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Computed tomography (CT) angiography for confirmation of the clinical diagnosis of brain death

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess from the current literature the utility and sensitivity of CT cerebral angiography as a confirmatory or add-on test following a clinical diagnosis of death using neurological criteria. For the purpose of this review, CT angiography will be considered as an add-on or confirmatory test. As described above, CT angiography demonstrates opacification or otherwise of the intracranial vasculature following the intravenous injection of iodinated contrast media. As such, it is very similar in nature to conventional catheter angiography (where contrast is injected intra-arterially, usually selectively into the major extracranial neck vessels).

No secondary objective is to be examined.

We will attempt to fully investigate all possible sources of heterogeneity. We anticipate this may include, but not be limited to, variances in methods of clinical diagnosis and heterogeneity in imaging techniques, as well as methodological sources of heterogeneity.

Wherever possible, we will consider the following:

- incorporation bias;
- verification bias;
- diagnostic review bias;
- clinical review bias;
- design bias (retrospective reviews versus prospective studies).

There are several specific factors that we anticipate may contribute to clinical heterogeneity, which we will divide into clinical and imaging factors.
Clinical factors

As has previously been mentioned, the clinical criteria involved in establishing a diagnosis of brain death vary between countries. If study authors do not clarify the protocols used in clinical testing, we will seek further clarification from relevant lead authors. However, all international clinical standards also act as legal standards and we anticipate that, for this reason, there is likely to be strict adherence to testing protocols within individual studies.

Although there is anticipated heterogeneity in testing for whole brain function, all current clinical protocols necessitate the satisfaction of the minimum clinical criteria as outlined above.

It is possible that there may be greater differences between patients diagnosed according to irreversible cessation of brain-stem function and those diagnosed according to cessation of all functions of the entire brain. We will aim, therefore, to identify the clinical protocol used to diagnose brain death. Should there be sufficient available data, we will analyse these two major groups as subgroups.

A further source of bias to consider is the possibility that any clinical diagnosis of brain death may potentially be influenced by an existing CT angiographic study; that is, the role of CT angiography may have inadvertently become the reference standard. This will be difficult to account for in the published literature unless authors explicitly clarify the blinded states of both clinical testers and image reviewers. However, as clinical testing for brain death is a legal standard (regardless of the clinical protocol used), in all countries, it should be subject to a higher level of scrutiny than many other clinical tests and as such is considered much less likely to be influenced by other tests.

Imaging factors

There is moderate heterogeneity in the exact protocol and CT angiographic technique between CT scanner manufacturers and centres. The following aspects of the investigation and reporting will need to be defined: timing, contrast dose, quality of study (that is absence of motion artefact, which may degrade a CT series), volume of contrast, volume of acquisition, scanner type (single spiral, multislice, detector type, scan time), single or double reviewer, and experience of reviewer. If this is not clear in the selected studies we will seek further information from the relevant lead authors.

In particular, there may be heterogeneity in the protocols used for imaging, which may have significant effects on the quality of any subsequent report. It would be expected that most centres will follow a protocol similar to that detailed by Frampas et al (Frampas 2009) wherein three separate CT acquisitions are performed within the study: one pre-contrast, one 20 sec following contrast (to confirm opacification of the superficial temporal arteries and hence appropriate contrast injection and cardiac output to deliver contrast to the vessels of the neck and head), and one at 60 sec to evaluate opacification of the cortical segments of the middle cerebral arteries and the deep cerebral veins. This protocol differs from the typical CT angiographic protocol used for assessment of the intracranial vasculature in other clinical groups but is considered necessary in this group to confirm appropriate contrast passage and absence of pre-contrast vessel opacification or densities. We will specifically look for the protocol used. If this is not available, we will seek further information from the relevant lead authors. If further information is not forthcoming and the protocol cannot be clarified, we will not include the study.

In addition, we will also consider the time of imaging compared with clinical assessment (that is time from suspected onset of the target condition, or time interval between the index test and the reference standard). In the anticipated patient cohort, the time interval between the index test and reference standard is of importance as significant changes in clinical condition may occur over a relatively short space of time. We will also attempt to establish that patients are not in a state of hypovolaemia or cardiovascular insufficiency (factors which would contribute to cerebral hypoperfusion and potential variance in imaging findings), although this may be accounted for depending on the imaging protocols used, as described above.

We will also consider heterogeneity that may be introduced due to the interpretation of imaging test results and the variance of interpretation between reviewers. Again, due to the ethically sensitive nature of this subject, we anticipate that many studies will be interpreted by at least two authors and although the reports of these studies will naturally fall into two dichotomous groupings (‘intracranial vessel enhancement’ versus ‘no intracranial vessel enhancement’) there may be a small number of studies reported with a more indeterminate or intermediate opinion.
BACKGROUND

The diagnosis of brain death is an important and potentially emotive clinical task, with a formal diagnosis having significant implications for the patient, family and wider transplant population. In specific patient populations, most notably heavily sedated patients, standard clinical tests may not be possible. Therefore it is critical that the diagnosis is made in a robust, defensible and timely fashion.

