00)

Prevalences	50%	90%	95%

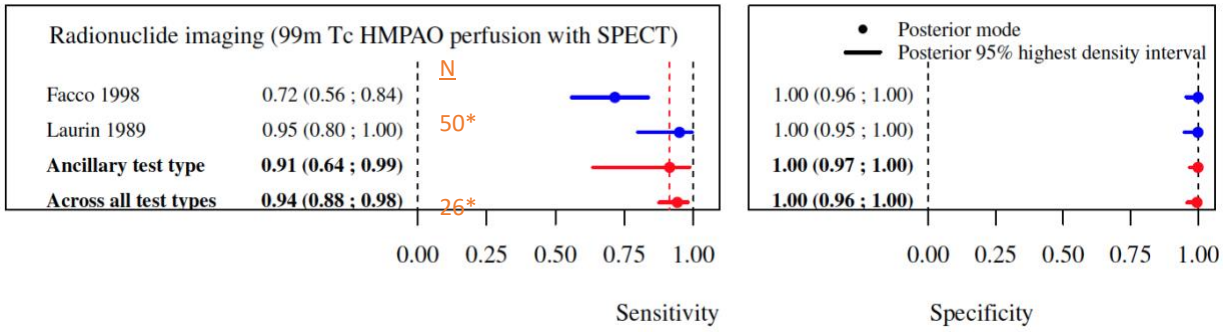
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	2 studies 254 patients [8, 9]	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	not serious	Total number of patients with DNC ("dead"): 241 Total TP: 235 Total FN: 6	495 (465 to 500)	891 (837 to 900)	941 (884 to 950)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								5 (0 to 30)	9 (0 to 63)	9 (0 to 66)	
True negatives (patients without death by neurologic criteria)	2 studies 254 patients [8, 9]	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	Total number of patients without DNC ("not dead"): 13 Total TN: 8 Total FP: 5	495 (275 to 500)	99 (55 to 100)	50 (28 to 50)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having death by neurologic criteria)								5 (0 to 225)	1 (0 to 45)	0 (0 to 22)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.

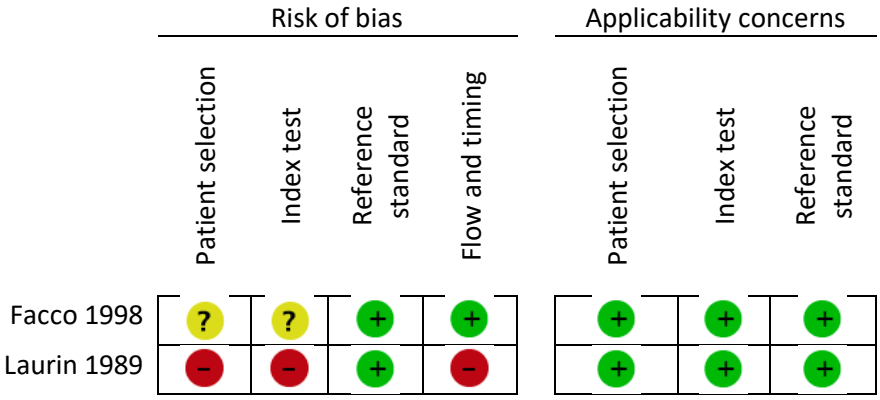
Radionuclide imaging (99m Tc HMPAO with SPECT)

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Radionuclide imaging (99m Tc HMPAO perfusion with SPECT)

Sensitivity	0.91 (95% CI: 0.64 to 0.99)
Specificity	1.00 (95% CI: 0.97 to 1.00)

Prevalences	50%	90%	95%

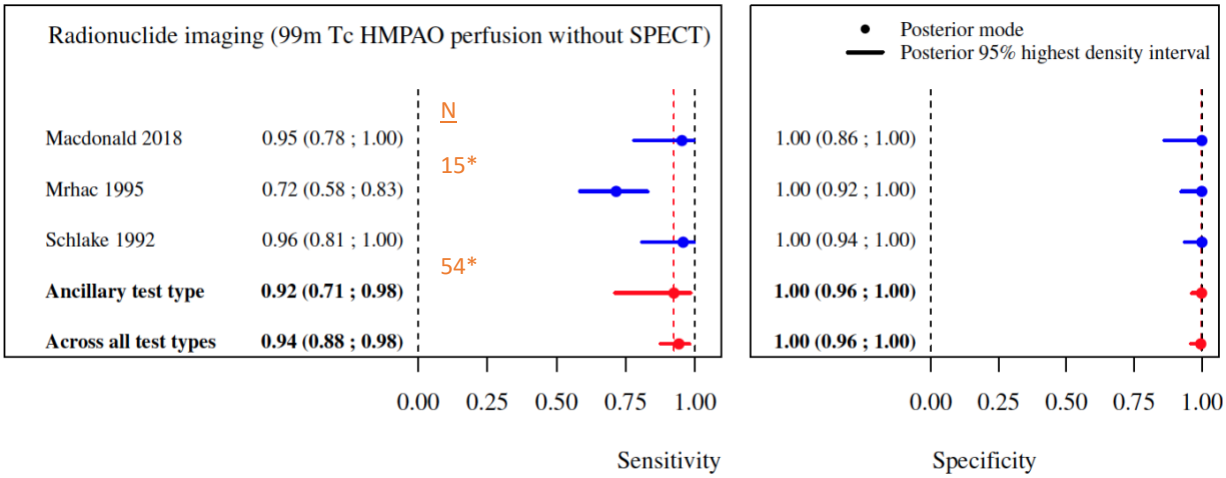
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	2 studies 76 patients [10, 11]	cross-sectional (cohort type accuracy study)	serious[a]	not serious	serious[b]	serious[c]	Total number of patients with DNC ("dead"): 55 Total TP: 42 Total FN: 13	455 (320 to 495)	819 (576 to 891)	864 (608 to 941)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								45 (5 to 180)	81 (9 to 324)	86 (9 to 342)	
True negatives (patients without death by neurologic criteria)	2 studies 76 patients [10, 11]	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[d]	Total number of patients without DNC ("not dead"): 21 Total TN: 21 Total FP: 0	500 (485 to 500)	100 (97 to 100)	50 (49 to 50)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having death by neurologic criteria)								0 (0 to 15)	0 (0 to 3)	0 (0 to 1)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.
c. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.
d. We rated down to the limited number of patients included in the meta-analysis estimate.

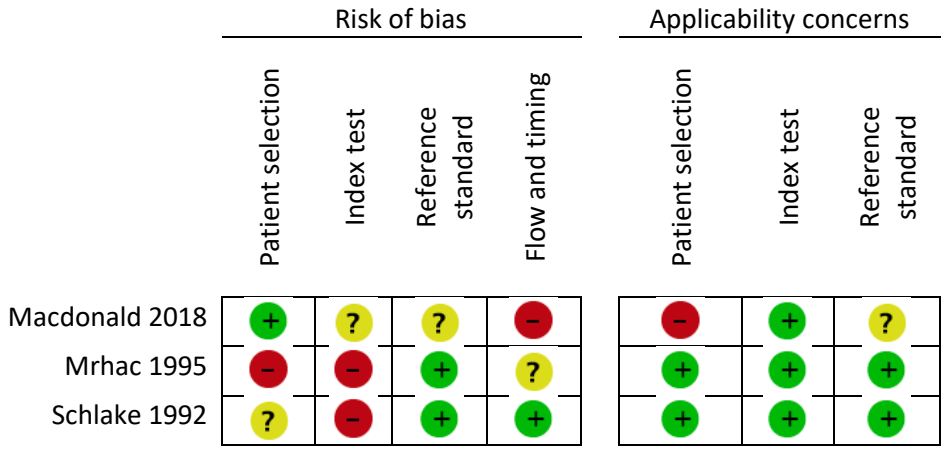
Radionuclide imaging (99m Tc HMPAO without SPECT)

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Radionuclide imaging (99m Tc HMPAO perfusion without SPECT)

Sensitivity	0.92 (95% CI: 0.71 to 0.98)
Specificity	1.00 (95% CI: 0.96 to 1.00)

Prevalences	50%	90%	95%

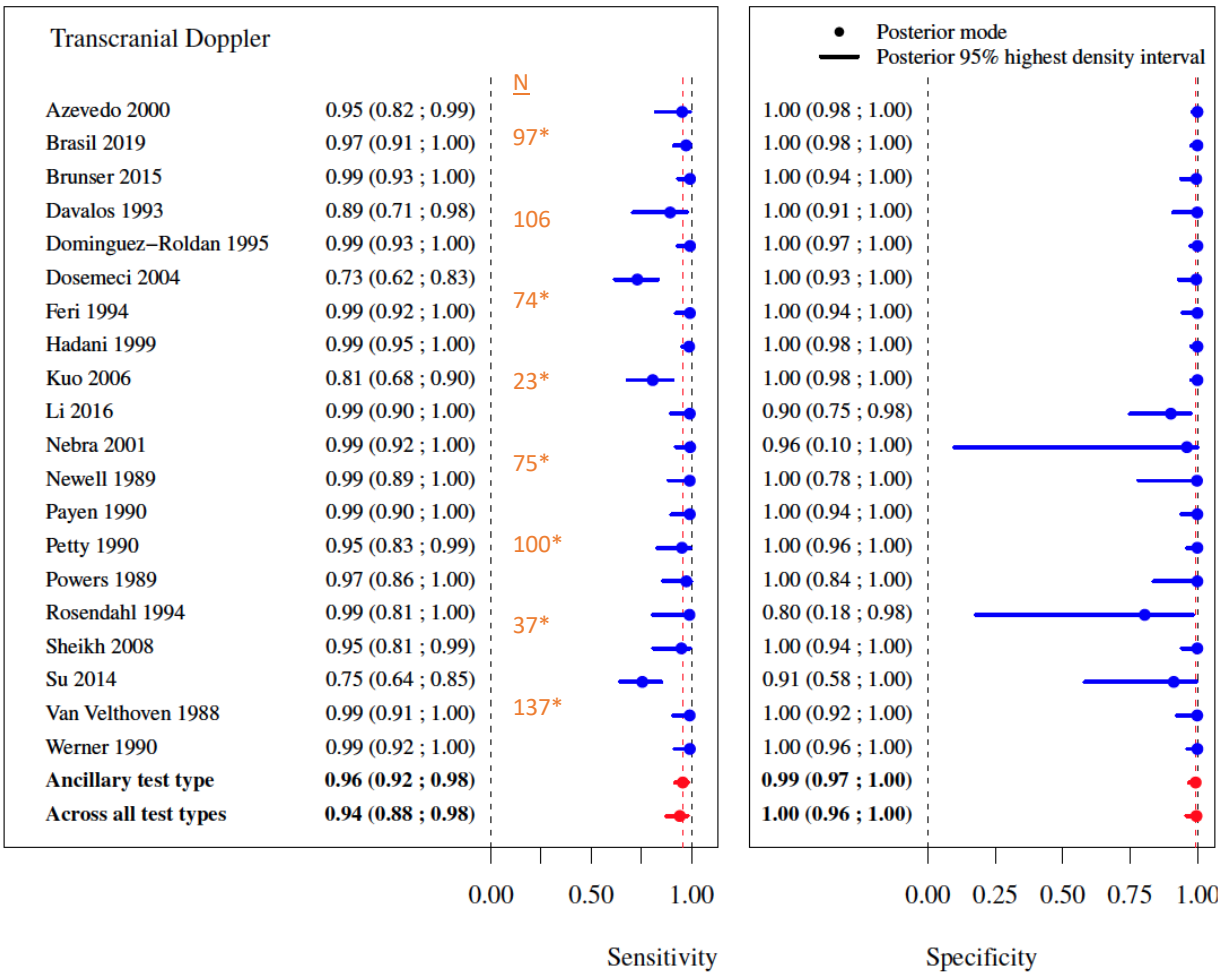
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	3 studies 93 patients [4, 12, 13]	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	serious[d]	Total number of patients with DNC ("dead"): 80 Total TP: 63 Total FN: 17	460 (355 to 490)	828 (639 to 882)	874 (675 to 931)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								40 (10 to 145)	72 (18 to 261)	76 (19 to 275)	
True negatives (patients without death by neurologic criteria)	3 studies 93 patients [4, 12, 13]	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	serious[d]	Total number of patients without DNC ("not dead"): 13 Total TN: 13 Total FP: 0	500 (480 to 500)	100 (96 to 100)	50 (48 to 50)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having death by neurologic criteria)								0 (0 to 20)	0 (0 to 4)	0 (0 to 2)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.
d. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

