NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Normothermic ex-vivo preservation of hearts from brainstem dead donors for clinical transplantation (1289/1)**
Name of Specialist Advisor:	**Mr Andre Simon**
Specialist Society:	**NHS Blood and Transplant**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

X Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

X Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

X Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

☐ I have never performed this procedure.

☐ I have performed this procedure at least once.

X I perform this procedure regularly.

Comments:

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

X I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

x I have undertaken bibliographic research on this procedure.

x I have undertaken research on this procedure in laboratory settings (e.g. device-related research).

x I have undertaken clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

X Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter that procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

3.2 What would be the comparator (standard practice) to this procedure?

3.3 Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

X Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

4 Safety and efficacy

4.1 What are the adverse effects of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

A transplantable organ could be lost to transplantation due to a device malfunction

2. Anecdotal adverse events (known from experience)

A small number of organs have been lost due to accidental disconnects from the perfusion system after a change to the connector that has not reoccurred.

3. Adverse events reported in the literature (if possible please cite literature)

No adverse events have been recorded with the current iteration of the device

4.2 What are the key efficacy outcomes for this procedure?

Use of normothermic ex-vivo preservation of hearts from brainstem dead donors for clinical transplantation has 4 potential effects:

1- Use of this technique may allow for treatment of organs in the system
2- It allows for a significant increase in cross-clamp to cross-clamp time in heart transplantation. This is due to the minimisation of true ischemia
3- Use of normothermic ex-vivo perfusion allows for additional assessment of the organ beyond what is possible in the organ donor
4- Use of normthermic ex-vivo preservation of hearts in clinical transplantations significantly decreases ischemia time and the detrimental effects of prolonged ischemia

The above effects allow for a significant increase in the number of organs transplanted

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

There have been a number of publications demonstrating the efficacy of this procedure specifically the results of the PROCEED II trial which show safety and non-inferiority of the only currently available device when compared to cold storage, and results from our group which have clearly shown successful transplantation of extended criteria hearts, or hearts that are not transplantable with standard cold storage, and high risk complex recipient / donor combinations.

4.4 What training and facilities are required to undertake this procedure safely?

Organ retrieval teams have to be fully trained in the use of ex-vivo perfusion. This requires basic training and regular exposure to ex-vivo perfusion by all members of the multi-disciplinary team. The team should include a perfusionist as well as a physician / surgeon. There are no specific facilities required to undertake training, however the procedure is carried out clinically within the operating theatre.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

One clinical trial – clinicaltrials.gov.NCT00855712 (PROCEED II) has been registered and completed. The results have been published in The Lancet.

A second clinical trial is approved and registered, EXPAND Heart Pivotal Trial NCT 02323321 in the United States, and is about to commence.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

There is a current controversy on-going about the cost:benefit ratio of this procedure.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

Measures should include

1) Numbers of organ transplanted with the use of ex-vivo perfusion.
2) Outcomes of transplantations, then compared to cold storage
3) Increase in numbers of patients transplanted from ventricular assist devices and outcomes, as well as other specific patient groups, e.g. congenital heart disease
4) Outcomes related to out of body time vs expected ischemia time (this includes time from cross-clamp to arrival in the recipient operating theatre)
5) Travel distance
6) Length of post-operative intensive care and hospital stay
7) Percentage of patients requiring hemofiltration
8) Percentage of patients experiencing prolonged right heart failure
9) Cost analysis of observed savings vs necessary investment

5.2 Adverse outcomes (including potential early and late complications):

As above, as well as

1) System failures

2) Pathological anatomical analysis of hearts turned down during ex-vivo perfusion and numbers of 'faults'

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

It is to be expected, that should this procedure be approved and appropriately funded it will be adopted into immediate clinical use and become the standard of care in all transplant centres.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

X Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

X Major.

☐ Moderate.

☐ Minor.

Comments:

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

8 Data protection and conflicts of interest

8.1 Data protection statement

The Institute is committed to transparency. As part of this commitment your name and specialist society will be placed in the public domain, in future publications and on our website (www.nice.org.uk) and therefore viewable worldwide. This information may be passed to third parties connected with the work on interventional procedures.