In 2008 the Academy of Medical Royal Colleges, UK, published a Code of Practice for the Diagnosis and Confirmation of Death, including the diagnosis of death following the irreversible cessation of brain-stem function (Academy of Medical Royal Colleges 2008). While neuroimaging is not recommended in the majority of cases where clinical diagnosis is possible, the report acknowledges that there may be a minority of cases where clinical testing cannot be completed. The report suggests that ancillary tests, including a variety of neuroimaging techniques, may help to reduce any clinical uncertainty. However, no firm recommendation as to which test should be used was made in the report.

Consensus statements have been published in other countries, notably from the Canadian Council for Donation and Transplantation (2006) (Heran 2008; Young 2006), recommending either radionuclide or computed tomography (CT) cerebral angiography as the preferred imaging test. However, no ratified international guidelines or current systematic reviews exist which review the combined accuracy or utilisation of these tests relative to the current reference standard of clinical testing. Any change in current practice would have legal and ethical implications.

There are disputes about the clinical diagnosis of brain death and the potential role of radiological tests in the diagnosis of brain death. Recent controversial case reports have highlighted physician uncertainty in this complex and challenging area of medical practice and are likely to promote an increased use of ancillary brain blood flow radiological investigations (Roberts 2010; Webb 2011). If the use of CT cerebral angiography to assist or confirm the diagnosis of death using neurological criteria becomes more widespread, then a greater understanding of its utility and sensitivity becomes clinically essential.

The authors of this review are aware of current controversies both in the clinical diagnosis of brain death and in the use of radiological tests, and their potential role in the diagnosis of brain death. Each of the currently available ancillary tests has proponents and detractors, and there remains significant heterogeneity in the clinical application of all of these tests, the test methodology and the analysis of the findings.

CT angiography has been chosen as the first test to study for the reasons listed in the ‘index test’ section below. Should such a study be considered technically appropriate as a diagnostic test accuracy (DTA) test, this would then allow comparison of the other ancillary tests in the future using a similar framework.

Target condition being diagnosed

The target condition is the clinical diagnosis of brain death, that is, death diagnosed by neurological criteria. The neurological determination of death represents a set of criteria for confirming death when cardio-respiratory criteria for determining death cannot be used. This is usually because cardio-respiratory activity is being maintained artificially on in an intensive care unit.

The history of diagnosing death using neurological criteria is generally dated from 1968 when the Ad Hoc Committee of the Harvard Medical School defined ‘irreversible coma as a new criterion for death’, which led to widespread adoption (JAMA 1968). There is now international acceptance and legal support for criteria to determine death on neurological grounds in individuals being artificially maintained in an intensive care unit. The specific criteria themselves have been refined since 1968 and vary internationally. In the United Kingdom, India and Canada, clinical confirmation of irreversible cessation of brain-stem activity or function is sufficient to diagnose brain death. In the USA the Uniform Declaration of Death Act codifies a whole-brain formulation of brain death, “an individual who has sustained... irreversible cessation of all functions of the entire brain, including the brainstem, is dead” (President’s Commission 1981). Additionally in the USA the use of ‘complementary diagnostic tests’ is recommended (Canadian Council 2003). Other countries including Australia, Canada and some European countries have adopted criteria for brain death somewhere in between those of the UK and the USA. Whole brain death including the absence of brain blood flow (although the demonstration of absent flow is not routinely required) is required for the legal determination of death in Australia and New Zealand (ANZICS 2010). Many European countries have similar criteria to the USA and Australasian standard (Wijdicks 2002).

Despite this difference in conceptual understanding of brain death, in all countries which recognize the diagnosis of death using neurological criteria (brain death) a clinical examination of the brain stem demonstrating absent brain-stem reflexes and a clinical demonstration of apnoea, demonstrating the loss of the brainstem mediated reflexes to breathe, is considered mandatory and essential. Thus the clinical criteria outlined by the UK Academy of Medical Royal Colleges in 2008 represent the minimum clinical criteria, which all countries recognize as absolutely essential for the determination of brain death.

It is not possible in any jurisdiction to be diagnosed as deceased using neurological criteria without first satisfying minimum clinical criteria. These minimum clinical criteria are:

1. an established aetiology capable of causing structural damage to the brain, which could lead to the irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe;
2. an exclusion of reversible conditions capable of mimicking or confounding the diagnosis of death using neurological criteria;
3. A clinical examination of the patient, which demonstrates:
   a. profound coma,
b. absent brain-stem reflexes,
c. apnoea.