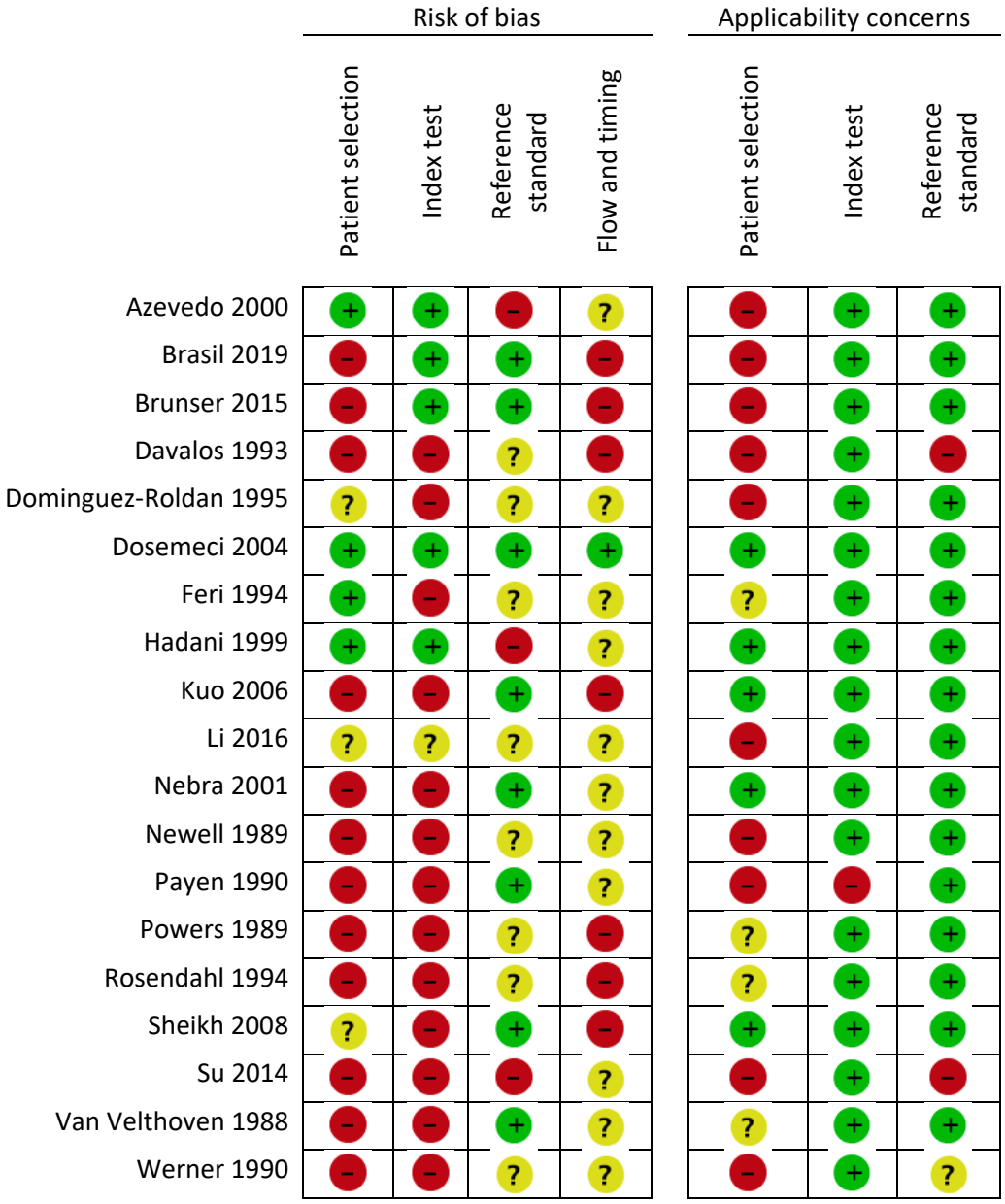
Transcranial Doppler

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Transcranial Doppler

Sensitivity	0.96 (95% CI: 0.92 to 0.98)
Specificity	0.99 (95% CI: 0.97 to 1.00)

Prevalences	50%	90%	95%

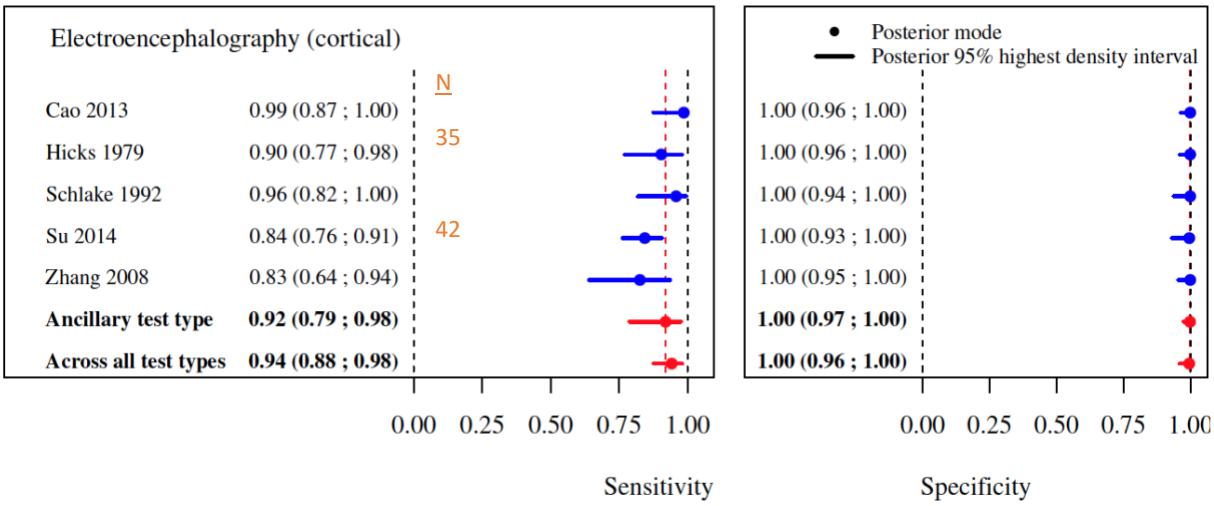
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	20 studies 1108 patients [1, 14-32]	cohort (18) & case-control (2) type studies	serious[a]	serious[b]	serious[c]	not serious	Total number of patients with DNC ("dead"): 584 Total TP: 526 Total FN: 58	480 (460 to 490)	864 (828 to 882)	912 (874 to 931)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								20 (10 to 40)	36 (18 to 72)	38 (19 to 76)	
True negatives (patients without death by neurologic criteria)	20 studies 1108 patients [1, 14-32]	cohort (18) & case-control (2) type studies	serious[a]	serious[b]	not serious	not serious	Total number of patients without DNC ("not dead"): 524 Total TN: 513 Total FP: 11	495 (485 to 500)	99 (97 to 100)	50 (49 to 50)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having death by neurologic criteria)								5 (0 to 15)	1 (0 to 3)	0 (0 to 1)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for inconsistency since studies with the largest samples deviated the most from the pooled estimates.

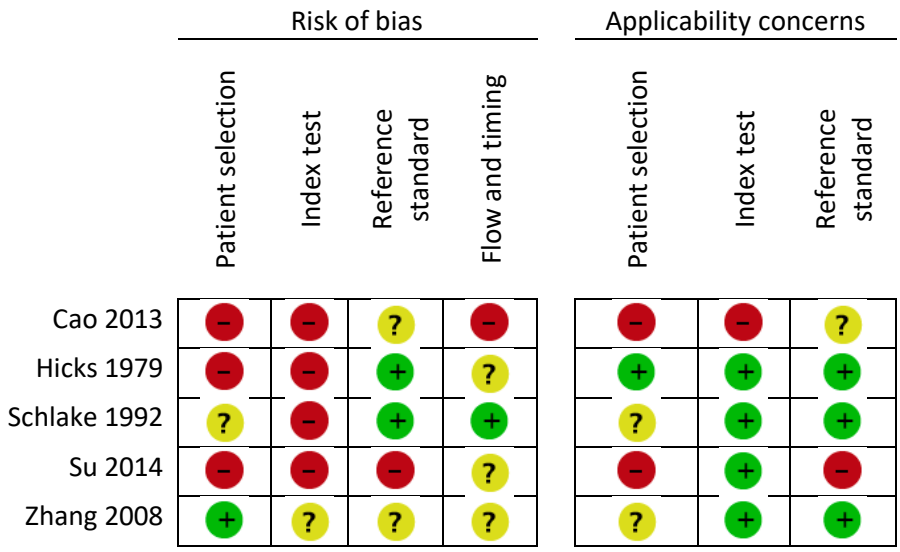
Electroencephalography

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Electroencephalography

Sensitivity	0.92 (95% CI: 0.79 to 0.98)
Specificity	1.00 (95% CI: 0.97 to 1.00)

Prevalences	50%	90%	95%

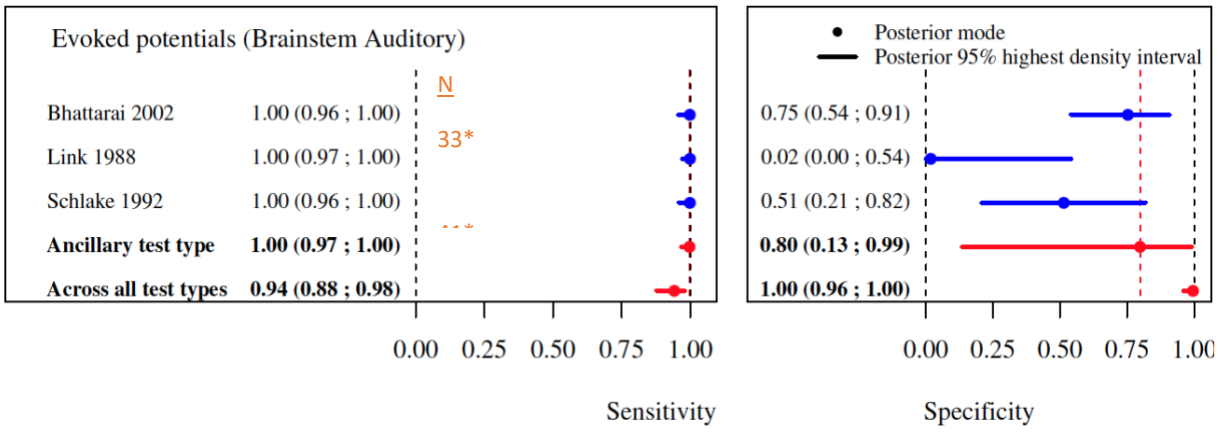
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	5 studies 264 patients [13, 30, 33-35]	cohort (3) & case-control (2) type studies	serious[a]	serious[b]	serious[c]	serious[d]	Total number of patients with DNC ("dead"): 175 Total TP: 150 Total FN: 25	460 (395 to 490)	828 (711 to 882)	874 (751 to 931)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								40 (10 to 105)	72 (18 to 189)	76 (19 to 199)	
True negatives (patients without death by neurologic criteria)	5 studies 264 patients [13, 30, 33-35]	cohort (3) & case-control (2) type studies	serious[a]	serious[b]	not serious	not serious	Total number of patients without DNC ("not dead"): 89 Total TN: 88 Total FP: 1	500 (485 to 500)	100 (97 to 100)	50 (49 to 50)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having death by neurologic criteria)								0 (0 to 15)	0 (0 to 3)	0 (0 to 1)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.
d. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

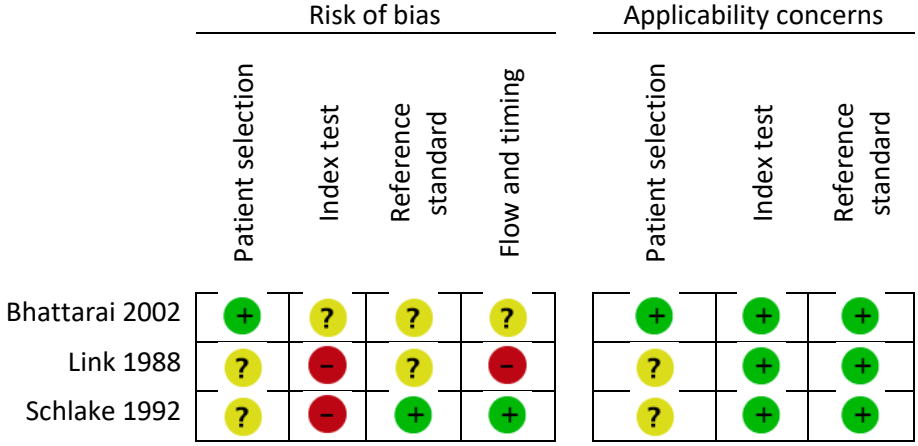
Brainstem auditory evoked potentials

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Brainstem auditory evoked potentials

Sensitivity	1.00 (95% CI: 0.97 to 1.00)
Specificity	0.80 (95% CI: 0.13 to 0.99)

