

The diagnosis of death by neurological criteria in infants less than two months old: Guideline methodology

1. Introduction

This document describes in detail the methodology used to develop the recommendation presented in the report '(see [full report](#) for further details). The report provides recommendations for the diagnosis of death by neurological criteria (DNC) in infants. The report aims to enable health care professionals to diagnose DNC in infants by ensuring that all recommendations are based upon predetermined systematic methods to identify and evaluate evidence relating to specific review questions. In areas where no evidence was found an informal group consensus method was used to formulate recommendations.

The report was developed by the Royal College of Paediatrics and Child Health (RCPCH) in accordance with the RCPCH *Standards for Development of Clinical Guidelines in Paediatrics and Child Health Guideline Manual*.

While the report assists the practice of health care professionals, it does not replace their knowledge and skills.

2. Scope

2.1 Remit

The RCPCH, by the request of the Academy of Medical Royal Colleges (AoMRC), aims to update the 1991 British Paediatric Association (BPA)² report on the diagnosis of DNC in infants from 37 weeks corrected gestation (post menstrual) to two months post term.

2.2 Population covered

The report addresses the diagnosis of DNC in infants from 37 weeks corrected gestation (post menstrual) to two months post term.

2.3 Target audience

The report is intended for use by all UK paediatric and neonatal health care practitioners and other groups involved in the regulation or practice of the health care of critically ill neonates and young infants.

2.4 What this guideline covers

- a) The application of clinical criteria currently used to diagnose DNC in older infants, children and adults to infants between 37 weeks corrected gestation (post menstrual) and two months post term.
- b) Pre-conditions that should be observed in infants under two months prior to attempting to diagnose DNC.
- c) The possible diagnostic use of ancillary tests in the diagnosis of DNC.

2.5 What this guideline does not cover

This guideline does not cover:

- a) Broader issues around redirection or withholding medical treatment in children
- b) Issues surrounding organ donation and transplantation
- c) The recommendations detailed in this report do not cover the management of pre term infants, below 37 weeks gestation.

3. Developers and conflicts of interest

A working group was appointed to oversee the development process. The group carried out the critical appraisal, data extraction of papers and the informal consensus process. The RCPCH Clinical Standards Team carried out the systematic searches and coordinated the development of the report, providing methodological advice and support to the working group. The report was drafted by the working group in consultation with the RCPCH Clinical Standards Team. The report was not funded directly and instead developed through time and efforts volunteered from the working group and RCPCH Clinical Standards Team. The group met regularly (every one to three months) during the development of the report. The working group declared all conflicts of interest, which were recorded.

No conflicts of interest were reported by Jane Abbott, Colin Kennedy, Victoria Marshment, Jillian McFadzean, Neil McIntosh, Claire Snowdon, Neil Stoodley, Brenda Strohm, Robert Tasker, Dominic Wilkonson and Leann Willis.

Conflicts of interests were reported by Denis Azzopardi, Joe Brierley and John Wyatt. Denis Azzopardi received a Medical Research Council grant to carry out clinical research in infants with encephalopathy, Joe Brierley is the Clinical lead in organ donation at Great Ormond Street Hospital (GOSH) and is paid annually for this role, as well as being a member of the University College, London (UCL), Donation Ethics Committee. Joe Brierley took part in the early meetings when reviewing the evidence but did not take part in the discussions to develop the recommendations. John Wyatt received Medical Research Council funding for brain research (completed in 2014) via UCL; however, there was no personal gain and this was deemed not related to the current work carried out by the working group.

4. Aims and objectives

The report is an update of the 1991 BPA report² and 2008 AoMRC's Code of Practice³ and aims to take account of contributions to evidence in the medical literature from 1990 to 2014 relating to the diagnosis of death in young infants from 37 weeks corrected gestation (post menstrual) to two months post term. See [full report](#) for further details

5. Review questions

The report sets out to address the following three questions in regard to infants from 37 weeks corrected gestation (post menstrual) to two months post term:

1. Can the clinical criteria used to diagnose DNC in older infants, children and adults be applied to these young infants?
2. Should there be preconditions for the diagnosis of DNC in these young infants that are additional to those applied to older infants, children and adults?
3. Can ancillary tests provide us with additional relevant information in the diagnosis of DNC?

The working group formed the review questions based on the scope and a protocol was prepared by the RCPCH Clinical Standards Team. The review questions were developed in a framework of population, intervention, comparison and outcome for reviews of interventions in order to examine the diagnosis of death in the presence of persisting cardiac function. This was to guide the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the working group. The working group drafted the clinical questions which were validated by the RCPCH Clinical Standards Team.