Fulfilment of the above minimum clinical criteria for the neurological determination of death, combined with clinician belief that death has been diagnosed using neurological criteria acceptable in that jurisdiction, will act as the target condition for this Cochrane review. Hereafter the target condition of death using neurological criteria will be referred to as clinical brain death.

**Index test(s)**

Standard practice for ancillary diagnosis of brain death varies between centres and across countries, depending to a great extent on consensus guidance, local availability and local experience with techniques. A detailed discussion of the relative merits of current tests that are available is beyond the scope of this review, but is elegantly covered by Heran et al (Heran 2008). It is, however, relevant to note that the currently available tests measure different aspects of cerebral blood supply or function. An electroencephalogram (EEG) and somatosensory evoked potentials measure cerebral function as evidenced by neuronal electrical activity or response to a presented stimulus. Transcranial Doppler demonstrates absolute flow rates within individual cerebral vessels. Scintigraphic, CT and magnetic resonance imaging (MRI) perfusion studies directly calculate the relative or absolute perfusion of cerebral parenchyma over time. In contrast, both cerebral catheter angiography and CT angiography indirectly measure flow or vessel patency within the cerebral circulation by monitoring the presence or absence of a radiodense contrast medium within the intracranial vessels. As technology improves, advanced techniques such as time-resolved CT angiography and MR angiography, perfusion, diffusion series have the potential to combine both vessel delineation and calculation of parenchymal perfusion, but they are uncommonly available as yet.

As technology has developed over the last 20 years, CT cerebral angiography has now become an easily available, widely used technique, which is routinely used in the diagnosis of many intracranial vascular abnormalities. The ability to obtain high quality dynamic images of the cerebral vasculature in clinically unstable or ventilated patients in a short space of time (several seconds), and the subsequent ease of image review and lack of operator dependence, confers several practical advantages to CT cerebral angiography over both MRI and sonographic assessment of cerebral blood flow, with supportive publications demonstrating high sensitivity and specificity (Escudero 2009; Frampas 2009).

Methodologically, CT angiography is a straightforward investigation with recordable and reproducible imaging techniques, contrast volumes, concentrations, injection rates and other technical imaging factors (kV, mAs, rotation, timing) that are useful for any robust analysis. Moreover, and in contrast to conventional catheter cerebral angiography, CT cerebral angiography can be performed at a hospital site without on-site neuroradiological support. It can be reviewed by an experienced neuroradiologist distant to the patient at a regional centre. In the UK there are significantly more hospitals with intensive care units managing the anticipated patient population than there are tertiary neuroradiological centres with catheter angiographic facilities, and therefore this is an important practical consideration when considering the role of CT angiography versus a traditionally favoured (and older) catheter angiographic study.

The aim of this review is to assess the utility and sensitivity of CT cerebral angiography as a confirmatory or add-on test following a clinical diagnosis of death using neurological criteria as outlined above.

**Alternative test(s)**

No alternative tests are to be considered within the scope of this systematic review.

**Rationale**

This study was originally conceived to answer a currently pertinent question; that is, ‘what evidence is there for the role of a widely available and commonly performed radiological study (CT angiography), in isolation, in the management pathway of patients who are (or are suspected to be) clinically brain dead?’

**OBJECTIVES**

To assess from the current literature the utility and sensitivity of CT cerebral angiography as a confirmatory or add-on test following a clinical diagnosis of death using neurological criteria. For the purpose of this review, CT angiography will be considered as an add-on or confirmatory test. As described above, CT angiography demonstrates opacification or otherwise of the intracranial vasculature following the intravenous injection of iodinated contrast media. As such, it is very similar in nature to conventional catheter angiography (where contrast is injected intra-arterially, usually selectively into the major extracranial neck vessels).

**Secondary objectives**

No secondary objective is to be examined.

**Investigation of sources of heterogeneity**

We will attempt to fully investigate all possible sources of heterogeneity. We anticipate this may include, but not be limited to,
variances in methods of clinical diagnosis and heterogeneity in imaging techniques, as well as methodological sources of heterogeneity.

Wherever possible, we will consider the following:

- incorporation bias;
- verification bias;
- diagnostic review bias;
- clinical review bias;
- design bias (retrospective reviews versus prospective studies).

There are several specific factors that we anticipate may contribute to clinical heterogeneity, which we will divide into clinical and imaging factors.

**Clinical factors**

As has previously been mentioned, the clinical criteria involved in establishing a diagnosis of brain death vary between countries. If study authors do not clarify the protocols used in clinical testing, we will seek further clarification from relevant lead authors. However, all international clinical standards also act as legal standards and we anticipate that, for this reason, there is likely to be strict adherence to testing protocols within individual studies.