Prevalences	50%	90%	95%

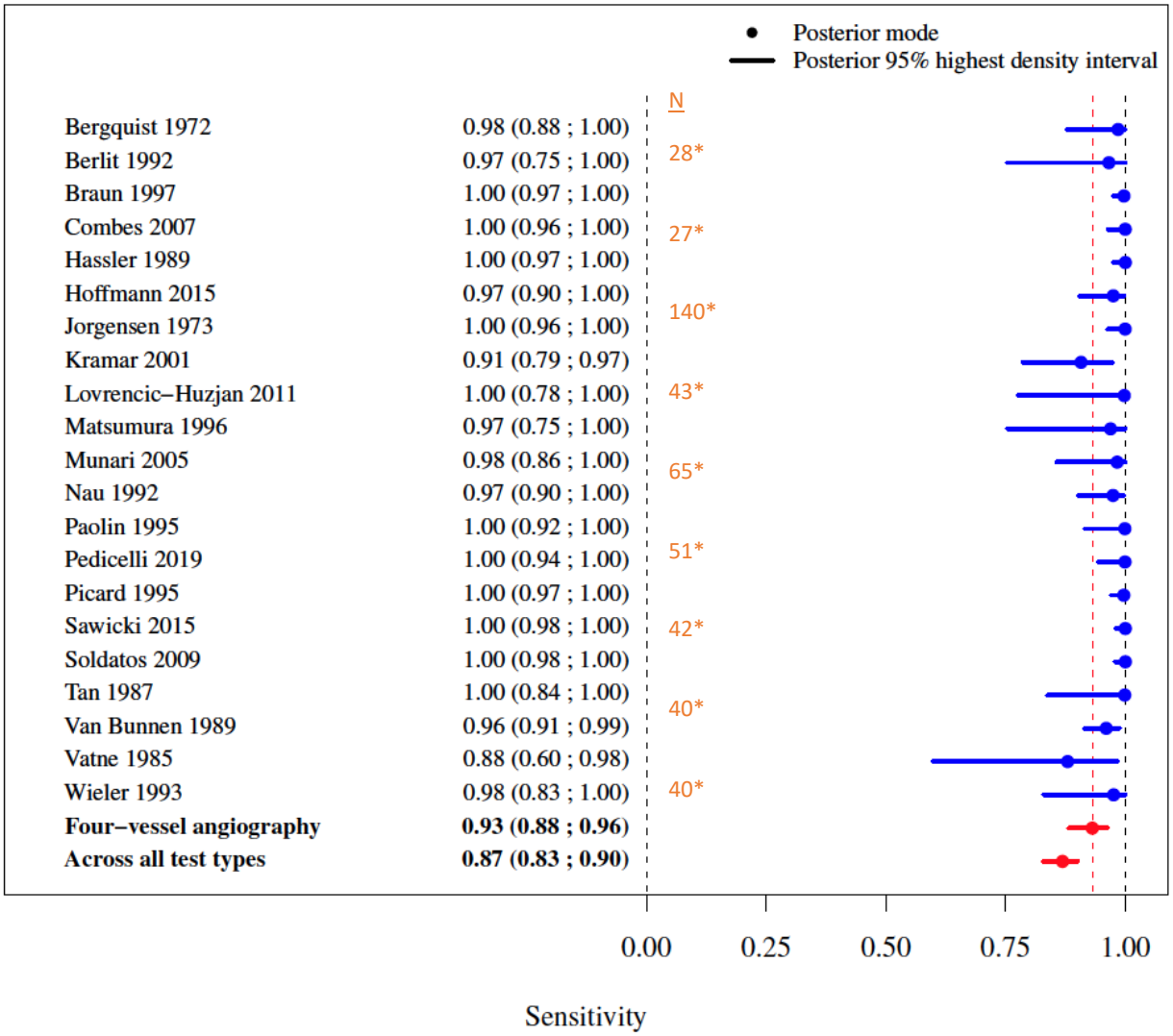
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	3 studies 98 patients [9, 13, 36]	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	not serious	Total number of patients with DNC ("dead"): 68 Total TP: 68 Total FN: 0	500 (485 to 500)	900 (873 to 900)	950 (922 to 950)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								0 (0 to 15)	0 (0 to 27)	0 (0 to 28)	
True negatives (patients without death by neurologic criteria)	3 studies 98 patients [9, 13, 36]	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	very serious[d]	Total number of patients without DNC ("not dead"): 30 Total TN: 18 Total FP: 12	400 (65 to 495)	80 (13 to 99)	40 (7 to 50)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having death by neurologic criteria)								100 (5 to 435)	20 (1 to 87)	10 (0 to 43)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.
d. We rated down for imprecision since the pooled estimate's highest density intervals were very wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

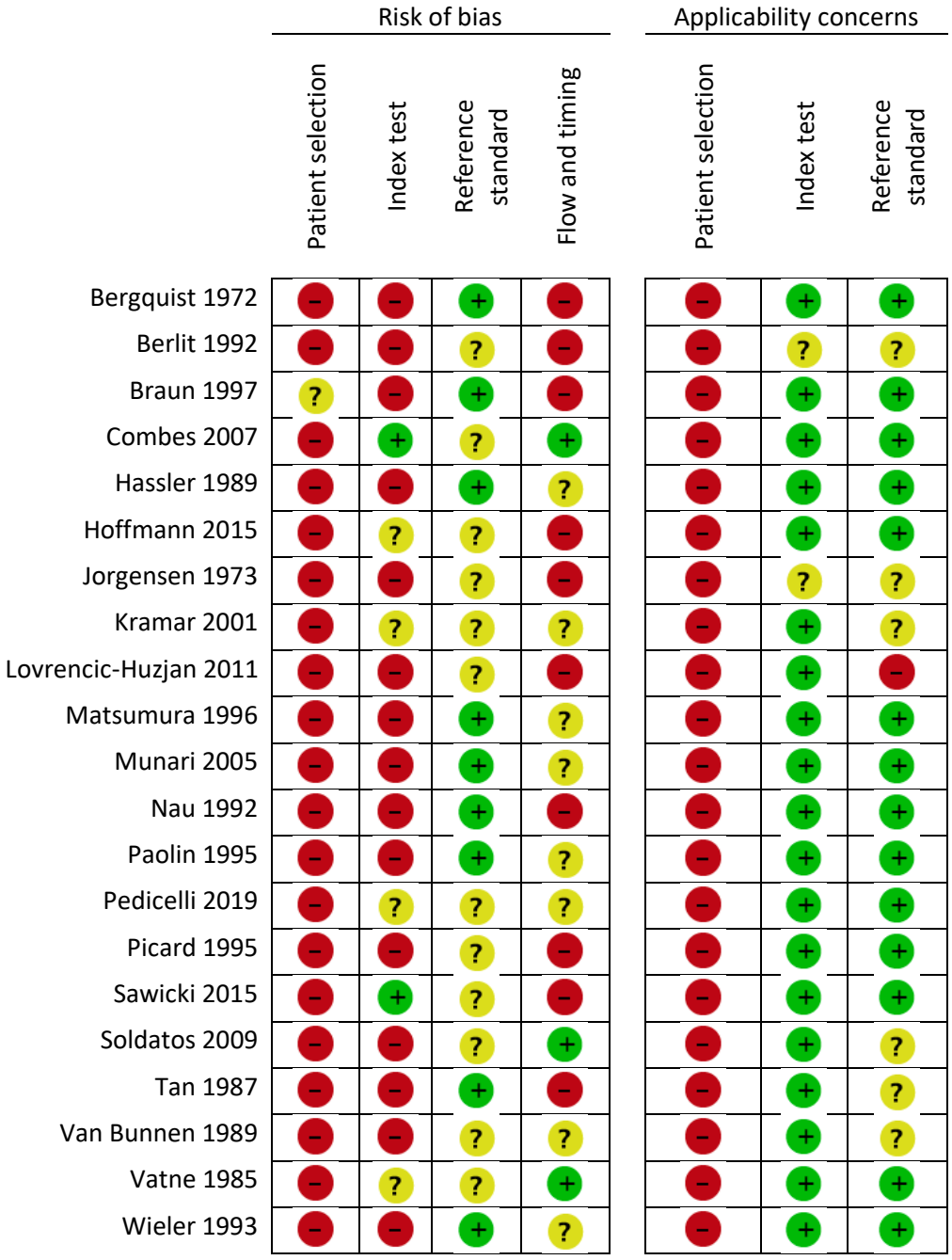
Four-vessel angiography

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Four-vessel angiography

Sensitivity	0.93 (95% CI: 0.88 to 0.96)
Specificity	-- (95% CI: -- to --)

Prevalences	50%	90%	95%

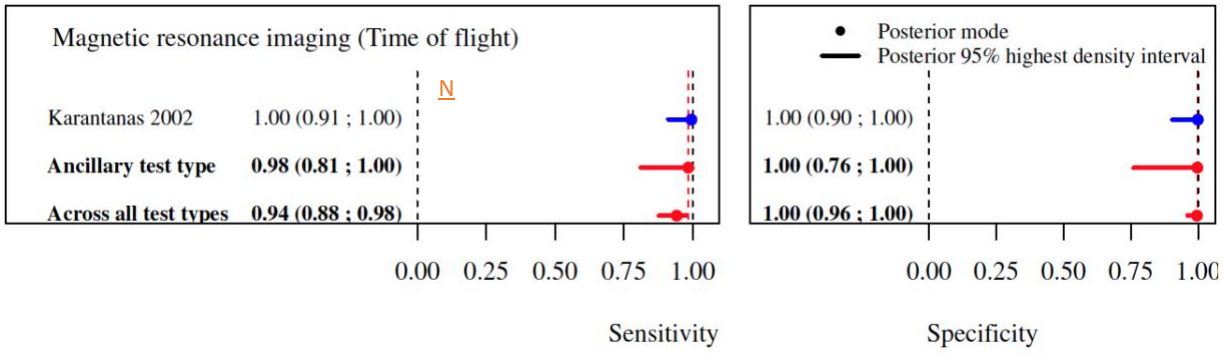
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	21 studies 951 patients [37-57]	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[c]	not serious	Total number of patients with DNC ("dead"): 951 Total TP: 929 Total FN: 22	465 (440 to 480)	837 (792 to 864)	884 (836 to 912)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								35 (20 to 60)	63 (36 to 108)	66 (38 to 114)	
True negatives (patients without death by neurologic criteria)	0 studies 0 patients	-	-	-	-	-	-	-	-	-	-
False positives (patients incorrectly classified as having death by neurologic criteria)								-	-	-	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since studies only included patients with the condition of interest (death by neurologic criteria), meaning there was no assessment of specificity or the trade-off between sensitivity and specificity.
c. We rated down for inconsistency since there was significant heterogeneity in study sensitivity estimates based on funnel plot inspection.

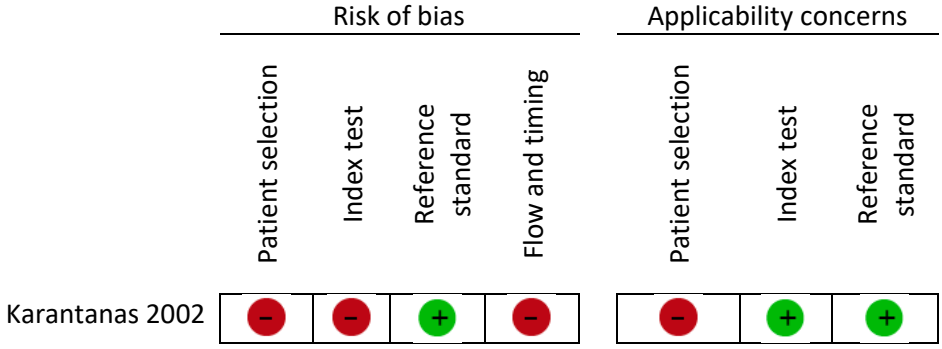
Magnetic resonance imaging with time-of-flight angiography

Meta-analysis forest plot



The total number of patients in each study is provided in orange. Studies with a cohort methodology are labeled with a star (*).

Risk of bias (QUADAS-2)



Magnetic resonance imaging with time-of-flight angiography

Sensitivity	0.98 (95% CI: 0.81 to 1.00)
Specificity	1.00 (95% CI: 0.76 to 1.00)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with death by neurologic criteria)	1 study 30 patients [58]	case-control type accuracy study	serious[a]	serious[b]	not serious	serious[c]	Total number of patients with DNC ("dead"): 20 Total TP: 20 Total FN: 0	490 (405 to 500)	882 (729 to 900)	931 (770 to 950)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having death by neurologic criteria)								10 (0 to 95)	18 (0 to 171)	19 (0 to 180)	
True negatives (patients without death by neurologic criteria)	1 study 30 patients [58]	case-control type accuracy study	serious[a]	serious[b]	not serious	serious[c]	Total number of patients without DNC ("not dead"): 10 Total TN: 10 Total FP: 0	500 (380 to 500)	100 (76 to 100)	50 (38 to 50)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having death by neurologic criteria)								0 (0 to 120)	0 (0 to 24)	0 (0 to 12)	

Explanations

a. We rated down for risk of bias since most studies had high risk of bias in multiple QUADAS-2 domains sufficient to lower confidence in the estimates.
b. We rated down for indirectness since there were concerns regarding applicability regarding patient selection (namely, that the study population was not representative of the target population).
c. We rated down for imprecision since the pooled estimate's highest density intervals were wide and ranged from values supporting recommendation of this test to values not supporting recommendation of this test.