6. Literature search

The review questions formed the starting point for systematic reviews of relevant evidence. A focused search was carried out on Medline and EMBASE databases. A search strategy was developed by the RCPCH Clinical Standards Team to ensure that all studies identified met the pre-defined inclusion and exclusion criteria. Searches were limited by English language and there was no searching of grey literature, nor was hand searching of journals undertaken. The full search strategy can be found in the Appendix.

All searches were updated and re-executed within four months before the start of the stakeholder consultation to ensure the reviews were up-to-date. The process was completed by December 2014 and no publications after this date were considered.

7. Identifying the evidence

Evidence was screened and identified by the chair of the working group and a member of the RCPCH Clinical Standards Team. Full articles were then obtained and full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review questions in the appropriate population and reported outcomes of interest.

7.1 Included studies

Studies were considered for inclusion if they were primary studies (case reports or case series) reporting on the clinical assessment of death by certain neurological criteria despite persisting cardiac function in infants. Due to the lack of evidence retrieved, when assessing studies for the use of ancillary tests, publications were included for infants from 37 weeks gestation to 12 months of age.

7.2 Excluded studies

Publications were excluded if:

- Studies focusing on clinical assessment of death by certain neurological criteria despite persisting

cardiac function related to children where data in infants younger than 2 months could not be separated.

- Studies focusing on ancillary tests where data for infants under one year old and older children could not be separated.
- Publications of the following type were also excluded: personal practice, comments, correspondence, reviews, guidelines, book chapters, reports and publications by or commissioned for professional bodies, governmental institutions and organizations of a comparable nature (unless based on systematic review) and conference proceedings.
- Articles published in languages other than English.

7.3 Selecting the evidence

Abstracts were screened for relevance by the working group chair and RCPCH project team. Full text articles were sought and screened according to the inclusion and exclusion criteria to identify studies that addressed the review questions. Those studies meeting the inclusion criteria were sent to members of the working group for a final decision on whether to include the papers. The working group chair was asked to confirm that the excluded studies had been correctly selected, and to resolve any queried articles by making a final decision.

8. Data extraction

Papers were critically appraised using checklists developed by the Institute of Health Economics⁴ and key information about the study's population, methods and results were extracted and recorded on report forms designed for this process. Each reviewer independently extracted data and data were extracted from all papers by at least two working group members.

In keeping with the RCPCH *Standards for Development of Clinical Guidelines Manual*^l the type of clinical question would determine the highest level of evidence that may be sought. In assessing the quality of the evidence, each study received a quality rating using Scottish Intercollegiate Guidelines Network (SIGN) levels of evidence⁵. See Table 1 for the *levels* of evidence and Table 2 for the *grading* of recommendations.

9. Data synthesis

Extracted data were placed into an evidence table by the RCPCH Clinical Standards Team and reviewed by the working group to develop recommendations.

Further to this the working group assessed the degree of detail provided in each publication of the diagnosis of death in the presence of persisting cardiac function (Table 3). Each publication was reviewed in detail and depending on the clinical features described in the report, was assigned a degree of detail I, II or III.

Table 1. Levels of evidence.

Level	Type of evidence (based on SIGN, 2000) ⁵
1++	Evidence from high quality meta analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Evidence from well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Evidence from meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	Evidence from high quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2+	Evidence from well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Evidence from case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Evidence from non-analytic studies, e.g. case reports, case series
4	Evidence from expert opinion

Table 2. Grading of recommendations.

Grade	Type of Recommendation (based on SIGN, 2000) ⁵
A	Requires at least one meta analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, and demonstrating overall consistency of results
B	Requires a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	Requires a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Table 3. Degree of information given in reports of diagnosis of death in the presence of persisting cardiac function in infants under two months.

Degree of detail	Clinical features of death in the presence of persisting cardiac function described in the report
I	Coma; brain stem reflexes individually described; reflex respiratory response to hypercarbia formally tested (the apnoea test)
II	As for degree I, but brain stem reflexes not individually reported
III	Death in the presence of persisting cardiac function reported, but individual clinical features not elaborated in any detail

10. Consensus

For areas where there was a lack of evidence to answer the clinical question, informal group consensus was applied. A meeting was held to discuss the evidence and agree recommendations and drafts of the report were circulated to all members until consensus was achieved.