A copy of the completed Specialist Adviser advice will be sent to the Specialist Society who nominated the Specialist Adviser.

Specialist Advisers should be aware that full implementation of the Freedom of Information Act 2000 may oblige us to release Specialist Advice from 2005. The Freedom of Information Act 2000 favours the disclosure of information however requests will be considered on a case by case basis. If information is made available, personal information will be removed in accordance with the Data Protection Act 1998. In light of this please ensure that you have not named or identified individuals in your comments.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Please state any potential conflicts of interest, or any involvements in disputes or complaints, relevant to this procedure. Please use the "Conflicts of Interest for Specialist Advisers" policy (attached) as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	**x**	**YES**
	☐	**NO**
Fee-paid work – any work commissioned by the healthcare	☐	**YES**

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

industry **– this includes income earned in the course of private practice**	x	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	x	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	x	**NO**
Investments – any funds which include investments in the healthcare industry	☐	**YES**
	x	**NO**
Do you have a **personal non-pecuniary** interest – eg have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	x	**YES**
	☐	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	x	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	x	**NO**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

February 2010

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where

the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 Personal family interest

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Normothermic ex-vivo preservation of hearts from brainstem dead donors for clinical transplantation (1289/1)**
Name of Specialist Advisor:	**Mr Anselm Priest**
Specialist Society:	**Society of Clinical Perfusion Scientists of Great Britain and Ireland**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

☒ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☒ Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☒ Yes.

☒ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

Controversy exists about the practice regarding reperfusion of brains post cardiac death

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

☒ I have never performed this procedure.

☐ I have performed this procedure at least once.

☐ I perform this procedure regularly.

Comments:

I have staff members who regulalrly do this procedure

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☒ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☐ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☐ I have undertaken bibliographic research on this procedure.

☐ I have undertaken research on this procedure in laboratory settings (e.g. device-related research).

☐ I have undertaken clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☒ Other (please comment)

Comments:

My staff have done regular research, both bibliographic and clinical, involving patients

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter that procedure's safety and efficacy.

☒ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

3.2 What would be the comparator (standard practice) to this procedure?

Cardioplegic arrest followed by transport on ice, albeit for a different patient cohort

3.3 Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

☒ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

4 Safety and efficacy

4.1 What are the adverse effects of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

breakdown of the perfusion machine during transportation

2. Anecdotal adverse events (known from experience)

Clotting of the circuit whilst supporting the patient prior to explant

3. Adverse events reported in the literature (if possible please cite literature)

not known

4.2 What are the key efficacy outcomes for this procedure?

optimising organs for transplantation and growing the number of transplantable organs

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

yes, that organ function isnt optimised for long term post implant function

4.4 What training and facilities are required to undertake this procedure safely?

device training, procedural training

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

not sure

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.

not sure

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

not sure

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

An increase in the number of tranplanatble organs. Improved function of those organs. Shorter ITU and hospital stay

5.2 Adverse outcomes (including potential early and late complications):

primary graft failure prior to transplant, graft failure post implant

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

1 - 2 years

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☒ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☒ Minor.

Comments:

Minor in the number of patients who would benefit but moderate in the cost associated with the procedure

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

no

8 Data protection and conflicts of interest

8.1 Data protection statement

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Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☒	**YES**
	☐	**NO**
Fee-paid work – any work commissioned by the	☒	**YES**

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

healthcare industry **– this includes income earned in the course of private practice**	☐	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☒	**YES**
	☐	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	☒	**NO**
Investments – any funds which include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – eg have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☐	**YES**
	☒	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	☒	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	☒	**NO**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

I am the Chief Perfusionist at PapworthNHS Trust. The Clinical Perfusion service here is subcontracted to my "for profit" company CPS LLP.I invoice the Trust for our services and then pay the staff that undertake this research and clinical role.

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

February 2010

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

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2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

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2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where

the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 Personal family interest

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

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4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

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5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Normothermic ex-vivo preservation of hearts from brainstem dead donors for clinical transplantation (1289/1)**
Name of Specialist Advisor:	**John Dark**
Specialist Society:	**Society of Cardiothoracic Surgeons of Great Britain and Ireland**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

X☐ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☐ Yes.