References

1. Brasil S, Bor-Seng-Shu E, de-Lima-Oliveira M, Taccone FS, Gattas G, Nunes DM, et al. Computed tomography angiography accuracy in brain death diagnosis. *J Neurosurg*. 2019:1-9.
2. Chassé M, Shankar J, Titova P, editors. Improving Neurological Diagnostic Death Evaluation : a prospective Canadian multicenter diagnostic test study – Preliminary results. Canadian Critical Care Forum; 2021; Canada.
3. Garrett MP, Williamson RW, Bohl MA, Bird CR, Theodore N. Computed tomography angiography as a confirmatory test for the diagnosis of brain death. *J Neurosurg*. 2018;128(2):639-44.
4. MacDonald D, Stewart-Perrin B, Shankar JJS. The Role of Neuroimaging in the Determination of Brain Death. *J Neuroimaging*. 2018;28(4):374-9.
5. Nunes DM, Maia ACM, Jr., Boni RC, da Rocha AJ. Impact of Skull Defects on the Role of CTA for Brain Death Confirmation. *AJNR Am J Neuroradiol*. 2019;40(7):1177-83.
6. Sawicki M, Solek-Pastuszka J, Chamier-Cieminska K, Walecka A, Bohatyrewicz R. Accuracy of Computed Tomographic Perfusion in Diagnosis of Brain Death: A Prospective Cohort Study. *Med Sci Monit*. 2018;24:2777-85.
7. Dupas B, Gayet-Delacroix M, Villers D, Antonioli D, Veccherini MF, Soulillou JP. Diagnosis of brain death using two-phase spiral CT. *AJNR Am J Neuroradiol*. 1998;19:641-7.
8. Flowers WM, Patel BR. Radionuclide angiography as a confirmatory test for brain death a review of 229 studies in 219 patients. *Southern Medical Journal*. 1997;90(11):1091-6.
9. Link J, Wagner W, Rohling R. Auditory evoked potentials and determinatin of brain death. *Klin Wochenschr*. 1988;66:62-6.
10. Facco E, Zucchetta P, Munari M, Baratto F, Behr AU, Gregianin M, et al. 99mTc-HMPAO SPECT in the diagnosis of brain death. *Intensive Care Med*. 1998;24:911-7.
11. Laurin NR, Driedger AA, Hurwitz GA, Mattar AG, Powe JE, Chamberlain MJ, et al. Cerebral perfusion imaging with technetium-99m HM-PAO in brain death and severe central nervous system injury. *J Nucl Med*. 1989;30:1627-35.
12. Mrhac L, Zakko S, Parikh Y. Brain death: The evaluation of semi-quantitative parameters and other signs in HMPAO scintigraphy. *Nuclear Medicine Communications*. 1995;16:1016-20.
13. Schlake HP, Bottger IG, Grotomeyer KH, Husstedt IW, Brandau W, Schober O. Determination of cerebral perfusion by means of planar brain scintigraphy and 99mTc-HMPAO in brain death, persistent vegetative state. *Intensive Care Med*. 1992;18:76-81.
14. Azevedo E, Teixeira J, Neves JC, Vaz R. Transcranial Doppler and Brain Death. *Transplant Proc*. 2000;32:2579-81.
15. Brunser AM, Lavados PM, Cárcamo DA, Hoppe A, Olavarría VV, López J, et al. Accuracy of Power Mode Transcranial Doppler in the Diagnosis of Brain Death. *Journal of Medical Ultrasound*. 2015;23(1):29-33.
16. Davalos A, Rodriguez-Rago A, Mate G, Molins A, Genis D, Gonzalez JL, et al. Value of the transcranial Doppler examination in the diagnosis of brain death. *Med Clin (Barc)*. 1993;100:249-52.
17. Dominguez-Roldan JM, Murillo-Cabezas F, Munoz-Sanchez A, Santamaria-Mifsut JL, Villen-Nieto J. Changes in the Doppler waveform of intracranial arteries in patients with brain-death status. *Transplant Proc*. 1995;27(4):2391-2.
18. Dosemeci L, Dora B, Yilmaz M, Cengiz M, Balkan S, Ramazanoglu A. Utility of transcranial doppler ultrasonography for confirmatory diagnosis of brain death: two sides of the coin. *Transplantation*. 2004;77(1):71-5.
19. Feri M, Ralli L, Felici M, Vanni D, Capria V. Transcranial Doppler and brain death diagnosis. *Crit Care Med*. 1994;22(7):1120-6.

20. Hadani M, Bruk B, Ram Z, Knoller N, Spiegelmann R, Segal E. Application of transcranial doppler ultrasonography for the diagnosis of brain death. *Intensive Care Med*. 1999;25:822-8.
21. Kuo JR, Chen CF, Chio CC, Chang CH, Wang CC, Yang CM, et al. Time dependent validity in the diagnosis of brain death using transcranial Doppler sonography. *J Neurol Neurosurg Psychiatry*. 2006;77(5):646-9.
22. Li Y, Liu S, Xun F, Liu Z, Huang X. Use of Transcranial Doppler Ultrasound for Diagnosis of Brain Death in Patients with Severe Cerebral Injury. *Med Sci Monit*. 2016;22:1910-5.
23. Nebra AC, Virgos B, Santos S, Tejero C, Larraga J, Araiz JJ, et al. Clinical diagnostic of brain death and transcranial Doppler, looking for middle cerebral arteries and intracranial vertebral arteries. Agreement with scintigraphic techniques. *Rev Neurol*. 2001;33(10):916-20.
24. Newell DW, Grady MS, Sirotta P, Winn HR. Evaluation of brain death using transcranial Doppler. *Neurosurgery*. 1989;24(4):509-13.
25. Payen DM, Lamer C, Pilorget A, Moreau T, Beloucif S, Echter E. Evaluation of pulsed Doppler common carotid blood flow as a noninvasive method for brain death diagnosis a prospective study. *Anesthesiology*. 1990;72:222-9.
26. Petty GW, Mohr JP, Pedley TA, Tatemichi TK, Lennihan L, Duterte DI, et al. The role of transcranial Doppler in confirming brain death sensitivity, specificity, and suggestions for performance and interpretation. *Neurology*. 1990;40:300-3.
27. Powers AD, Graever MC, Smith RR. Transcranial Doppler ultrasonography in the determination of brain death. *Neurosurgery*. 1989;24(6):884-9.
28. Rosendahl TH, Muller C, Foran R, Cossman D, Carroll R, Ellison J, et al. Internal carotid and vertebral duplex scanning for the determination of brain death. *The Journal of Vascular Technology*. 1994;18(2):89-93.
29. Shiekh BY, Al Jihani H. Implementing transcranial Doppler as confirmatory test in brain death criteria. *Pan Arab Journal of Neurosurgery*. 2008;12(1):46-9.
30. Su Y, Yang Q, Liu G, Zhang Y, Ye H, Gao D, et al. Diagnosis of brain death confirmatory tests after clinical test. *Chin Med J*. 2014;127(7):1272-7.
31. Van Velthoven V, Calliauw L. Diagnosis of brain death. Transcranial Doppler sonography as an additional method. *Acta Neurochir (Wien)*. 1988;95:57-60.
32. Werner C, Kochs E, Rau M, Schulte am Esch J. Transcranial Doppler sonography as a supplement in the detection of cerebral circulatory arrest. *Journal of Neurosurgical Anesthesiology*. 1990;2(3):159-65.
33. Cao J, Watabe D, Zhang L, editors. An EEG diagnosis system for quasi brain death based on complexity and energy analyses. 35th Annual International Conference of the IEEE EMBS; 2013.
34. Hicks RG, Torda TA. The vestibulo-ocular (caloric) reflex in the diagnosis of cerebral death. *Anaesth Intensive Care*. 1979;7:169-73.
35. Zhang Y, Sun B, Wu XY. Spectrum analysis of the EEG in patients with brain death. *J Clin Neurol*. 2008;21(3):213-5.
36. Bhattarai BK, Kaul HL, Muralidhar V, Bhatia M. An analysis of brainstem auditory evoked potentials (BAEP) in brain death and its usefulness in the diagnosis of braint death. *J Anesth Clin Pharmacol*. 2002;18(4):397-404.
37. Bergquist E, Bergstrom K. Angiography in cerebral death. *Acta Radiologica Diagnosis*. 1972;12(3):283-8.
38. Berlit P, Wetzel E. HM-PAO cerebral blood flow scintigraphy in the manifestation stage of brain death. *Nervenarzt*. 1992;63:101-4.
39. Braun M, Ducrocq X, Huot JC, Audibert G, Anxionnat R, Picard L. Intravenous angiography in brain death report of 140 patients. *Neuroradiology*. 1997;39:400-5.

40. Combes JC, Chomel A, Ricolfi F, d'Athis P, Freysz M. Reliability of computed tomographic angiography in the diagnosis of brain death. *Transplant Proc*. 2007;39(1):16-20.
41. Hassler W, Steinmetz H, Pirschel J. Transcranial Doppler study of intracranial circulatory arrest. *J Neurosurg*. 1989;71:195-201.
42. Hoffmann O, Masuhr F. Use of Observational Periods or Ancillary Tests in the Determination of Brain Death in Germany. *Eur Neurol*. 2015;74(1-2):11-7.
43. Jorgensen PB, Jorgensen EO, Rosenklint A. Brain death pathogenesis and diagnosis. *Acta Neurol Scand*. 1973;49:355-67.
44. Kramar F, Mohapl M, Benes V. Diagnosis of brain death with TCD. *Anesteziologie a neodkladna pece*. 2001;3:145-7.
45. Lovrencic-Huzjan A, Vukovic V, Gopcevic A, Vucic M, Kriksic V, Demarin V. Transcranial Doppler in brain death confirmation in clinical practice. *Ultraschall Med*. 2011;32(1):62-6.
46. Matsumura A, Meguro K, Tsurushima H, Komatsu Y, Kikuchi Y, Wada M, et al. Magnetic resonance imaging of brain death. *Neurol Med Chir (Tokyo)*. 1996;36:166-71.
47. Munari M, Zucchetta P, Carollo C, Gallo F, De Nardin M, Marzola MC, et al. Confirmatory tests in the diagnosis of brain death: comparison between SPECT and contrast angiography. *Crit Care Med*. 2005;33(9):2068-73.
48. Nau R, Prange HW, Klingelhöfer J, Kukowski B, Sander D, Tchorsch R, et al. Results of four technical investigations in fifty clinically brain dead patients. *Intensive Care Med*. 1992;18:82-8.
49. Paolin A, Manuali A, Di Paola F, Boccaletto F, Caputo P, Zanata R, et al. Reliability in diagnosis of brain death. *Intensive Care Med*. 1995;21:657-62.
50. Pedicelli A, Bartocci M, Lozupone E, D'Argento F, Alexandre A, Garignano G, et al. The role of cervical color Doppler ultrasound in the diagnosis of brain death. *Neuroradiology*. 2019;61(2):137-45.
51. Picard L, Braun M, Anxionnat R, Claise B, Ducrocq X, Pincemaille B, et al. Venous angiography importance in the diagnosis of brain death. 125 cases. *Bull Acad Natle Med*. 1995;179(1):27-40.
52. Sawicki M, Solek-Pastuszka J, Jurczyk K, Skrzywanek P, Guzinski M, Czajkowski Z, et al. Original Protocol Using Computed Tomographic Angiography for Diagnosis of Brain Death: A Better Alternative to Standard Two-Phase Technique? *Ann Transplant*. 2015;20:449-60.
53. Soldatos T, Karakitsos D, Chatzimichail C, Papathanasiou M, Gouliamos A, Karabinis A. Transcranial doppler sonography as a confirmatory test in the diagnosis of brain death. *Neuroradiology*. 2009;51 Suppl 1:S71.
54. Tan WS, Wilbur AC, Jafar JJ, Spigos DG, Abejo R. Brain death use of dynamic CT and intravenous digital subtraction angiography. *AJNR Am J Neuroradiol*. 1987;8:123-5.
55. Van Bunnen Y, Delcour C, Wery D, Richoz B, Struyven J. Intravenous digital subtraction angiography. A criteria of brain death. *Ann Radiol*. 1989;32(4):279-81.
56. Vatne K, Nakstad P, Lundar T. Digital subtraction angiography (DSA) in the evaluation of brain death. A comparison of conventional cerebral angiography with intravenous and intraarterial DSA. *Neuroradiology*. 1985;27:155-7.
57. Wieler H, Marohl K, Kaiser KP, Klwaki P, Frossler H. Tc-99m HMPAO cerebral scintigraphy. A reliable, noninvasive method for determination of brain death. *Clinical Nuclear Medicine*. 1993;18(2):104-9.
58. Karantanas AH, Hadjigeorgiou GM, Paterakis K, Sfiras D, Komnos A. Contribution of MRI and MR angiography in early diagnosis of brain death. *Eur Radiol*. 2002;12(11):2710-6.

Ancillary Investigation – Pediatrics

PICO Question: In pediatric patients (≥37 weeks gestational age and <18 years of age) appearing to meet criteria for death determination by neurologic criteria (DNC) who require ancillary testing, which ancillary test should be performed to complete the neurological determination of death?

Reviewers:

Core Group: Nicole McKinnon, John Basmaji, Julie Kromm, Marat Slessarev, J Gordon Boyd, Lionel Zuckier, Owen Mooney, Andreas Kramer, Laura Hornby

Citation review: Christina Maratta, Jason Park

Literature Search:

Citations Screened: 2329
Citations Included: 39

Recommendation(s):

We suggest performing a radionuclide brain perfusion study employing a lipophilic radiopharmaceutical such as 99mTc-HMPAO or equivalent (which incorporates both a flow and parenchymal phase) with or without tomographic imaging in pediatric patients who require an ancillary investigation for DNC (Weak recommendation, low certainty in evidence).

We suggest performing a radionuclide brain perfusion study employing a lipophobic radiopharmaceutical such as 99mTc -DTPA, 99mTc-GHA, 99mTc -pertechnetate or equivalent (which incorporate only a flow phase) when a study employing a lipophilic radiopharmaceutical cannot be performed, in pediatric patients who require an ancillary investigation for DNC (Weak recommendation, low certainty in evidence).

We suggest against performing electroencephalography, transcranial Doppler, brainstem auditory evoked potentials, somatosensory evoked potentials, computer tomography (CT) angiography and four-vessel angiography in pediatric patients who require an ancillary investigation for DNC (Weak recommendation, very low certainty in evidence).

We suggest against performing ancillary testing in infants under 2 months corrected gestational age who require an ancillary investigation for DNC (Strong recommendation, very low certainty in evidence).

Evidence Summary:

We found 39 studies which met inclusion criteria, published between 1972 and 2020. Of these, we meta-analyzed the data from 38 studies and narratively reported the outcomes of 1 study[1]. 36 studies were cohort and 3 were case-controlled designs. Eighteen different ancillary tests for brain death were evaluated across the included studies, with a total of 55 comparative evaluations of these tests. Of the 18 different ancillary tests, 8 were found in only a single study: bispectral index[2], ophthalmic ultrasound of central retinal vessels[3], cranial sector ultrasound[4], carotid doppler ultrasound[5], CT angiography[6], 4-vessel cerebral angiography[7], N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP)[8] and ^{99m}Tc-glucoheptonate (GHA)[9] radionuclide studies.