11. Consultation: External review

The draft version of the report was sent to key stakeholders for consultation. All comments were considered by the working group and any necessary changes made prior to the finalised report being submitted to the RCPCH Clinical Standards Committee for endorsement.

12. Funding

The report update was internally funded by the RCPCH. The views or interest of the funding body have not influenced the final recommendations.

13. Lay involvement

The working group sought to include involvement from parents and carers from the outset of the report development process and included a lay representative on the group, as well as seeking advice from charities and the RCPCH Child and Young Person Advocacy Team.

References

1. Royal College of Paediatrics and Child Health. Standards for development of clinical guidelines in paediatrics and child health. 2006. Available from http://www.rcpch.ac.uk/sites/default/files/asset_library/Research/Clinical%20Effectiveness/Standards%20Document%20June%202006.pdf
2. British Paediatric Association. Diagnosis of brain stem death in children: A Working Party Report. 1991.
3. Academy of Medical Royal Colleges. A code of practice for the diagnosis and confirmation of death. 2008. Available from http://www.aomrc.org.uk/doc_details/42-a-code-of-practice-for-the-diagnosis-and-confirmation-of-death
4. Moga C., Guo B., Schopflocher D., *et al.* Development of a quality appraisal tool for case series studies using a modified Delphi technique. 2012. Available from <http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?ID=32012000811#.VRA8nO6sWCZ>
5. Scottish Intercollegiate Guidelines Network (SIGN). A guideline developer's handbook. Available from <http://www.sign.ac.uk/pdf/sign50.pdf>

Appendix

Search strategies

Clinical Question 1: Can the clinical criteria used to diagnose DNC in older infants, children and adults be applied to young infants?

Search #1: MEDLINE and EMBASE

- Embase 1996 to 2014 Week 12
- Ovid MEDLINE(R)1946 to Present (27 March 2014)
- Ovid MEDLINE(R) Daily Update 27 March 2014
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
(Dates searched: 1 January 1990 - 27 march 2014)

1. infant\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
2. neonate\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
3. newborn\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
4. baby.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
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6. child.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
7. children.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
8. full term.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. brainstem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
11. brain stem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
12. brain death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
13. neurological death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
14. neurologic death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
15. irreversible coma.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
16. cerebral death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
17. cerebral coma.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
18. brain damage.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
19. irreversible brain damage.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
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21. 9 and 20
22. diagnosis.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
23. diagnoses.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
24. diagnostic procedure\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
25. diagnostic criteria.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
26. assesment.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
27. clinical observation\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
28. 22 or 23 or 24 or 25 or 26 or 27
29. 21 and 28
30. limit 29 to english language
31. limit 30 to yr="1990 -Current" (27 March 2014)

Clinical Question 2: Should there be preconditions for the diagnoses of DNC in young infants that are additional to those applied to older infants, children and adults?

Search #2: MEDLINE and EMBASE

- Embase1996 to 2014 Week 12
- Ovid MEDLINE(R)1946 to Present (27 March 2014)
- Ovid MEDLINE(R) Daily Update 27 March 2014
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
(Dates searched: 1 January 1990 - 27 March 2014)

1. infant\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
2. neonate\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
3. newborn\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
4. baby.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
5. babies.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
6. child.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
7. children.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
8. full term.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. brainstem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
11. brain stem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
12. brain death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
13. neurological death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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15. irreversible coma.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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17. cerebral coma.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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19. irreversible brain damage.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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21. 9 and 20
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23. diagnoses.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
24. diagnostic procedure\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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26. assesment.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
27. clinical observation\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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29. 21 and 28
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32. remove duplicates from 31
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41. 9 and 20 and 28 and 40
42. limit 41 to english language
43. limit 42 to yr="1990 -Current"
44. remove duplicates from 43

Clinical Question 3: Can ancillary tests provide with additional relevant information in the diagnoses of DNC?

Search #3: MEDLINE and EMBASE

- Embase1996 to 2014 Week 12
- Ovid MEDLINE(R)1946 to Present (27 March 2014)
- Ovid MEDLINE(R) Daily Update 27 March 2014
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
(Dates searched: 1 January 1990 - 27 March 2014)

1. infant\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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28. 22 or 23 or 24 or 25 or 26 or 27
29. 21 and 28
30. limit 29 to english language
31. limit 30 to yr="1990 -Current"
32. remove duplicates from 31
33. angiography.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
34. radionuclides angiography.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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36. cerebral arteriography.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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43. brainstem auditory evoked response\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
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45. apnoea test.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
46. apnea test.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
47. pH.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
48. PCO2.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
49. PO2.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
50. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. 9 and 20 and 28 and 50
52. limit 51 to english language
53. limit 52 to yr="1990 -Current"

Brain stem reflexes in the diagnoses of DNC.