X☐ No. If no, please enter any other titles below.

Comments:

Any current assessment of this technology must appreciate it's use for the preservation and assessment of hearts from Donation after Circulatory Death (DCD). This is a new and very rapidly developing field.

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

X☐ Yes.

X☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The only currently available device for performing ex-vivo perfusion of the heart is the Organ Care System (OCS) made by the Transmedics company, based in the USA. It is engineered to a very high standard, but the just the *disposables* cost between £25000 and £35000. Until recently, the only published results with the device were non-inferiority with the standard form of cold static preservation – most recent paper from Ardehali et al, Lancet 2015; 385: 2577–84. But the group at Harefield, in the UK, published a series of donor heart retrievals using the OCS system, showing that at least some hearts believed to be of marginal usability could be retrieved with very good results. So the *controversy* revolves around whether the very substantial costs can be justified by increasing the number of heart transplants performed, with possibly better outcomes.

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

X☐ I have never performed this procedure.

☐ I have performed this procedure at least once.

☐ I perform this procedure regularly.

Comments:

Because of the costs involved, only one centre in the UK has any substantial experience – and it is not clear how they pay for the device. But as there is gradually more persuasive data, one other centre has the device available, and two others have charitable support for its' introduction.

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

X☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☐ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

x☐ I have undertaken bibliographic research on this procedure.

x☐ I have undertaken research on this procedure in laboratory settings (e.g. device-related research).

☐ I have undertaken clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

In my centre we have limited experience with a non-portable version of this technology. We also have a collaboration with a group in Lund, Sweden, and with them hope to be involved in clinical introduction in due course

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter that procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

X☐ The first in a new class of procedure.

Comments:

Only the Transmedics OCS device is available and CE marked

In addition to the use for routine and marginal heart preservation, the device has also been used in a ground-breaking series of transplants using hearts from DCD – Donation after Circulatory Death – donors. In this setting, the donor heart can only be removed after death is certified by cessation of heartbeat, and after waiting a further 5 minutes to ensure the heart does not restart. In this setting, the donor heart suffers a significant ischaemic insult. Energy stores must be restored by perfusion with oxygenated blood, and at present only the Transmedics device is available to do this.

After 3 such transplants were done in Sydney, Australia, a further 10 have been done in the UK, at Papworth and Harefield hospitals. This is a ground-breaking advance in which the UK is taking an international lead.

3.2 What would be the comparator (standard practice) to this procedure?

Cold static preservation. This involves flushing the donor heart with a cold cardioplegic solution and then storing on ice at 4C. This has been used for more than 30 years. There is a close relation between ischaemic time and early outcome. Donor graft failure due to prolonged ischaemia is the dominant cause of early death after heart transplant

This approach cannot be used for the DCD heart

3.3 Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

x☐ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

See above, about costs and consequent slow adoption

4 Safety and efficacy

4.1 What are the adverse effects of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

Cost – theoretical and real

The extent of “marginality” of the donor heart which is acceptable is not known. There is no relevant animal work. So the true volume of the additional heart transplants which might be performed from “Marginal” donors is difficult to quantify

2. Anecdotal adverse events (known from experience)

It is known that the heart may become disconnected from the device. In at least one of the early series, this happened twice. This has not been published! Disconnection results in loss of the donor heart

3. Adverse events reported in the literature (if possible please cite literature)

4.2 What are the key efficacy outcomes for this procedure?

Early mortality after heart transplant, and other surrogates for poor performance of the donor heart, such as ITU stay

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

Only the extent to which hearts can be improved, and so the number of additional transplants which might be performed

4.4 What training and facilities are required to undertake this procedure safely?

Training is offered by the company – it involved practising organ retrieval with animal hearts (outside the UK) and then supervision with human hearts

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

Yes, the company is sponsoring a series of trials

The PROCEED ll trail was recently published (see below)
The website mentions a “Heart EXPAND Trial”, but there are no details

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.