Eighteen studies included patients who had met clinical exam criteria for DNC and 18 studies included patients who were suspected of DNC but had not undergone formal testing. The case-controlled studies (n=3, 7.5%) included pediatric patients who were confirmed to have met DNC[10–12]. Only one study used 4-vessel angiography as the reference standard[13], while the remaining studies used either the clinical

exam or the clinical exam and an ancillary test as the gold standard. Estimates for false positive (FP) and false negatives (FN) rates were calculated from data for patients suspected of brain death.

Imaging Based Ancillary Tests:

Radiopharmaceutical Studies

Introduction

Studies involving RPs have been grouped in consultation with a nuclear medicine specialist (LZ). Historically, the initial class of RPs used for ancillary studies were any of several ^{99m}Tc-labeled lipophobic RPs which do not cross the blood brain barrier. The diagnostic component of these studies is the initial dynamic angiogram-like flow phase where a sequence of 1-2 second images is captured in planar (non-tomographic) imaging mode. The specific RP used is immaterial to the examination because the diagnostic content depends on visualization of arrival of RP bolus within the vasculature and is independent of subsequent binding or metabolism of the RP molecule. Subsequently, lipophilic RPs were introduced, designed to cross the blood brain barrier and be retained in the parenchyma thereby identifying perfused tissue. Imaging of this parenchymal uptake is performed using either a planar imaging technique, or a more demanding tomographic (SPECT) method. Flow imaging, the mainstay of lipophobic RP studies, can also be performed with lipophilic RPs as an additional, though probably less specific, component of the examination. In most published reports which utilize lipophilic RPs, emphasis is on the parenchymal phase of the examination though in some instances both flow and parenchymal phases have been separately reported.

Accuracy of radionuclide dynamic flow imaging

Thirteen studies (n=249) describing flow imaging employed several disparate lipophobic RPs: 5 studies with ^{99m}Tc-DTPA[8,13–16], 4 studies with ^{99m}Tc-pertechnetate[7,17–19], 1 study with ^{99m}Tc-glucoheptonate (GHA)[9], 2 studies had unspecified RPs[20,21] and one study reported the initial flow phase of a ^{99m}Tc-labeled lipophilic RP in sufficient detail such that it could also be included[22] (table 1). We meta-analyzed these studies together based on their identical properties, as noted above. Of these 13 studies, 5 included patients with confirmed brain death[8,14,16,17,20], and 8 studies included patients suspected of DNC[7,9,13,15,18,19,21,22]. Four studies[7,8,18,19] included variables that would potentially confound clinical testing including hypothermia (n= 4) [7,8,19], detectable serum phenobarbital (n= 10) [8,18,19] or thiopental (n=1)[8]. Five patients had unclear etiologies of neurologic injury listed as “other”[16]. In 8 studies that enrolled patients suspected of DNC (n=116), radionuclide flow imaging had a sensitivity of 0.965 (95% CI 0.89 to 0.98) and a specificity of 0.88 (95% CI 0.67 to 0.98) If radionuclide dynamic flow imaging was applied to 1000 patients with a pre-test probability of 95% for meeting DNC criteria, there would be 47 false negatives (FN, 95% CI 19 to 105), and 6 false positives (FP, 95% CI 1 to 6). The certainty of evidence was downgraded to moderate due to serious risk of bias. A detailed breakdown of the studies containing the 2 most studied lipophobic RPs (^{99m}Tc-DTPA and ^{99m}Tc-pertechnetate) is provided below.

Table 1. **Number of studies for each combination of radiopharmaceutical and criteria of interpretation**

Radiopharmaceutical (RP)	Criteria of interpretation		
	Flow	Parenchyma (planar)	Parenchyma (SPECT)
^{99m}Tc -Diethylenetriamine pentaacetate (DTPA)	5		
^{99m}Tc-pertechnetate	4		
^{99m}Tc-glucoheptonate (GHA)	1		
^{99m}Tc-unspecified or multiple	2		
^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO)	1	4	5

^{123}I-iodoamphetamine (^{123}I-IMP)		1	

^{99m}Tc -DTPA

Five studies (n= 100) assessed cerebral blood flow using ^{99m}Tc-DTPA[8,13–16]; 3 studies (n=93) [8,14,16] were performed in patients with complete brain death while 2 studies (n=7) [13,15] reported diagnostic accuracy outcomes in patients with suspected brain death. Of the two studies involving children with suspected brain death, no patients with confounders to unresponsive coma were included. deTribolet et al (1977)[13] included 2 patients with suspicion of DNC of which no radionuclide flow was detected in the cranium. Erbengi et al (1990)[15] included 5 pediatric age patients suspected of brain death. Absence of intracranial arterial flow and absence of sagittal sinus activity on dynamic and static images was the criteria determined for a test to be consistent with brain death. Of the 5 pediatric patients, 3 had absent flow and no uptake on static blood pool images, consistent with DNC. One patient had flow present, and another had no flow present but sagittal sinus activity on static images. In patients with suspected DNC, ^{99m}Tc-DTPA had a sensitivity of 0.87 (95% CI 0.53 to 0.99). Specificity estimates could not be derived due to a lack of false positive events in the cohort. If ^{99m}Tc-DTPA was applied to 1000 patients with a pre-test probability of 95% for meeting DNC criteria, there would be 123 FN (95% CI 9 to 447). The certainty of evidence is very low due to serious risk of bias, indirectness, and imprecision.

Of the three studies involving patients with confirmed DNC, Erbengi et al (1991)[14], included only one pediatric subject in whom both the dynamic and static images showed an absence of cerebral circulation.. In Schober et al (1987)[8], 2 patients, both with detectable levels of phenobarbital (10mg/l, 21mg/l), demonstrated no flow, consistent with DNC. Ruiz-Garcia et al (2000)[16] published the largest study in this group which included 90 patients without confounders. The authors evaluated flow and defined absence of cerebral blood flow as consistent with DNC. In 83 patients no cerebral blood flow was detected, whereas persistent intracranial blood flow, not consistent with DNC was present in 7 patients. Pooled analysis for these three studies has a sensitivity of 0.92 (95% CI 0.86 to 0.97).

^{99m}Tc-pertechnetate

Four studies enrolling 49 patients assessed cerebral blood flow using ^{99m}Tc-pertechnetate[7,17–19]. Of those, 30 patients in three studies were suspected of DNC while 19 patients [7,18,19] in one study were confirmed to be DNC[17]. In patients with suspected DNC, ^{99m}Tc-pertechnetate demonstrated a sensitivity of 0.91 (95% CI 0.77 to 0.99) and a specificity of (0.97, 95% CI 0.65 to 1.00). If applied to 1000 patients with a pre-test probability of 95% for meeting DNC criteria, ^{99m}Tc-pertechnetate would result in 85 FN (95% CI 9 to 219) and 1 FP (95% CI 0 to 17).

In Ashwal et al (1977)[18], 9 patients with a clinical exam concerning for brain death had no cranial isotope bolus detected in the presence of a systemic bolus. Three children with a clinical exam not consistent with DNC, including presence of spontaneous respirations, had a positive cranial and systemic isotope bolus detected, consistent with not meeting criteria for DNC. Two patients had detectable phenobarbital levels during their radionuclide study.

For the remaining 2 studies, Schwartz et al (1984)[7] studied 9 children with exams suggestive of DNC. None of the 9 patients had arterial flow detected after systemic isotope injection, however activity was detected in the sagittal sinus which they discounted as insignificant (n=3). Thompson et al (1986)[19] graded dynamic brain scintigraphy from 0 to +4. 0 being no cerebral activity and absent or minimal but delayed sinus activity to +4 describing peak cerebral activity to sagittal sinus less than 6 seconds. A study with a grade of 0 meets criteria for consistent with DNC. The study results included 3 true positives, patients without cerebral activity and clinical exams consistent with brain death; 4 true negatives with graded flow of +3 and +4 detected and a clinical exam inconsistent with brain death and 2 false

negatives, graded flow of +1 and +3 but meeting clinical exam criteria for DNC; both these infants survived.

Flowers et al (2000)[17], was the only study to include patients with a confirmed diagnosis of DNC. They defined a study with absence of arterial flow in the cerebral circulation as consistent with DNC. No arterial flow was detected on the 19 patients studied; however, one patient did have evidence of radiopharmaceutical detected in the superior sagittal sinus which they discounted as not indicative of brain viability and irrelevant. Sensitivity for this study was 1.0.

Accuracy of radionuclide parenchymal uptake studies

Ten studies utilized lipophilic RPs, 1 using ^{123}I-IMP[8] and 9 with ^{99m}Tc-HMPAO [8,14,15,22-27]. Of the nine ^{99m}Tc-RP studies, 5 utilized planar imaging [8,22–25] and 4 SPECT imaging [14,15,26,27]. Only a small cohort of patients were studied using the RP ^{123}I-IMP with the majority studied with ^{99m}Tc-HMPAO. We combined the parenchymal uptake studies using ^{99m}Tc-HMPAO. The pooled sensitivity and specificity were 0.99 (95% CI 0.89 to 1.00) and 0.97 (95% CI 0.65 to 1.00), respectively. If applied to 1000 patients with a pre-test probability of 95% for meeting DNC criteria, ^{99m}Tc-HMPAO with or without SPECT would result in 9 FN (95% CI 0 to 105) and 1 FP (95% CI 0 to 17).

Lipophilic radionuclide ^{99m}Tc-HMPAO (parenchymal uptake with planar imaging)

Five studies involving 65 children utilized ^{99m}Tc-HMPAO with planar imaging [8,22–25], 2 in patients with confirmed DNC by clinical exam[8,24] and 3 in patients with unresponsive coma suggestive of DNC [22,23,25]. Parker et al (1995)[24] included 13 patients in whom DNC testing could not be completed because they were unable to perform apnea testing (n=11) or cold calorics due to skull base fractures n=2, or there was neuromuscular paralysis (n=3), somatic death before completion of the DNC exam (n= 3) or phenobarbital coma (n=1). None of these patients demonstrated parenchyma uptake. Laurin et al (1985)[22] described a mixed population study which included children and adults with exams concerning for DNC. The sensitivity and specificity of ^{99m}Tc-HMPAO was 0.99 (95% CI 0.83 to 1.00) and 0.97 (95% CI 0.65 to 1.00), respectively. If applied to 1000 patients with a pre-test probability of 95% for meeting DNC criteria, ^{99m}Tc-HMPAO would yield 9 FN (95% CI 0 to 161) and 1 FP (95% CI 0 to 17). Certainty of evidence is low due to serious risk of bias and imprecisions.

^{99m}Tc-HMPAO SPECT (parenchymal uptake with SPECT imaging)

Four studies which including 19 pediatric patients utilized ^{99m}Tc-HMPAO with SPECT imaging[14,15,26,27]. One study investigated patients with suspected DNC[15], and no studies reported confounding variables. All studies defined a scan consistent with DNC as absence of parenchymal uptake in both the cerebral hemispheres and cerebellum on the tomographic images. None of the 19 patients had parenchymal uptake in either their cerebral hemispheres or cerebellum. In patients with suspected DNC (n=4), sensitivity of ^{99m}Tc-HMPAO SPECT was 1.00 (95% CI 0.4 to 1.00). Specificity could not be determined due to no FP events. If applied to 1000 patients, ^{99m}Tc-HMPAO SPECT would result in zero FN (95% CI 0 to 570). Certainty of evidence is low due to serious risk of bias and very serious concerns with imprecision.

CT angiography

One study included pediatric aged patients, of which all met DNC criteria (n= 19)[6]. The authors did not report confounding variables, nor do they report if 4, 7, or 10 vessels were imaged and analyzed. If applied to 1000 patients CT angiography would result in zero FN (95% CI 0-114), sensitivity 1.00 (95% CI 0.88- 1.00). For evaluation of FP rates and specificity, we incorporated adult studies into our analysis. Adult studies were subdivided to account for 4, 7, and 10 vessel angiography scoring. Across all these variations the FP rate with a 95% pre-test probability was 0 per 1000 patients and the FN was 142, 96, and 105 per 1000 patients for studies including 4, 7, and 10 vessel angiography scoring, respectively.

The certainty of this evidence was very low due to high risk of bias, indirectness, and imprecision. There were very serious concerns with indirectness given the sizes of arterial and venous vessels in infants and children and challenges performing the rapid contrast boluses required for this form of imaging in infants and young children.

4-vessel angiography

Only one study independently investigated 4-vessel angiography as the ancillary test in children (n=9) with clinical exams suggestive of brain death[7]. Confounding variables included barbiturate coma (n=3). The authors state that no "direct cerebral arterial filling" was noted in all 9 of the children[7]. If applied to 1000 patients, 4-vessel angiography would result in zero FN (95% CI 0- 323) (sensitivity 1.00, 95% CI 0.66- 1.00). The certainty of this evidence is low due to unclear risk of bias and imprecision. A second study had 28 patients who underwent either 4-vessel angiography or an unspecified radionuclide scan following clinical exam consistent with DNC[28]. Phenobarbital levels ranging from 18- 171ug/dl were present (n=9). No cerebral blood flow was present for any patients with suspected DNC (n=28), however, given the tests were not stratified per patient, we were unable to utilize the data in the 4-vessel angiography analysis. Unfortunately, no pediatric or adult studies included patients with confirmed brain death, and hence, no data exists to calculate specificity or number of FP per 1000 patients.