Although there is anticipated heterogeneity in testing for whole brain function, all current clinical protocols necessitate the satisfaction of the minimum clinical criteria as outlined above. It is possible that there may be greater differences between patients diagnosed according to irreversible cessation of brain-stem function and those diagnosed according to cessation of all functions of the entire brain. We will aim, therefore, to identify the clinical protocol used to diagnose brain death. Should there be sufficient available data, we will analyse these two major groups as subgroups.

A further source of bias to consider is the possibility that any clinical diagnosis of brain death may potentially be influenced by an existing CT angiographic study; that is, the role of CT angiography may have inadvertently become the reference standard. This will be difficult to account for in the published literature unless authors explicitly clarify the blinded states of both clinical testers and image reviewers. However, as clinical testing for brain death is a legal standard (regardless of the clinical protocol used), in all countries, it should be subject to a higher level of scrutiny than many other clinical tests and as such is considered much less likely to be influenced by other tests.

**Imaging factors**

There is moderate heterogeneity in the exact protocol and CT angiographic technique between CT scanner manufacturers and centres. The following aspects of the investigation and reporting will need to be defined: timing, contrast dose, quality of study (that is absence of motion artefact, which may degrade a CT series), volume of contrast, volume of acquisition, scanner type (single spiral, multislice, detector type, scan time), single or double reviewer, and experience of reviewer. If this is not clear in the selected studies we will seek further information from the relevant lead authors.

In particular, there may be heterogeneity in the protocols used for imaging, which may have significant effects on the quality of any subsequent report. It would be expected that most centres will follow a protocol similar to that detailed by Frampas et al (Frampas 2009) wherein three separate CT acquisitions are performed within the study: one pre-contrast, one 20 sec following contrast (to confirm opacification of the superficial temporal arteries and hence appropriate contrast injection and cardiac output to deliver contrast to the vessels of the neck and head), and one at 60 sec to evaluate opacification of the cortical segments of the middle cerebral arteries and the deep cerebral veins. This protocol differs from the typical CT angiographic protocol used for assessment of the intracranial vasculature in other clinical groups but is considered necessary in this group to confirm appropriate contrast passage and absence of pre-contrast vessel opacification or densities. We will specifically look for the protocol used. If this is not available, we will seek further information from the relevant lead authors. If further information is not forthcoming and the protocol cannot be clarified, we will not include the study.

In addition, we will also consider the time of imaging compared with clinical assessment (that is time from suspected onset of the target condition, or time interval between the index test and the reference standard). In the anticipated patient cohort, the time interval between the index test and reference standard is of importance as significant changes in clinical condition may occur over a relatively short space of time. We will also attempt to establish that patients are not in a state of hypovolaemia or cardiovascular insufficiency (factors which would contribute to cerebral hypoperfusion and potential variance in imaging findings), although this may be accounted for depending on the imaging protocols used, as described above.

We will also consider heterogeneity that may be introduced due to the interpretation of imaging test results and the variance of interpretation between reviewers. Again, due to the ethically sensitive nature of this subject, we anticipate that many studies will be interpreted by at least two authors and although the reports of these studies will naturally fall into two dichotomous groupings (‘intracranial vessel enhancement’ versus ‘no intracranial vessel enhancement’) there may be a small number of studies reported with a more indeterminate or intermediate opinion.

**METHODS**

Computed tomography (CT) angiography for confirmation of the clinical diagnosis of brain death (Protocol)
Criteria for considering studies for this review

Types of studies
We will include studies of populations of human subjects, published in all languages. However, if relevant non-English articles are identified but full-text translations cannot be obtained in press, we will place them in the 'studies awaiting assessment' section and will seek help from colleagues within The Cochrane Collaboration to obtain accurate translations.

We will consider studies to be acceptable if:
- the studies have a cross-sectional design, comparing CT cerebral angiography (with or without other imaging or ancillary tests) with a clinical diagnosis of brain death, that is, death diagnosed by clinical neurological criteria;
- the participant population is defined as those in whom either a clinical diagnosis of brain death has already been made or a clinical diagnosis of brain death is established as part of the study;
- the absolute numbers of true and false positives, and true and false negatives, are either available directly from the published study data either secondarily derivable from data within the published study or as supplementary published material, or available directly from the original study authors.

Other comparator tests will not be reviewed as part of this study. It is anticipated that many studies may include at least one other comparator imaging or investigative test; if these studies fulfill our criteria for acceptance they will be included.

There may be further studies in which CT cerebral angiography has been considered as a reference test and a further clinical test compared against it. Our search strategy will be tailored to include these studies; however they will not be included unless they also include a statement to the effect of, ‘all included subjects satisfied a clinical diagnosis of brain death’, or similar, allowing CT cerebral angiography to be viewed as an index test against the reference test of clinical testing. We will contact authors of any such studies to obtain relevant supplementary data.