PROCEED ll was published this year -. **Ardehali et al, Lancet 2015; 385: 2577–84.**

The initial experience from Sydney with DCD Heart donation was published this year in the Lancet - **Published online April 15, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60038-1**

The experience from Harefield Hospital in using the Transmedics OCS device to successfully use heart from outside standard criteria was published last year – **Garcia-Saez et al Ann Thorac Surg 2014;98:2099–106**

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

Rapidly evolving area, with much uncertainty

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

Increased numbers of heart transplants
Better survival after Heart Transplantation
Less Morbidity – shorter ITU stay, less need for renal replacement therapy, for instance

5.2 Adverse outcomes (including potential early and late complications):

Cost-Benefit analysis
Unlikely to be late disadvantages if early function is better

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

Severely limited by funding in the UK. But several other adult heart transplant centres – and there are only 6 in the UK – are intending to use the device in the next 12 months

If the cost-benefit analysis for using this device for marginal hearts and DCD hearts is positive, there might be an additional 50 heart transplants from this donor source, all using the Transmedics device.

If cheaper alternatives come available, as is almost inevitable, the eventual use in the UK might be 200-300 per year

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

X☐ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

See above

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☒ Minor.

Comments:

Minor in terms of numbers, major in terms of cost. If the cost stays at £30,000 per set of disposables, the additional costs might be £3-9M per year. The additional transplants generated would be another significant cost

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

Comments above, and the three papers cited, together with the Transmedics website, will give most of the additional information

8 Data protection and conflicts of interest

8.1 Data protection statement

The Institute is committed to transparency. As part of this commitment your name and specialist society will be placed in the public domain, in future publications and on our website (www.nice.org.uk) and therefore viewable worldwide. This information may be passed to third parties connected with the work on interventional procedures.

A copy of the completed Specialist Adviser advice will be sent to the Specialist Society who nominated the Specialist Adviser.

Specialist Advisers should be aware that full implementation of the Freedom of Information Act 2000 may oblige us to release Specialist Advice from 2005. The Freedom of Information Act 2000 favours the disclosure of information however requests will be considered on a case by case basis. If information is made available, personal information will be removed in accordance with the Data Protection Act 1998. In light of this please ensure that you have not named or identified individuals in your comments.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Please state any potential conflicts of interest, or any involvements in disputes or complaints, relevant to this procedure. Please use the "Conflicts of Interest for Specialist Advisers" policy (attached) as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	x	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐	**YES**
	x	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	x	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	x	**NO**
Investments – any funds which include investments in the healthcare industry	☐	**YES**
	x	**NO**
Do you have a **personal non-pecuniary** interest – eg have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	**x**	**YES**
	☐	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	x	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	**x**	**YES**
		NO

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

Personal non-pecuniary interest:
I work 1 day per week for the Organ Donation and Transplantation (ODT) Directorate of NHS Blood and Transplant (NHSBT) and have been involved in organising the logistics of DCD heart retrieval. I have no links with either of the hospitals carrying out this work, and no links with the company

Support by the healthcare industry or NICE:
As an Academic at Newcastle University, I am a section lead in the Cambridge/Newcastle NIHR sponsored Blood and Transplant Research Unit (BTRU). This work will involve collaboration with an academic group at Lund University in Sweden, and an associated company – Vivoline – in the development and projected clinical use of a rival device to the Transmedics machine

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whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

February 2010

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where

the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 Personal family interest

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Normothermic ex-vivo preservation of hearts from brainstem dead donors for clinical transplantation (1289/1)**
Name of Specialist Advisor:	**Stephen Clark**
Specialist Society:	**Society of Cardiothoracic Surgeons of Great Britain and Ireland**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

☒ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☒ Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☒ Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

☐ I have never performed this procedure.

☐ I have performed this procedure at least once.

☒ I will perform this procedure regularly.

Comments:

My centre is training in this technique currently and will very shortly commence regular use of the device

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☒ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☒ I have undertaken bibliographic research on this procedure.

☐ I have undertaken research on this procedure in laboratory settings (e.g. device-related research).

☐ I have undertaken clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☒ Other (please comment)

Comments:

Clinical study to commence in September using this device in patients with adult congenital heart disease

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter that procedure's safety and efficacy.