Trans Cranial Doppler (TCD)

Seven studies[11,29–34] involving 149 patients were included, one study included a case control design[11]. Three studies defined a priori the waveforms which were consistent with brain death [31,33,34], with two studies further clarifying the required waveforms to be present bilaterally for the test to be consistent with brain death[31,34]. One study did not define transcranial waveforms consistent with brain death, however states that "cerebral circulatory arrest" is consistent with brain death.[32] The remaining studies described waveforms in patients with exams suspicious for brain death but did not a priori define the criteria for a TCD consistent with brain death[11,29,30]. In patients with suspected brain death (4 studies, n= 79 patients), the sensitivity and specificity were 0.91 (95% CI 0.77 to 0.98) and 0.88 (95% CI 0.77 to 0.95), respectively. The FN rate for a pre-test probability of 95% was 86 (95% CI 19 to 219) out of 1000 patients, and the FP rate was 6 (95% CI 2 to 11) out of 1000 patients. The certainty of the evidence was very low due to serious risk of bias, indirectness, and imprecision.

Non-Imaging Based Ancillary Tests:

Electroencephalography (EEG)

A total of 299 patients were included in the 13 studies which evaluated EEG as an ancillary test for DNC[4,9,10,16,18–20,24,26,28,35–37]. Confounding variables included detectable phenobarbital levels (n=11) at the time of EEG[18,24,28], or hypothermia and a detectable phenobarbital level (n=2)[19]. EEG criteria for a test consist with brain death was defined in all studies, 11 defined an EEG with electrocerebral silence as consistent with brain death, one stated an isoelectric EEG was consistent and another defined a "flat" EEG as consistent with brain death[26]. Seven studies included patients with confirmed DNC[16,20,24,26,28,36,37]. In patients with suspected brain death, pooled analysis demonstrated a sensitivity of 0.88 (95% CI 0.78 to 0.96) and specificity of 0.96 (95% CI 0.82 to 1.00). If applied to 1000 patients with a pre-test probability of 95% for meeting DNC criteria, EEG would yield be 114 false negatives (95% CI 37 to 209) and 2 false positives (95% CI 0 to 9). The certainty of evidence is very low due to serious risk of bias, indirectness, and imprecision.

Brain auditory evoked potentials (BAEP)

Three studies involving 31 patients[12,14,36], including one study with a case control design[12], with only one study defining a BAEP consistent with brain death as a recording with no response in the C2 to A1/A2 electrode[14], whereas the other studies were descriptive[12,36]. Confounding variables were not present in two studies[12,14] and not reported in the third[36]. In the one study (n=23) of patients with suspected brain death, the sensitivity and specificity were 0.90 (95% CI 0.55 to 1.) and 1.00 (95% CI 0.75 to 1.0), respectively. If applied to 1000 patients the FN rate is 95 (95% CI 0 to 427) and the FP rate is zero (95% CI 0 to 25). The certainty of the evidence was very low due to serious risk of bias, indirectness, and imprecision.

Brain auditory evoked potentials (BAEP) and somatosensory evoked potentials (SSEP)

Two studies involving 158 patients all of which were confirmed to have a clinical exam consistent with DNC[16,38]. Confounding variables such as barbiturate coma or hypothermia are not described as present in any patients, however the cause of neurologic injury leading to brain death is unclear in 7 patients [16,38]. Ruiz-Garcia[16] defines a test consistent with brain death as no observable waveforms for both brainstem and somatosensory evoked potentials. Ruiz-Lopez[38] does not explicitly define in their methodology waveforms consistent with brain death and instead describe waveforms in the patient population. Pooled sensitivity for the two studies is 0.92 (95% CI 0.87, 0.96). The certainty of the evidence was very low due to serious risk of bias, indirectness, and imprecision.

Justification/Rationale

The ancillary testing panel evaluated EEG, TCD, BAEP, radionuclide studies, CT angiography and 4-vessel angiography.

The panel considered the question to be a priority as it is essential to minimize the risks of false positives (determining someone dead who is alive) and false negative (determining someone is not dead who is dead) when declaring DNC in pediatric patients. The certainty of evidence for flow-based radionuclide studies was deemed moderate, while the certainty of evidence for all other aforementioned ancillary tests ranged from very low to low.

No studies included in the review reported adverse events related to the provision of the test. The panel noted that 4-vessel angiography has a known increased risk of thromboembolic stroke, whereas radionuclide studies, CT angiography and 4-vessel angiography all required transporting a critically ill patient out of the critical care department.

Radionuclide tests resulted in low false positive and false negative rates with respect to declaring death by neurologic criteria with low potential for harm in patients. The certainty of the evidence was higher in radionuclide tests compared to other ancillary test evaluated in pediatrics. As a result, the panel suggests the use of radionuclide studies for the diagnosis of neurological death. The panel suggests the use of liphophobic (which incorporates only a flow phase) RP for the diagnosis of brain death when lipophilic RPs (which incorporates both a flow and parenchymal phase) radionuclide studies cannot be readily performed. Given the broad access to nuclear medicine experts at pediatric tertiary care centers, this ensures flexibility, equitable access, and expeditious diagnosis of neurological death when lipophilic RPs are not available.

When compared to radionuclide scans, SSEPs, BAEPs, and TCDs produced higher false positive and negative rates. As a result, the potential harms outweighed any benefits that were associated with administering a non-invasive test at the bedside. The panel also suggested against Four-vessel angiography given the lack of specificity data from both pediatric and adult studies as well as the increased potential from harm (e.g stroke risk, technical difficulty in performing 4 vessel angiography in children). Although EEG demonstrated adequate sensitivity and specificity for determining neurologic

death, the evidence base did not include patients with confounders. Since the diagnostic accuracy of EEG can vary with confounders, the true FP and FN remain uncertain. As a result, the panel suggested against the use of EEG. CT angiography demonstrated adequate sensitivity with pediatric data, and the adult data had adequate specificity. The risk of indirectness for extrapolation of the adult data was graded as very serious, and as such CT angiography was recommended against for infants and children.

Further studies are required to better understand the effectiveness of ancillary testing for DNC in infants (less than two months corrected gestational age). At present, the available evidence is not sufficiently robust to confidently suggest ancillary testing be used to determine death in these patients. As such, if two complete clinical assessments are not possible for infants less than two months corrected gestational age, DNC cannot be determined. If DNC remains a priority, the clinical assessment can be repeated at another time or alternative end of life care may be consideredmay considered.

Implementation Considerations:

The panel suggests several key implementation considerations. Of the two conditionally recommended ancillary tests, the panel suggests that *if available* a radionuclide scan be preferentially performed. This requires a center with expertise in pediatric nuclear medicine, however DNC in infants and children in Canada is almost exclusively made at tertiary and quaternary care centers with this expertise.

The panel furthers suggests that *if available*, the type of radionuclide scan performed should employ a lipophilic RP such as ^{99m}Tc-HMPAO or equivalent, incorporating a parenchymal in addition to flow phase. This recommendation is founded on evidence generated using ^{99m}Tc-HMPAO combined with planar or SPECT imaging with a combined sensitivity of 0.99 (95% CI 0.89 to 1.00) and specificity 0.97 (95% CI 0.65 to 1.00). If applied to 1000 patients with a pre-test probability of 95% for meeting DNC criteria, utilizing ^{99m}Tc-HMPAO as the RP with or without SPECT would result in 9 FN (95% CI 0 to 105) and 1 FP (95% CI 0 to 17). When a lipophilic radiopharmaceutical is not available and waiting for access is clinically not advisable, the panel then suggest use of a lipophobic RP such as ^{99m}Tc -DTPA, ^{99m}Tc -pertechnetate or equivalent, which will provide dynamic flow images through the major cerebral vessels though lacking the additional parenchyma phase.

Knowledge Gaps/Research Considerations:

The most prominent research gaps lie in better delineating which ancillary tests can be used for DNC in infants and children. Overall, for the 39 studies the certainty of evidence was generally low to very low due to serious risk of bias, indirectness, and imprecision. Practically, having non-imaging modalities which could be implemented bedside would have advantages over the need to transport patients out of the critical care unit for imaging studies. Unfortunately, all these modalities require further research.

While lipophilic RPs are recommended, no studies evaluated ^{99m}Tc-bicisate, which is a second lipophilic radiopharmaceutical in common use today and which may exhibit comparable properties. It would be useful to validate this radiopharmaceutical in a formal manner.

BAEP, SSEP, and TCDs are non-invasive, readily-available ancillary tests that can be implemented at the patient bedside. However, the current evidence base is limited by imprecision, heterogeneous diagnostic thresholds and variability in the flow and timing of when these tests are administered. Future studies utilizing brainstem auditory evoked potentials and somatosensory evoked potentials would benefit from a clear definition of which waveforms are consistent with brain death, and if these waveforms should be present bilaterally, and under which circumstances bilateral waveforms are not required. Future studies investigating the diagnostic accuracy of TCD should standardize the vessels under investigation and evaluate waveform and flow in bilateral middle cerebral arteries, bilateral anterior cerebral arteries, basilar and vertebral arteries.

The panel was concerned about utilizing EEG as an ancillary test given its ability to be affected by confounders such as serum levels phenobarbital or pentobarbital and hypothermia. Future research should focus on determining the sensitivity and specificity of EEG in a cohort of patients with confounders in a dose dependent fashion.

Regarding the imaging-based modalities, research focused on improving numbers of patients in coma and following their trajectory would improve the sensitivity and specificity for all imaging modalities but in particular CT angiography and 4-vessel angiography for there was no pediatric data to calculate specificity.

Subgroup analysis is another important area for future research in pediatric ancillary testing. There is a minuscule amount of data for ancillary test in children under 2 months and less for pre-term infants. The panel recommends further studies in this area to be able to make recommendations in the future.

References

1. Hindy-François, C. *et al.* Pediatric Brain Death Diagnosis in the View of Organ Donation in France. *Transplantation* 87, 616–617 (2009).
2. Okuyaz, Ç., Birbiçer, H., Doruk, N. & Atici, A. Bispectral Index Monitoring in Confirmation of Brain Death in Children. *J Child Neurol* 21, 799–801 (2006).
3. Riggs, B. J. *et al.* Doppler Ultrasonography of the Central Retinal Vessels in Children With Brain Death* *Pediatr Crit Care Me* 18, 258–264 (2017).
4. Furgiuele, T. L., Frank, L. M., Riegle, C., Wirth, F. & Earley, L. C. Prediction of cerebral death by cranial sector scan. *Crit Care Med* 12, 1–3 (1984).
5. Jalili, M., Crade, M. & Davis, A. L. Carotid Blood-Flow Velocity Changes Detected By Doppler Ultrasound in Determination of Brain Death in Children. *Clin Pediatr* 33, 669–674 (1994).
6. Duyu, M. & Karakaya, Z. Evaluation of Patients Diagnosed with Brain Death in Paediatric Critical Care. *J Pediatric Res* 7, 250–256 (2020).
7. Schwartz, J. A., Baxter, J. & Brill, D. R. Diagnosis of brain death in children by radionuclide cerebral imaging. *Pediatrics* 73, 14–8 (1984).
8. Schober, O., Galaske, R. & Heyer, R. Determination of brain death with ^{123}I-IMP and ^{99}mTc-HMPAO. *Neurosurg Rev* 10, 19–22 (1987).
9. Holzman, B. H., Curless, R. G., Sfakianakis, G. N., Ajmone-Marsan, C. & Montes, J. E. Radionuclide cerebral perfusion scintigraphy in determination of brain death in children. *Neurology* 33, 1027–1027 (1983).
10. Ashwal, S., Schneider, S. & Thompson, J. Xenon computed tomography measuring cerebral blood flow in the determination of brain death in children. *Ann Neurol* 25, 539–546 (1989).
11. Rodriguez, R. A., Cornel, G., Alghofaili, F., Hutchison, J. & Nathan, H. J. Transcranial Doppler during suspected brain death in children: Potential limitation in patients with cardiac “shunt.” *Pediatr Crit Care Me* 3, 153–157 (2002).
12. Steinhart, C. M. & Weiss, I. P. Use of brainstem auditory evoked potentials in pediatric brain death. *Crit Care Med* 13, 560–562 (1985).
13. Tribolet, N. de, Schäfer, K., Oberson, R. & Zander, E. Radioisotope diagnosis of brain death. *Schweiz Med Wschr* 107, 464–7 (1977).
14. Erbengi, A. *et al.* Brain death: Determination with brain stem evoked potentials and radionuclide isotope studies. *Acta Neurochir* 112, 118–125 (1991).
15. Erbengi, G., A.Erbengi, E.Erbas & T.Aras. Diagnosis of Brain Death using TC-^{99}m-HMPAO/SPECT, Tc-^{99}m-DTPA Scintigraphy and Radionuclide Angiography. *NucCompact* 21, 177–179 (1990).