Studies will ideally define clinical and imaging parameters that have been employed as part of their methodology. In particular, if details of the following are not specifically included we will contact the author(s) and attempt to obtain these items.

Methodological parameters
- Time interval from reference standard to CT angiography (or vice versa)
- Evidence of blinding of clinicians, reporters to CT angiography, reference standard findings

Clinical parameters
- Criteria used for diagnosis of brain death (including country of origin, name of approving regulatory body if applicable)
- Experience of clinician(s)

Imaging acquisition
- Contrast dose, contrast volume, acquisition volume, scanner type (single spiral or multislice), study time

Imaging reporting
- Single, double, consensus reporting
- Experience of reporter(s)

We will exclude study reports that have been written to focus on specific technical aspects of either clinical or imaging technique. We will also exclude commentary or opinion-forming articles that do not have a clinical study component.

In the case of multiple publications by the same author or group of authors with similar data, we will attempt to contact the author(s) to establish the degree of similarity within their described patient populations. If this is not possible, we will include only the most recent or complete study. Should data be missing from studies selected for review, we will contact the author(s) and attempt to obtain these items.

Participants
We will include patients in whom a diagnosis of brain death is suspected or in whom a clinical diagnosis of brain death has been made. We will identify both adult and paediatric populations; this is consistent with the recommendations of the Working Party from the Academy of Royal Colleges that standard adult clinical criteria and testing can be used in those over two months of age to diagnose brain death. However, there are several physiological and procedural differences in the performance of CT angiography in the paediatric population, namely the volume of contrast administered (which is related to weight) and cardiac output. These factors may significantly affect the utility of CT angiography in the paediatric population and, therefore, the authors will analyse adult (over 16 years old) and paediatric populations separately.

It is conceivable that we may encounter two patient subgroups in reviewed articles. That is:
- patients who have already received a diagnosis of clinical brain death prior to undergoing CT angiography;
- patients who do not have a diagnosis of clinical brain death but are suspected to be in such a state at the time of CT angiography and who subsequently go on to receive a diagnosis of clinical brain death.

It is possible that this temporal relationship may be of significance when looking for sources of heterogeneity, particularly as this review aims to assess the role of CT angiography as a confirmatory test rather than a replacement, triage or screening test. We will
record this data and, if required, perform a subgroup analysis between these two cohorts.

**Index tests**
The index test will be CT cerebral angiography. Image acquisition and reporting parameters will ideally be defined as listed above.

**Comparator tests**
No comparator tests are to be considered as part of this study. However, it is anticipated that many studies may include at least one other imaging or investigative test (from those described in the index test section above) as a comparator, or that there are studies in which CT angiography may have been considered a reference test but will suffice as an index test for the purposes of this review. Our search strategy will be tailored to include these possibilities as described above.

**Target conditions**
The target condition is the clinical diagnosis of brain death. Studies will need to define the clinical method used to establish a diagnosis of brain death. This is described in much greater detail in the initial 'Background' section of this protocol document.

**Reference standards**
The reference standard is the diagnosis of brain death, which is in effect the same as the target condition. In order to reduce heterogeneity, we will record the clinical method used to diagnose brain death. Although this information may not be immediately available, we will contact authors or establish the legal requirements in the country of article authorship, or both, to establish this. It should then be possible to perform a subgroup analysis between cohorts diagnosed according to a 'no brain-stem function' clinical method and those diagnosed according to a 'no brain or brain-stem function' clinical method.

**Search methods for identification of studies**

**Electronic searches**
We will perform a comprehensive literature search to identify relevant studies in various electronic databases. There are difficulties with searching for studies to include in any diagnostic test accuracy review. "Diagnostic test accuracy" is not a commonly used keyword/phrase in the same way that "randomised trial" is, thus preventing a simple search. Free text word searches rather than the use of subject headings or exploded terms from electronic database thesauruses are required. We have therefore designed a series of search strategies that cast as wide a net as possible.

To investigate which strategy would be best for our purposes we conducted a minor test search using "brain death" as an exploded subject heading from the EMBASE (Ovid SP) database, and the free text wildcard term "brain dea*" from the same database. The free text search returned 88,803 results compared with just 6167 from the exploded subject heading. While we believe it is likely that the exploded search strategy will return relevant papers, we are keen that any search we undertake has the best possible chance of returning all relevant information for further review. Our search strategy is therefore labour intensive and time consuming but is also as detailed and complete as possible.

We will search the electronic databases using free text words in all fields only. We will set the limits to studies of human subjects only, but otherwise the searches will not be limited by language or study design. Although spiral CT technology was commercially available in 1989, CT angiography became a useful clinical technique in 1992, and therefore we will search the databases from January 1992. We will set age limitations to include those articles studying patients over two months of age only.