☒ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

3.2 What would be the comparator (standard practice) to this procedure?

Cold ischaemic heart preservation

3.3 Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☒ 10% to 50% of specialists engaged in this area of work.

☐ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

4 Safety and efficacy

4.1 What are the adverse effects of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

Poor preservation and primary graft dysfunction, Technical issues leading to loss of organs, Mechanical failure, Economically unsound

2. Anecdotal adverse events (known from experience)

Organ loss, Primary graft dysfunction, High cost, Organ loss due to disconnection

3. Adverse events reported in the literature (if possible please cite literature)

4.2 What are the key efficacy outcomes for this procedure?

Lower rates of primary graft dysfunction, Prolonged acceptable ischaemic times, Organ reconditioning, Improved outcomes in high risk recipients, increased number of transplants performed

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

Studies thus far suggest non inferiority to conventional presrvation techniques rather than benefit. Some evidence of improved outcomes in high risk recipients, no trials of perfusion regime or perfusate, no cost-benefit or economic analysis but there is a suggestion that using the system may increase transplant volumes and shorten length of ITU stay

4.4 What training and facilities are required to undertake this procedure safely?

Experienced heart transplant team, previous experience of ex vivo organ perfusion, approved training by the system manufacturer with technical support initially

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

PROTECT Study
PROCEED II Trial – Published in the Lancet April 2015
EXPAND Trial

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.

The American Journal of Transplantation
Normothermic *Ex Vivo* Perfusion Provides Superior Organ Preservation and Enables Viability Assessment of Hearts From DCD Donors.
Iyer, K. K. Dhital and P. S. MacDonald et. al.

Annals of Thoracic Surgery
Evaluation of the Organ Care System in Heart Transplantation With an Adverse Donor/Recipient Profile.
Diana Garcia Saez, Nicholas R. Banner, Andre R Simon et. al.

Journal of Thoracic and Cardiovascular Surgery
Continuous Perfusion of Donor Hearts in the Beating State Extends Preservation Time and Improves Recovery of Function.
Hassanein WH, Zellos L, Khuri S et. al.

Transplant International
Normothermic donor heart perfusion: current clinical experience and the future.
Simon Messer, Abbas Ardehali and Steven Tsui

Appl Cardiopulmonary Pathophysiology
Organ Preservation with the Organ Care System.
Yeter R, Hübler M, Knosalla, Cet al.

Deng M, Soltesz E, Naka Y et al. Is Lactate Level During Warm Perfusion a Predictor for Post Transplant Outcomes? Poster Session 1: Heart Donor Management Organ Allocation at The International Society of Heart & Lung Transplantation (ISHLT). Montréal, Canada. *The Journal of Heart and Lung Transplantation.* April 2013. Vol. 32, Issue 4. Supplement. Pgs. S516- 57.

Deng M, Soltesz E, Naka Y et al. Ex-Vivo Perfusion of Human Donor Hearts Reduces Cold Ischemia Time. Poster Session 1: Heart Donor Management

Organ Allocation at The International Society of Heart & Lung Transplantation (ISHLT). Montréal, Canada. *The Journal of Heart and Lung Transplantation.* April 2013. Vol. 32, Issue 4. Supplement. Pg. S156.

Esmailian F, Kobashigawa J, Naka Y et al. The PROCEED II International Heart Transplant Trial with the Organ Care System Technology (OCS). Presentation at the International Society of Heart & Lung Transplantation (ISHLT). Montréal Canada. *The Journal of Hearth and Lung Transplantation*. April 2013; Vol. 32: Number 4S. Pgs. S95 – S96.

Ghodsizad A. Ex vivo coronary angiography of a donor heart in the Organ Care System. *The Heart Surgery Forum*. June 2012. Vol. 15, Issue 2. Pg. 161.

Goldsmith, K, Demiris, N, Gooi, J, et al. Life-Years Gained by Reducing Donor Heart Ischemic Times. *Transplantation*. January 2009; Vol. 87: Number 2. Pgs. 243 – 48.