16. Ruiz-García, M., Gonzalez-Astiazarán, A., Collado-Corona, M. A., Rueda-Franco, F. & Sosa-de-Martínez, C. Brain death in children: clinical, neurophysiological and radioisotopic angiography findings in 125 patients. *Child's Nerv Syst* 16, 40–46 (2000).
17. Flowers, W. Mel. & Patel, B. R. Accuracy of Clinical Evaluation in Determination of Brain Death. *J Southern Med* 93, 203–6 (2000).
18. Ashwal, S., Smith, A. J. K., Torres, F., Loken, M. & Chou, S. N. Radionuclide bolus angiography: A technique for verification of brain death in infants and children. *J Pediatrics* 91, 722–727 (1977).
19. Thompson, J. R. *et al.* Comparison of cerebral blood flow measurements by xenon computed tomography and dynamic brain scintigraphy in clinically brain dead children. *Acta Radiologica Suppl* 369, 675–9 (1986).
20. Ashwal, S. Brain death in early infancy. *J Hear Lung Transplant Official Publ Int Soc Hear Transplant* 12, S176-8 (1993).
21. Coker, S. B. & Dillehay, G. L. Radionuclide cerebral imaging for confirmation of brain death in children: The significance of dural sinus activity. *Pediatr Neurol* 2, 43–46 (1986).
22. Laurin, N. R. *et al.* Cerebral perfusion imaging with technetium-99m HM-PAO in brain death and severe central nervous system injury. *J Nucl Med* 30, 1627–35 (1989).
23. Kraft, O., Samlík, J. & Chmelová, J. The diagnosis of brain death--own experience. *Nucl Medicine Rev Central East Europe* 9, 132–7 (2006).
24. Parker, B. L. *et al.* Declaring pediatric brain death: current practice in a Canadian pediatric critical care unit. *Can Medical Assoc J J De L'association Medicale Can* 153, 909–16 (1995).
25. Wilson, K., Gordon, L. & Selcy, J. B. The Diagnosis of Brain Death with Tc-^{99}m HMPAO. *Clin Nucl Med* 18, 428–434 (1993).
26. Okuyaz, Ç. *et al.* Tc-^{99}m-HMPAO SPECT in the diagnosis of brain death in children. *Pediatr Int* 46, 711–714 (2004).
27. Kahveci, F., Bekar, A. & Tamgac, F. Tc-^{99} HMPAO cerebral SPECT imaging in brain death patients with complex spinal automatism. *Ulusal Travma Dergisi Turkish J Trauma Emerg Surg Tjtes* 8, 198–201 (2002).
28. Fackler, J. C., Troncoso, J. C. & Gioia, F. R. Age-Specific Characteristics of Brain Death in Children. *Am J Dis Child* 142, 999–1003 (1988).
29. Powers, A. D., Graeber, M. C. & Smith, R. R. Transcranial Doppler Ultrasonography in the Determination of Brain Death. *Neurosurgery* 24, 884–889 (1989).
30. Qian, S. Y., Fan, X. M. & Yin, H. H. Transcranial Doppler assessment of brain death in children. *Singap Med J* 39, 247–50 (1998).
31. Bode, H., Sauer, M. & Pringsheim, W. Diagnosis of brain death by transcranial Doppler sonography. *Arch Dis Child* 63, 1474 (1988).
32. Blanot, S., Montmayeur, J., Salvadori, A., Ottonello, G. & Orliaguet, G. Évaluation rétrospective de l'épreuve d'apnée chez l'enfant en mort encéphalique. *Médecine Intensive Réanimation* 25, 171–178 (2016).
33. Newell, D. W., Grady, S. M., Sirotta, P. & Winn, R. H. Evaluation of Brain Death Using Transcranial Doppler. *Neurosurgery* 24, 509–513 (1989).
34. Gencipinar, P. *et al.* Pediatric Brain Death: Experience of a Single Center. *Turkiye Klinikleri J Medical Sci* 35, 60–66 (2015).
35. Ashwal, S. & Schneider, S. Failure of electroencephalography to diagnose brain death in comatose children. *Ann Neurol* 6, 512–517 (1979).
36. Goh, A. & Mok, Q. Clinical course and determination of brainstem death in a children's hospital. *Acta Paediatr* 93, 47–52 (2004).
37. Mohandas, A. & Chou, S. N. Brain Death. *J Neurosurg* 35(2), 211-18 (1971).

38. Ruiz-Lopez, M. J., Azagra, A. M. de, Serrano, A. & Casado-Flores, J. Brain death and evoked potentials in pediatric patients. *Crit Care Med* 27, 412-416. (1999).
39. Pistoia, F. *et al.* The role of xenon CT measurements of cerebral blood flow in the clinical determination of brain death. *Ajnr Am J Neuroradiol* 12, 97–103 (1991).

^{99m}Tc flow based nuclear medicine studies

Sensitivity	0.95 (95% CI: 0.89 to 0.98)
Specificity	0.88 (95% CI: 0.67 to 0.98)

Prevalence	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of50%	pre-test probability of90%	pre-test probability of 95%	
True positives (patients with neurological death)	8 studies 116 patients	cross-sectional (cohort type accuracy study)	serious	not serious	not serious	not serious	475 (445 to 490)	855 (801 to 882)	903 (845 to 931)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having neurological death)							25 (10 to 55)	45 (18 to 99)	47 (19 to 105)	
True negatives (patients without neurological death)	8 studies 116 patients	cross-sectional (cohort type accuracy study)	serious	not serious	not serious	not serious	440 (335 to 490)	88 (67 to 98)	44 (34 to 49)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having neurological death)							60 (10 to 165)	12 (2 to 33)	6 (1 to 16)	

References

1. Ashwal, S., Smith, A. J. K., Torres, F., Loken, M. & Chou, S. N. Radionuclide bolus angiography: A technique for verification of brain death in infants and children. *J Pediatrics* 91, 722–727 (1977).
2. Coker, S. B. & Dillehay, G. L. Radionuclide cerebral imaging for confirmation of brain death in children: The significance of dural sinus activity. *Pediatr Neurol* 2, 43–46 (1986).
3. Erbengi, G., A.Erbengi, E.Erbas & T.Aras. Diagnosis of Brain Death using TC-99m-HMPAO/SPECT, Tc-99m-DTPA Scintigraphy and Radionuclide Angiography. *NucCompact* 21, 177–179 (1990).
4. Holzman, B. H., Curless, R. G., Sfakianakis, G. N., Ajmone-Marsan, C. & Montes, J. E. Radionuclide cerebral perfusion scintigraphy in determination of brain death in children. *Neurology* 33, 1027–1027 (1983).
5. Laurin, N. R. *et al.* Cerebral perfusion imaging with technetium-99m HM-PAO in brain death and severe central nervous system injury. *J Nucl Medicine Official Publ Soc Nucl Medicine* 30, 1627–35 (1989).
6. Schwartz, J. A., Baxter, J. & Brill, D. R. Diagnosis of brain death in children by radionuclide cerebral imaging. *Pediatrics* 73, 14–8 (1984).
7. Thompson, J. R. *et al.* Comparison of cerebral blood flow measurements by xenon computed tomography and dynamic brain scintigraphy in clinically brain dead children. *Acta Radiologica Suppl* 369, 675–9 (1986).
8. Tribolet, N. de, Schäfer, K., Oberson, R. & Zander, E. Radioisotope diagnosis of brain death. *Schweiz Med Wschr* 107, 464–7 (1977).

^{99m}Tc Pertechnetate

Sensitivity	0.91 (95% CI: 0.77 to 0.99)
Specificity	0.97 (95% CI: 0.65 to 1.00)

Prevalence	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with neurological death)	3 studies 30 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[b]	456 (385 to 495)	820 (693 to 891)	865 (731 to 941)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having neurological death)							44 (5 to 115)	80 (9 to 207)	85 (9 to 219)	
True negatives (patients without neurological death)	3 studies 30 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[b]	485 (325 to 500)	97 (65 to 100)	49 (33 to 50)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having neurological death)							15 (0 to 175)	3 (0 to 35)	1 (0 to 17)	

Explanations

[a]We rated down due to high risk of bias in patient selection and flow as well as the conduct and timing of the index test and reference standard.

[b]We rated down for imprecision because of the low number of patients across all studies and because the confidence intervals could range from an important to a not important difference in diagnostic accuracy.

References

1. Ashwal, S., Smith, A. J. K., Torres, F., Loken, M. & Chou, S. N. Radionuclide bolus angiography: A technique for verification of brain death in infants and children. *J Pediatrics* 91, 722–727 (1977).
2. Schwartz, J. A., Baxter, J. & Brill, D. R. Diagnosis of brain death in children by radionuclide cerebral imaging. *Pediatrics* 73, 14–8 (1984).
3. Thompson, J. R. *et al.* Comparison of cerebral blood flow measurements by xenon computed tomography and dynamic brain scintigraphy in clinically brain dead children. *Acta Radiologica Suppl* 369, 675–9 (1986).

^{99m}Tc-DTPA

Sensitivity	0.87 (95% CI: 0.53 to 0.99)
Specificity	-- (95% CI: -- to --)

Prevalence	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of50%	pre-test probability of90%	pre-test probability of95%	
True positives (patients with neurological death)	2 studies 7 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious	not serious	very serious[b]	435 (265 to 495)	783 (477 to 891)	827 (503 to 941)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having neurological death)							65 (5 to 235)	117 (9 to 423)	123 (9 to 447)	
True negatives (patients without neurological death)	-	-	-	-	-	-	-	-	-	-
False positives (patients incorrectly classified as having neurological death)							-	-	-	

Explanations

[a]We rated down due to high risk of bias in patient selection and flow as well as the conduct and timing of the index test and reference standard.

[b]We rated down for imprecision because of the low number of patients across all studies and because the confidence intervals could range from an important to a not important difference in diagnostic accuracy.

References

1. Erbengi, G., A.Erbengi, E.Erbas & T.Aras. Diagnosis of Brain Death using TC-99m-HMPAO/SPECT, Tc-99m-DTPA Scintigraphy and Radionuclide Angiography. *NucCompact* 21, 177–179 (1990).
2. Tribolet, N. de, Schäfer, K., Oberson, R. & Zander, E. Radioisotope diagnosis of brain death. *Schweiz Med Wschr* 107, 464–7 (1977).

^{99m}Tc-HMPAO SPECT

Sensitivity	1.00 (95% CI: 0.40 to 1.00)
Specificity	-- (95% CI: -- to --)

Prevalence	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of50%	pre-test probability of90%	pre-test probability of 95%	
True positives (patients with neurological death)	1 studies 4 patients	cross-sectional (cohort type accuracy study)	serious	not serious	not serious	very serious	500 (200 to 500)	900 (360 to 900)	950 (380 to 950)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having neurological death)							0 (0 to 300)	0 (0 to 540)	0 (0 to 570)	
True negatives (patients without neurological death)	-	-	-	-	-	-	-	-	-	-
False positives (patients incorrectly classified as having neurological death)							-	-	-	

Explanations

[a]We rated down due to high risk of bias in patient selection and flow as well as the conduct and timing of the index test and reference standard

[b]We rated down for imprecision because of the very low number of participants

References

1. Erbengi, G., A.Erbengi, E.Erbas & T.Aras. Diagnosis of Brain Death using TC-99m-HMPAO/SPECT, Tc-99m-DTPA Scintigraphy and Radionuclide Angiography. *NucCompact* 21, 177–179 (1990).

^{99m}Tc HMPAO (SPECT and non-SPECT)

Sensitivity	0.99 (95% CI: 0.89 to 1.00)
Specificity	0.97 (95% CI: 0.65 to 1.00)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with neurological death)	4 studies 31 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[a]	495 (445 to 500)	891 (801 to 900)	941 (845 to 950)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having neurological death)							5 (0 to 55)	9 (0 to 99)	9 (0 to 105)	
True negatives (patients without neurological death)	4 studies 31 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[a]	485 (325 to 500)	97 (65 to 100)	49 (33 to 50)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having neurological death)							15 (0 to 175)	3 (0 to 35)	1 (0 to 17)	

Explanations

[a]We rated down due to high risk of bias in patient selection and flow as well as the conduct and timing of the index test and reference standard

[b]We rated down for imprecision because of the low number of participants from all available studies

References

1. Erbengi, G., A.Erbengi, E.Erbas & T.Aras. Diagnosis of Brain Death using TC-99m-HMPAO/SPECT, Tc-99m-DTPA Scintigraphy and Radionuclide Angiography. *NucCompact* 21, 177–179 (1990).
2. Kraft, O., Samlík, J. & Chmelová, J. The diagnosis of brain death--own experience. *Nucl Medicine Rev Central East Europe* 9, 132–7 (2006).
3. Laurin, N. R. *et al.* Cerebral perfusion imaging with technetium-99m HM-PAO in brain death and severe central nervous system injury. *J Nucl Medicine Official Publ Soc Nucl Medicine* 30, 1627–35 (1989).
4. Wilson, K., Gordon, L. & Selby, J. B. The Diagnosis of Brain Death with Tc-99m HMPAO. *Clin Nucl Med* 18, 428–434 (1993).

^{99m}Tc HMPAO

Sensitivity	0.99 (95% CI: 0.87 to 1.00)
Specificity	0.97 (95% CI: 0.65 to 1.00)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with neurological death)	3 studies 27 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[b]	440 (390 to 480)	792 (702 to 864)	836 (741 to 912)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having neurological death)							60 (20 to 110)	108 (36 to 198)	114 (38 to 209)	
True negatives (patients without neurological death)	3 studies 27 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[b]	485 (325 to 500)	97 (65 to 100)	49 (33 to 50)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having neurological death)							15 (0 to 175)	3 (0 to 35)	1 (0 to 17)	

Explanations

[a] We rated down due to high risk of bias in patient selection and flow as well as the conduct and timing of the index test and reference standard

[b] We rated down for imprecision because of the low number of participants from all available studies

References

1. Kraft, O., Samlík, J. & Chmelová, J. The diagnosis of brain death--own experience. *Nucl Medicine Rev Central East Europe* 9, 132–7 (2006).
2. Laurin, N. R. *et al.* Cerebral perfusion imaging with technetium-99m HM-PAO in brain death and severe central nervous system injury. *J Nucl Medicine Official Publ Soc Nucl Medicine* 30, 1627–35 (1989).
3. Wilson, K., Gordon, L. & Selby, J. B. The Diagnosis of Brain Death with Tc-99m HMPAO. *Clin Nucl Med* 18, 428–434 (1993).