We will search the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); MEDLINE (Ovid) (January 1992 to date); EMBASE (Ovid) (January 1992 to date); BNI (Ovid) (January 1992 to date); CINAHL (EBSCO) (January 1992 to date); PASCAL (January 1992 to date); BioMed Central (January 1992 to date); African Index Medicus (January 1992 to date).

We will also search the following regional electronic bibliographic databases, subject-specific databases, ongoing trials databases and dissertation and theses databases:

- MEDION;
- IndMed;
- Google Scholar;
- Current Controlled Trials;
- clinicaltrials.gov.

Our search strategies can be found in Appendix 1.

**Searching other resources**
We will identify further studies for possible inclusion in our review by following the reference lists from studies located by our initial search strategies. Using the Science Citation Index will allow the identification of other studies referencing already identified relevant work. Two of the authors (AH, CB) will handsearch relevant conference proceedings. We will contact relevant experts in the field in order to identify other relevant studies not retrieved by our search strategies.

**Data collection and analysis**

**Selection of studies**
Two authors (AH, CB) will be responsible for initially assessing studies identified by the search strategy, based on title and abstract. We will retrieve potentially relevant studies in full, and the full text will be reviewed and assessed by two of three other authors (TT, RD, DG). We will resolve disagreements by the majority vote of the third author. We will use proprietary reference manager software to manage the large number of studies anticipated at this stage. We will document study selection in a detailed flow chart.

Data extraction and management
Following identification of relevant studies, two authors (AH, CB) will extract the relevant information from each study. In addition to that information, detailed in the Methods section above, we will also record the following information:
- journal name, Vancouver-style reference, study design (e.g. systematic review, cross-sectional study), method of recruitment (e.g. prospective or retrospective study), study setting, characteristics of patient population (including age, gender, underlying primary diagnosis leading to current clinical state, relevant medical history if available).

We will record this information in a dedicated database.

Assessment of methodological quality
We will use the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (Whiting 2003) tool (Appendix 3) to assess the methodological quality of each included study. The recommended QUADAS questions will be used, which provide a structured set of 14 questions each with a ‘yes’, ‘no’, or ‘unclear’ answer. These questions are designed to evaluate the presence of bias related to multiple aspects of study methodology. Each study will be reviewed by two of three authors (TT, RD, DG). We will resolve disagreement between the two reviewing authors by consensus. Should this not be possible, the third author will be the arbiter. We will combine the Individual author assessments and the agreed results of the QUADAS tool will be tabulated in graphic form to be included in the results of our review.

For the purposes of this review, we will define the following terms. For QUADAS question 1, ‘A representative spectrum of patients’ will be defined as ‘patients of > 2 months of age and either gender in whom there is a clinical suspicion of brain death, and who have undergone or are shortly to undergo clinical testing for the diagnosis of brain death’.

For QUADAS question 4, a time period of two days will be taken as the maximum reasonable interval between the reference standard and index test, or vice versa. This will account for any delays built into the process of clinical testing, the possibility of residual effects of sedative drugs, which may require elimination, and practical delays in acquiring a CT angiographic study.

For QUADAS question 8, CT cerebral angiography is now a widespread and well-understood technique among the worldwide radiology community. However, techniques vary considerably between centres and published protocols for CT angiography in this patient cohort differ significantly from standard CT angiography. ‘Sufficient detail’ will be defined as standard whole brain CT angiography following intravenous injection of water-soluble iodinated contrast media performed with a spiral CT scanner. Should any study diverge from this generalized definition, the study would return a positive response to this question only if further specific technical details are provided, either in the published study or from correspondence, and the technical details are such that the test can still be classified as a CT cerebral angiogram and that the index test was applied reproducibly in this way for all participants in the study in question. Should the study return a positive response to this question, two authors (TT, RD) will further examine the imaging protocol description within the study and will seek subsequent clarification from the study authors as to the exact nature of the imaging protocol if this is not explicitly clear.

For QUADAS question 9, studies containing a statement to the effect of ‘all included subjects already had a conclusive clinical diagnosis of brain death’, or similar, would return a positive response to this question only if the criteria for clinical testing or the national protocol used or the regulatory body approving the testing is also identified, either in the published study or following correspondence.

In addition, the authors will add four further questions which are relevant to this specific review to the tool, covering expertise and blinding of the reporting radiologist and also covering the expertise and blinding of the clinician(s) performing the reference study.

Additional question 1
With regard to the index test, was the expertise of the reporting radiologist(s) recorded?

Additional question 2
With regard to the reference study, was the expertise of the performing clinician(s) recorded?

Additional question 3
With regard to the index test, was the reporting radiologist blinded to the results of any prior clinical testing?