Hamed A, Tsui, S, Huberm J, et al. Serum lactate is a highly sensitive and specific predictor of post-cardiac transplant outcomes using The Organ Care System. Paper presented at The International Society of Heart & Lung Transplantation (ISHLT). , Palais des Congres, Paris, France. *The Journal of Heart and Lung Transplantation.* February 2009. Vol. 28, pg. S71.
Hassanein A.H, Elbetanony A, Abdelaziem A, et al. The Organ Care System (OCS) Enables Ex-Vivo Assessment of Donor Heart Coronary Perfusion Using Contrast Echocardiography. *The Journal of Heart and Lung Transplantation.* February 2009. Vol. 28. Pg. S150

Hassanein, W.H, Zellos, L, Tyrrell, T, et al. (1997). A novel technique for prolonged endothelial & myocardial preservation of the donor heart. Paper presented at Cardiac Allograft Vasculopathy symposium, The Second International Syposim on cardiac allograph vasculopothy. Hamilton, Bermuda.

Hassanein W.H, Zellos L, Tyrrell T, et al. (November 1997). A novel approach for 12-hour donor heart preservation. Paper presented at the 70th meeting of The American Heart Association. Orlando, Florida. AHA – look for the. Supplement.

Hassanein W.H. Continuous perfusion of donor hearts in the beating state extends preservation time and improves recovery of function. *Journal Thoracic Cardiovascular Surgery.* November 1998. Issue 116, Vol 5. Pgs. 821 - 30.

Hassanein W.H. (April, 1998). Presentation. Resuscitation of donor hearts for transplantation. Paper presented at the 22nd Scientific Session Annual Meeting of the Association of VA Surgeons. Baltimore, MD.

Iyer A, Gao, L, Doyle, A, et al. Hearts from donations after circulatory death (DCD) donors: assessment in a porcine transplant model utilizing TransMedics Organ Care System for Organ Perfusion Preservation.

Presentation at Mini Oral Session 5: Basic Science. *The International Society of Heart & Lung Transplantation (ISHLT).* Montréal, Canada. The Journal of Heart and Lung Transplantation. April 2013. Vol. 32, Number 4S. Pgs. S68 – S69.

McCurry K, Jeevanandam, T, Mihaljevic, G et al. Prospective multi-center safety and effectiveness evaluation of the Organ Care System Device for Cardiac Use (PROCEED). Paper presented at The International Society of Heart & Lung Transplantation (ISHLT). Boston, MA. *The Journal of Heart and Lung Transplantation.* February 2008. Vol. 27, Issue 2, Supplement, pgs. S167 – 68.

Schnitzler, M.A, Buchanan P.M, Swindle, J, et al. The cost-effectiveness of increasing the supply of hearts for transplant. Paper presented at The International Society of Heart & Lung Transplantation (ISHLT). Boston, MA. February 2007. *The Journal of Heart and Lung Transplantation*. Vol. 26, Issue 2. Supplement. Pg. S63

Schulte-Eistrup, S, Schultz, U, Elbetanony, A, et al. Ex-vivo evaluation of donor hearts in the beating functioning state in the organ care system. *The Journal of Heart and Lung Transplantation.* February 2007. Vol. 26, Issue 2. Supplement. Pg. S167.

Tenderich, S, Tsui, Khayal, et al. Increasing organ availability in heart transplantation with the use of warm blood perfusion for organ preservation. *The Journal of Heart and Lung Transplantation.* February 2007. Vol. 26. Supplement. Pgs. S167 – 68.

Tenderich G, El-Banayosy, A, Rosengard, B, et al. Prospective multi-center European trial to evaluate the safety and performance of the Organ Care System for Heart Transplants (PROTECT). Paper presented at The International Society of Heart & Lung Transplantation (ISHLT). San Diego, CA. *The Journal of Heart and Lung Transplantation.* February 2007. Vol. 26, Issue, 2, Supplement, pg. S64.

Tenderich, G, Tsui, S, El-Banayosy, A, et al. The 1-year follow-up results of the PROTECT Patient Population Using the Organ Care System. Paper presented at The International Society of Heart & Lung Transplantation (ISHLT). Boston, MA. *The Journal of Heart and Lung Transplantation.* February 2008. Vol. 27, Issue 3. Supplement. Pg. S200.