Search #4: MEDLINE and EMBASE

- Embase1996 to 2014 Week 12
 - Ovid MEDLINE(R)1946 to Present (27 March 2014)
 - Ovid MEDLINE(R) Daily Update 27 March 2014
 - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
- (Dates searched: 1 January 1990 - 27 March 2014)

1. infant\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
2. neonate\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]

3. newborn\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
4. baby.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
5. babies.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
6. child.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
7. children.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
8. full term.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. brainstem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
11. brain stem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
12. brain death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
13. neurological death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
14. neurologic death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
15. irreversible coma.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
16. cerebral death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
17. cerebral coma.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
18. brain damage.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
19. irreversible brain damage.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 9 and 20
22. diagnosis.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
23. diagnoses.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
24. diagnostic procedure\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
25. diagnostic criteria.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
26. assesment.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
27. clinical observation\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
28. 22 or 23 or 24 or 25 or 26 or 27
29. 21 and 28
30. limit 29 to english language
31. limit 30 to yr="1990 -Current"
32. remove duplicates from 31
33. reflex.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
34. reflexes.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
35. 33 or 34
36. pupil\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
37. ocular movement.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
38. vestibulo ocular.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
39. vestibulo-ocular.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
40. oculogyric.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
41. corneal.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
42. pupillary.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
43. facial sensation.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
44. facial motor response.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
45. pharyngeal.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]

46. tracheal.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
47. cough.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
48. gag.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
49. 36 or 37 or 38 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 35 and 49
51. 9 and 20 and 28 and 50
52. limit 51 to english language
53. limit 52 to yr="1990 -Current"
54. remove duplicates from 53
55. sedative\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
56. tranquiliser\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
57. tranquilliser\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
58. tranquilizer.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
59. tranquillizer\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
60. hypnotic\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
61. anxiolytic\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
62. soporific\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
63. barbiturate\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
64. benzodiazepine\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
65. non benzodiazepine\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
66. antihistamine\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
67. antiemetic\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
68. anesthetic\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
69. induction.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
70. muscle relaxant\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
71. narcotic\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
72. depressant\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
73. neuromuscular\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
74. hypothermia.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
75. 55 or 56 or 57 or 58 or 59 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
76. drug\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
77. medication\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
78. medicine\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
79. agent\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
80. treatment\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
81. therapy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
82. 76 or 77 or 78 or 79 or 80 or 81
83. 75 and 82
84. 50 and 83
85. limit 84 to english language
86. limit 85 to yr="1990 -Current"
87. remove duplicates from 86

'Death by neurological criteria' in infants- General searches

Search #5: MEDLINE and EMBASE

- Embase1996 to 2014 Week 12
 - Ovid MEDLINE(R)1946 to Present (27 March 2014)
 - Ovid MEDLINE(R) Daily Update 27 March 2014
 - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
(Dates searched: 1 January 1990 - 27 March 2014)
1. death by neurological criteria.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
 2. (infant\$ or neonate\$ or newborn or baby or babies or child or children or life birth\$ or full term).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
 3. (death and by and neurological and criteria).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
 4. 1 and 2
 5. 2 and 3
 6. 4 or 5
 7. limit 6 to yr="1990 -Current" (27 March 2014)

'Diagnoses of brain stem death' in infants-General search

Search #6: MEDLINE and EMBASE

- Embase1996 to 2014 Week 12
 - Ovid MEDLINE(R)1946 to Present (September 2014)
 - Ovid MEDLINE(R) Daily Update September, 2014
 - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
 - AutoAlert set up: Last review December 2014
1. infants\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 2. neonate\$ mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 3. newborn\$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rx, ui]
 4. baby.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rx, ui]
 5. babies.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rx, ui]
 6. full term.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 7. brainstem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 8. brain stem death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 9. brain death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 10. neurological death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 11. neurologic death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 12. irreversible coma.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 13. cerebral death.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
 14. 1 or 2 or 3 or 4 or 5 or 6

15. 7 or 8 or 9 or 10 or 11 or 12 or 13
16. 16.14 and 15
17. 17.limit 16 to english language
18. 18. limit 17 to yr="1990-Current"
19. 19. limit 18 to humans