Additional question 4
With regard to the reference test, was the performing clinician blinded to the results of any ancillary investigation for the investigation of brain death?
Statistical analysis and data synthesis

We will generate a 2 x 2 cross classification table of brain death and the CT angiography test result for each included study, using data either directly extracted from the study text or derived from presented data. Each table will contain the tally of true positive, false positive, true negative and false negative cases. We will enter the data into Review Manager version 5.0.25 or above (RevMan 5.1). Data entry will be double checked by a second author. We will use forest plots to graphically demonstrate heterogeneity within sensitivity and specificity estimates.

From a preliminary reading of typical reports that are likely to be included studies, three different analysis strategies may be necessary. First, if most or all included studies have structural zeros for false positives and true negatives, then specificity is not estimable. As the RevMan algorithms do not provide point estimates nor confidence intervals for summary statistics of sensitivity, meta-analysis of sensitivity will be performed in the meta-analysis package metafor version 1.4-0 or above running in R version 2.12.0 or above (R: a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). A random-effects model will be used with consideration of various transformations of the sensitivity proportion for variance stabilization. The point estimate with a 95% confidence interval (CI) of sensitivity and heterogeneity (tau²) will be reported. If study-level covariates are available, a reduction of heterogeneity with sensitivity will be modelled by meta-regression.

Second, some studies may contain non-zero tallies in all four cells of the 2 x 2 table but may be sparse and have insufficient data to permit convergence in the estimation of parameters in hierarchical or bivariate random-effects models. Then, both sensitivity and specificity will be analysed independently as in the first strategy.

Third, there may be sufficient data to estimate bivariate random-effects models. Estimation will be in the Metandi package running in Stata version 11.1 or above (StataCorp, College Station, Texas). The results will be reported in both the parameterization of the bivariate binomial model and the hierarchical summary ROC model. Results will be plotted as the summary ROC curve, the summary operating point (summary values of sensitivity and specificity), a 95% confidence region around the summary operating point and a 95% prediction region. The 95% prediction region illustrates the extent of heterogeneity by visualizing the bounds within which a future study's sensitivity and specificity would be found with 95% confidence. If study level covariates are found, then a reduction in heterogeneity will be modelled as possible within the capabilities of the software.

Investigations of heterogeneity

(See above)

Sensitivity analyses

(See above)

Assessment of reporting bias

(See above)

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References

Additional references

Academy of Medical Royal Colleges 2008

ANZICS 2010

Canadian Council 2003

Escudero 2009

Frampas 2009

Heran 2008
A P P E N D I C E S

Appendix 1. EMBASE and MEDLINE strategies via Ovid SP

**EMBASE**
1. (“brain dea*” OR “brain stem dea*” OR ”coma depasse” OR ”irreversible coma”).any field [Limit to: Publication Year 1992-Current and Human] (4980 results)
2. (“CT” OR “CTA” OR “comput* tomograph*” OR “comput* aided tomograph*” OR “comput* tomograph* angio*” OR “comput* aided tomograph* angio*”).any field [Limit to: Publication Year 1992-Current and Human] (278228 results)
3. 1 AND 2 [Limit to: Publication Year 1992-Current and Human] (236 results)

**MEDLINE**
1. (“brain death” OR “brain stem death” OR ”coma depasse” OR ”irreversible coma”).any field [Limit to: Publication Year 1992-Current and Human] (4228 results)
2. (“CT” OR “CTA” OR “comput* tomograph*” OR “comput* aided tomograph*” OR “comput* tomograph* angio*” OR “comput* aided tomograph* angio*”).any field [Limit to: Publication Year 1992-Current and Human] (188324 results)
3. 1 AND 2 [Limit to: Publication Year 1992-Current and Human] (142 results)

Search 1 to identify all human studies from 1992 - current with brain death or equivalent phrase as a term in any search field.
Search 2 to identify all human studies from 1992 - current with CT angiography or equivalent phrase as a term in any search field.
Search 3 to combine 1 & 2 and allow identification of all relevant studies in EMBASE/MEDLINE databases.
Appendix 2. Other database strategies

These databases do not allow combining search steps as in step 3 above. All results of the searches below will therefore be dealt with individually.