CT Angiography

Sensitivity	1.00 (95% CI: 0.88 to 1.00)
Specificity	-- (95% CI: -- to --)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with neurological death)	1 study 19 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	serious[c]	500 (440 to 500)	900 (792 to 900)	950 (836 to 950)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having neurological death)							0 (0 to 60)	0 (0 to 108)	0 (0 to 114)	
True negatives (patients without neurological death)	-	-	-	-	-	-	-	-	-	-
False positives (patients incorrectly classified as having neurological death)							-	-	-	

Explanations

[a]We rated down due to high risk of bias with respect to patient selection, conduct of the index test and reference standard, as well as the flow and timing of the index test and reference standard.

[b]We rated down for indirectness because the patient population constituted patients in whom brain death was confirmed, thereby underestimating the false negative rate.

[c] We rated down for imprecision because of the low number of participants from all available studies.

References

1. Duyu, M. & Karakaya, Z. Evaluation of Patients Diagnosed with Brain Death in Paediatric Critical Care. *J Pediatric Res* 7, 250–256 (2020).

Electroencephalogram

Sensitivity	0.88 (95% CI: 0.78 to 0.96)
Specificity	0.96 (95% CI: 0.82 to 1.00)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of50%	pre-test probability of90%	pre-test probability of95%	
True positives (patients with neurological death)	6 studies 68 patients	cohort & case-control type studies	serious	serious	not serious	serious[c]	440 (390 to 480)	792 (702 to 864)	836 (741 to 912)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having neurological death)							60 (20 to 110)	108 (36 to 198)	114 (38 to 209)	
True negatives (patients without neurological death)	6 studies 68 patients	cohort & case-control type studies	serious	serious	not serious	serious[c]	480 (410 to 500)	96 (82 to 100)	48 (41 to 50)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having neurological death)							20 (0 to 90)	4 (0 to 18)	2 (0 to 9)	

Explanations

[a]We rated down due to high risk of bias in patient selection and flow as well as the conduct and timing of the index test and reference standard.

[b]We rated down for Indirectness because the patient population did not have any clinical confounders, which are likely to overestimate the accuracy of EEG.

[c] We rated down for imprecision because the confidence intervals could range from an important to a not important difference in diagnostic accuracy.

References

1. Ashwal, S., Smith, A. J. K., Torres, F., Loken, M. & Chou, S. N. Radionuclide bolus angiography: A technique for verification of brain death in infants and children. *J Pediatrics* 91, 722–727 (1977).
2. Ashwal, S. & Schneider, S. Failure of electroencephalography to diagnose brain death in comatose children. *Ann Neurol* 6, 512–517 (1979).
3. Ashwal, S., Schneider, S. & Thompson, J. Xenon computed tomography measuring cerebral blood flow in the determination of brain death in children. *Ann Neurol* 25, 539–546 (1989).
4. Furgiuele, T. L., Frank, L.M., Riegle, C., Wirth, F. & Earley, L. C. Prediction of cerebral death by cranial sector scan. *Crit Care Med* 12, 1–3 (1984).
5. Holzman, B. H., Curless, R. G., Sfakianakis, G. N., Ajmone-Marsan, C. & Montes, J. E. Radionuclide cerebral perfusion scintigraphy in determination of brain death in children. *Neurology* 33, 1027–1027 (1983).
6. Thompson, J. R. *et al.* Comparison of cerebral blood flow measurements by xenon computed tomography and dynamic brain scintigraphy in clinically brain dead children. *Acta Radiologica Suppl* 369, 675–9 (1986).

Brainstem Auditory Evoked potentials (BAEP)

Sensitivity	0.90 (95% CI: 0.55 to 1.00)
Specificity	1.00 (95% CI: 0.75 to 1.00)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with neurological death)	1 study 23 patients	case-control type accuracy study	serious[a]	serious[b]	not serious	serious[c]	450 (275 to 500)	810 (495 to 900)	855 (523 to 950)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having neurological death)							50 (0 to 225)	90 (0 to 405)	95 (0 to 427)	
True negatives (patients without neurological death)	1 study 23 patients	case-control type accuracy study	serious[a]	serious[b]	not serious	serious[c]	500 (375 to 500)	100 (75 to 100)	50 (38 to 50)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having neurological death)							0 (0 to 125)	0 (0 to 25)	0 (0 to 12)	

Explanations

[a]We rated down due to high risk of bias of bias in the conduct and interpretation of the index test.

[b]We rated down for indirectness due to important differences in the patient population and the application of the index test. The patient population did not have any clinical confounders and are likely to overestimate the diagnostic accuracy of BAEP.

[c]We rated down for imprecision because the confidence intervals range from an important difference to a not important difference in diagnostic accuracy.

References

1. Steinhart, C. M. & Weiss, I. P. Use of brainstem auditory evoked potentials in pediatric brain death. *Crit Care Med* 13, 560–562 (1985).

Four Vessel Cerebral Angiography

Sensitivity	1.00 (95% CI: 0.66 to 1.00)
Specificity	-- (95% CI: -- to --)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of50%	pre-test probability of90%	pre-test probability of 95%	
True positives (patients with neurological death)	1 study 9 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	serious[b]	500 (330 to 500)	900 (594 to 900)	950 (627 to 950)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having neurological death)							0 (0 to 170)	0 (0 to 306)	0 (0 to 323)	
True negatives (patients without neurological death)	-	-	-	-	-	-	-	-	-	-
False positives (patients incorrectly classified as having neurological death)							-	-	-	

Explanations

[a] We rated down due to unclear risk of bias in the patient selection and flow as well as the conduct and timing of the index test and reference standard.

[b]We rated down for imprecision because the confidence intervals of summary estimates around false negative rates range from recommending four vessel cerebral angiography to not recommending four vessel cerebral angiography.

References

1. Schwartz, J. A., Baxter, J. & Brill, D. R. Diagnosis of brain death in children by radionuclide cerebral imaging. *Pediatrics* 73, 14–8 (1984).

Transcranial Doppler

Sensitivity	0.91 (95% CI: 0.77 to 0.98)
Specificity	0.88 (95% CI: 0.77 to 0.95)

Prevalences	50%	90%	95%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 50%	pre-test probability of 90%	pre-test probability of 95%	
True positives (patients with neurological death)	4 studies 79 patients	cohort & case-control type studies	serious[a]	serious[b]	not serious	serious[c]	455 (385 to 490)	819 (693 to 882)	864 (731 to 931)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having neurological death)							45 (10 to 115)	81 (18 to 207)	86 (19 to 219)	
True negatives (patients without neurological death)	4 studies 79 patients	cohort & case-control type studies	serious[a]	serious[b]	not serious	serious[c]	440 (385 to 475)	88 (77 to 95)	44 (39 to 48)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having neurological death)							60 (25 to 115)	12 (5 to 23)	6 (2 to 11)	

Explanations

[a]We rated down due to high risk of bias in patient selection and flow as well as the conduct and timing of the index test and reference standard.

[b]We rated down for indirectness because studies did not specify the setting and standard for implementing the index test. Furthermore, cut-off values and thresholds for a negative or positive result were not specified.

[c]We rated down for imprecision because the confidence intervals could range from an important to a not important difference in diagnostic accuracy.

References

1. Newell, D. W., Grady, S. M., Sirotta, P. & Winn, R. H. Evaluation of Brain Death Using Transcranial Doppler. *Neurosurgery* 24, 509–513 (1989).
2. Powers, A. D., Graeber, M. C. & Smith, R. R. Transcranial Doppler Ultrasonography in the Determination of Brain Death. *Neurosurgery* 24, 884–889 (1989).
3. Qian, S. Y., Fan, X. M. & Yin, H. H. Transcranial Doppler assessment of brain death in children. *Singap Med J* 39, 247–50 (1998).
4. Rodriguez, R. A., Cornel, G., Alghofaili, F., Hutchison, J. & Nathan, H. J. Transcranial Doppler during suspected brain death in children: Potential limitation in patients with cardiac “shunt.” *Pediatr Crit Care Me* 3, 153–157 (2002).

eAppendix 11 Knowledge gaps

Death Determination by Circulatory Criteria

- More research is required to identify non-invasive monitoring devices that are both sensitive and specific for determining the cessation of circulation in potential organ donors to provide alternative methods for cases in which the use of arterial line is not possible or not preferred.
- The limitations of clinical monitoring equipment at lower thresholds of arterial pulse pressure measurement are not well known or reported. It would be helpful for manufacturers to determine and provide this information for clinical monitoring systems. Future larger scale studies should address the presence of cerebral blood flow and cerebral electrical activity in relation to arterial pulse pressures to better delineate the changes to be expected in the brain following WLSM.

Death Determination by Neurologic Criteria

- To increase the strength of our recommendation, more direct evidence for the interval of time after injury to ensure permanence of the loss of brainstem reflexes is required. Currently we do not know the predictive value of a combination of Glasgow Coma Scale 3 and absence of all brainstem reflexes on the outcome of death determination by neurologic criteria. A study assessing patients post cardiac arrest who meet the minimal criteria for death by neurologic criteria at 24 hours post arrest would have to be examined at 48 hours and 72 hours post arrest to determine the rate of false positive death determinations, and which element(s) of the exam returned over time and thus were not permanently lost.
- We could not identify any comparative data indicating superiority of one temperature threshold over another for the accuracy of determination of DNC. Future studies could provide clarity in this regard and inform future revised recommendations.
- The body of literature would benefit from more direct evidence comparing quantitative pupillometry to routine clinical pupil assessment in this patient population. With more direct evidence and improved comfort and access to quantitative pupillometry, this recommendation can be re-visited.
- The literature on the use VOR and OCR testing as part of the clinical assessment for death determination by neurologic criteria was observational, of moderate quality and all studies were conducted more than 40 years ago. Current research examining the accuracy of these tests would be beneficial in determining their true sensitivity and specificity. Further, though there is no physiological premise for these reflexes to be different, outside of the premature neonatal population, studies in infants and children are warranted to increase certainty in the evidence for these populations.
- Prospective studies that compare the use of exogenous CO_2 administration to conventional apnea testing are needed to provide higher quality evidence to address this question.
- Future studies should examine the effect of positive pressure on family acceptance of apnea testing, accuracy of the apnea test and the ability for physicians to interpret the physical examination. In addition, from a transplant perspective, the effect of positive pressure on the number of lungs recovered for transplant and graft outcome in both groups would be helpful.
- Further research with regard to the number of complete clinical assessments may be required in newborn infants and patients with decompressive craniectomies, as these subgroups were under-represented in this sample.

Ancillary Investigations

- Studies assessing the diagnostic accuracy of ancillary investigations for death by neurologic criteria are overwhelmingly of moderate to high risk of bias. Most of these studies did not include pediatric patients. In most studies, interpretation of ancillary investigation results was performed by individuals with expertise that may not be available in all hospital settings.
- Further high-quality research is required to characterize the diagnostic accuracy of ancillary investigations for DNC. At the present time, the evidence base is mostly comprised of studies of moderate to high risk of bias, most of which did not include a sample entirely representative of the target population. Research is encouraged to develop and validate ancillary investigations that test cerebral function (without using blood flow or perfusion as a surrogate for function), without being significantly affected by intoxication or sedation. Particular attention to function assessment would be valuable. The validity of ancillary investigations based on interpretation by non-experts (for instance, in community settings) is another important topic of further research. Finally, the reliability and cost-effectiveness of ancillary investigations for DNC also merits further investigation.
- More research is required to clearly delineate which ancillary investigations can be used for the neurologic determination of death in children and adolescents. Overall, for the 39 studies the certain of evidence was very low to low due to serious risk of bias, indirectness, and imprecision. It would be ideal to have non-imaging modalities which could be utilized as ancillary investigations since they would be available bedside and would not require transferring a critically ill patient. Unfortunately, all these modalities require further research. Future studies utilizing transcranial doppler (TCD), brainstem auditory evoked potentials and somatosensory evoked potentials would benefit from a clear definition of which waveforms are consistent with neurologic death, and if these waveforms should be present bilaterally, and under which circumstances bilateral waveforms are not required. TCD studies are needed which standardize the vessels under investigation and evaluate waveform and flow in bilateral middle cerebral arteries, bilateral anterior cerebral arteries, basilar and vertebral arteries.
- The panel was concerned about utilizing EEG as an ancillary investigation given its ability to be affected by confounders such as phenobarbital, pentobarbital and hypothermia. Future research addressing the effects of these confounders in a dose dependent fashion on EEG would improve the ability to utilize this modality in children for neurologic death determination.
- Regarding imaging based modalities, research focused on improving numbers of patients in coma and following their trajectory would improve the sensitivity and specificity for all imaging modalities but in particular CT angiography and 4 vessel angiography for there was no pediatric data to calculate specificity.
- Subgroup analysis is another important area for future research in pediatric ancillary investigations. There is a minuscule amount of data for ancillary investigation in children under 2 months and less for pre-term infants. The panel recommends further studies in this area to be able to make recommendations in the future.