MEDION
1. “ICPC_code N (Neurological)”
2. “Signs_code I (Medical Imaging)”

Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library)
1. “brain and dead or death”
2. “coma depasse or irreversible coma”
3. “CT or CTA or CTCA or CAT or computer tomograph or computer aided tomograph or computer tomograph angiography or computer tomograph angiogram or computer aided tomograph angiography or computer aided tomograph angiogram or computer tomograph cerebral angiography or computer tomograph cerebral angiogram”

BNI (Ovid)
As the search strategy for MEDLINE and EMBASE above

CINAHL (EBSCO)
1. “TX brain death or TX brain dead or TX coma depasse or TX irreversible coma”
2. “TX CT or TX CTA or TX CAT or TX CTCA or TX computer tomograph or TX computer tomograph angiography or TX computer tomograph angiogram or TX computer aided tomograph angiography or TX computer aided tomograph angiogram or TX computer tomograph cerebral angiography or TX computer tomograph cerebral angiogram”

PASCAL

BioMed Central

African Index Medicus

IndMed

Google Scholar
1. “brain dead”
2. “brain death”
3. “coma depasse”
4. “irreversible coma”
5. “CT”
6. “CTA”
7. “CTCA”
8. “CAT”
9. “computer tomograph”
10. “computer aided tomograph”
11. “computer tomograph angiography”
12. “computer tomograph angiogram”
13. “computer aided tomograph angiography”
14. “computer aided tomograph angiogram”
15. “computer tomograph cerebral angiography”
16. “computer tomograph cerebral angiogram”

Appendix 3. Modified QUADAS checklist

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Was the spectrum of patients representative of the patients who will receive this test in practice?*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>Answer</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Were selection criteria clearly described?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Did patients receive the same reference standard regardless of the index test result?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Was the reference standard independent of the index test (i.e. did not form part of the reference standard?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Was the execution of the index test described in sufficient detail to permit its replication? ***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Was the execution of the reference standard described in sufficient detail to permit its replication? ****</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Were the reference standard results interpreted without knowledge of the results of the index test?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Were the same clinical data available when test results were interpreted as would be available when the test is used in clinical practice?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Were un-interpretable / indeterminate results reported?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Were study withdrawals explained?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Additional items**

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>With regard to the index test, was the expertise of the reporting radiologist/s recorded?</td>
</tr>
<tr>
<td>16</td>
<td>With regard to the reference study, was the expertise of the performing clinician/s recorded?</td>
</tr>
<tr>
<td>17</td>
<td>With regard to the index test, was the reporting radiologist blinded to the results of any prior clinical testing?</td>
</tr>
<tr>
<td>18</td>
<td>With regard to the reference test, was the performing clinician blinded to the results of any ancillary investigation for the investigation of brain death?</td>
</tr>
</tbody>
</table>

* defined as "patients over 2 months of age, and of either gender, in whom there is a clinical suspicion of brain death, and who have undergone or are shortly to undergo clinical testing for the diagnosis of brain death".

** a time period of 2 days will be taken as the maximum reasonable interval between reference standard and index test or vice versa, although the absolute time will be recorded and if data permits, subgroup analysis will be performed (answers Sycha Q3 point 3)

*** defined as "standard whole brain CT angiography following intravenous injection of water-soluble iodinated contrast media, performed with a spiral CT scanner". Should any study diverge from this generalised definition, return a YES response to this question only if further specific technical details are provided either in the published study or from correspondence and the technical details are such that the test can still be classified as a CT cerebral angiogram
the index test was applied reproducibly in this way for all participants in the study in question.

**** Return a YES response to studies containing a statement to the effect of “all included subjects already had a clinical diagnosis of brain death”, or similar, only if
the criteria for clinical testing
or
the national protocol used
or
the regulatory body approving the testing,
is also identified, either in the published study or following correspondence.

HISTORY


CONTRIBUTIONS OF AUTHORS

Conceiving the review: TT, RD, DG
Co-ordinating the review: TT
Undertaking manual searches: AH, CB
Screening search results: AH, CB
Organizing retrieval of papers: AH, CB
Screening retrieved papers against inclusion criteria: AH, CB
Appraising quality of papers: TT, RD, DG
Abstracting data from papers: AH, CB
Writing to authors of papers for additional information: AH, CB, TT, RD, DG
Providing additional data about papers: AH, CB, TT, RD, DG
Obtaining and screening data on unpublished studies: AH, CB, TT, RD, DG
Data management for the review: TT, AH, CB
Entering data into Review Manager (RevMan 5.1): AH, CB
RevMan statistical data: NC, NP
Other statistical analysis not using RevMan: NC, NP
Double entry of data: (data entered by person one: AH; data entered by person two: CB)
Interpretation of data: NC, NP
Statistical inferences: NC, NP
Writing the review: (all authors)
Securing funding for the review: DG
Performing previous work that was the foundation of the present study: n/a
Guarantor for the review (one author): TT
Person responsible for reading and checking review before submission: all authors
DECLARATIONS OF INTEREST

DG is the Clinical Lead for Organ Donation, Nottingham University Hospitals NHS Trust and the Midlands Regional Clinical Lead for Organ Donation. Nottingham University Hospitals NHS Trust is reimbursed by NHS Blood and Transplant for his time.

CB is a Specialist Nurse for Organ Donation employed and managed by NHS Blood and Transplant.

No other interests declared at time of publication.