Tsui, S, Dhital, K, Eisenring, C, et al. Ex-vivo assessment of donor hearts with the OCS to detect hidden pathologies. Paper presented at The International Society of Heart & Lung Transplantation (ISHLT). Boston, MA. The Journal of Heart and Lung Transplantation. February 2008. Vol. 27, Issue 2. Supplement. Pg. S200.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

The technique itself is not controversial although additional work on optimal perfusion regimes would be welcome. There are questions regarding whether this device provides superior preservation over conventional methods, whether it has a reconditioning role, whether the system would be more efficacious if it allowed more detailed organ functional assessment and whether it is cost-effective.
The disposables costs have made dissemination in the absence of NHS funding difficult to allow for thorough multicentre evaluation of this technology in the UK setting.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

warm and cold ischaemic times, perfusion times, Rate of primary graft dysfunction, post op inotropes/mechanical support, ITU stay, rejection rates, functional status, echo criteria – ejection fraction etc.

5.2 Adverse outcomes (including potential early and late complications):

death, primary graft dysfunction, itu stay, inotrope use, mechanical support

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

Rapid within all UK transplant units (if funded!)

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☒ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☒ Moderate.

☐ Minor.

Comments:

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

As above

8 Data protection and conflicts of interest

8.1 Data protection statement

The Institute is committed to transparency. As part of this commitment your name and specialist society will be placed in the public domain, in future publications and on our website (www.nice.org.uk) and therefore viewable worldwide. This information may be passed to third parties connected with the work on interventional procedures.

A copy of the completed Specialist Adviser advice will be sent to the Specialist Society who nominated the Specialist Adviser.

Specialist Advisers should be aware that full implementation of the Freedom of Information Act 2000 may oblige us to release Specialist Advice from 2005. The Freedom of Information Act 2000 favours the disclosure of information however requests will be considered on a case by case basis. If information is made available, personal information will be removed in accordance with the Data Protection Act 1998. In light of this please ensure that you have not named or identified individuals in your comments.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Please state any potential conflicts of interest, or any involvements in disputes or complaints, relevant to this procedure. Please use the "Conflicts of Interest for Specialist Advisers" policy (attached) as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	☒	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☒	**YES**
	☐	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	☒	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	☒	**NO**
Investments – any funds which include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – eg have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☐	**YES**
	☒	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	☒	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	☒	**NO**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

Private practice in cardiothoracic surgery but not in transplantation

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

February 2010

Conflicts of Interest for Specialist Advisers

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2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where

the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 Personal family interest

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3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

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3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

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4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

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- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Normothermic ex-vivo preservation of hearts from brainstem dead donors for clinical transplantation (1289/1)**
Name of Specialist Advisor:	**Steven Tsui**
Specialist Society:	**Society of Cardiothoracic Surgeons of Great Britain and Ireland**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

☒ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☒ Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☒ Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

☐ I have never performed this procedure.

☐ I have performed this procedure at least once.

☒ I perform this procedure regularly.

Comments:

We have carried out approximately 20 of these procedures between 2006-2009, and then again in 2013-14. During 2015, we have restricted this procedure for DCD donor hearts. (DCD = donation after circulatory death)

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☒ I take part in patient selection or refer patients for this procedure regularly.

Comments:

Decision of whether use this procedure or not is made by me as the Transplant Unit Clinical Director.

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☒ I have undertaken bibliographic research on this procedure.

☒ I have undertaken research on this procedure in laboratory settings (e.g. device-related research).

☒ I have undertaken clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

We have undertaken large animal research using this technique. We have also taken part in clinical trials using this technique.

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter that procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☒ The first in a new class of procedure.

Comments:

This procedure was first carried out clinically in 2006. Therefore, it is not that new. However, there remain a single device that has CE mark for this purpose. A prospective randomised trial of using this technique versus the conventional technique (cold storage) suggest that normothermic ex-vivo preservation of hearts is non inferior to the conventional technique. If is therefore say and efficacious.

3.2 What would be the comparator (standard practice) to this procedure?

The standard practice is cold ischaemic preservation of donor hearts. This can be with a variety of cold crystalloid cardioplegia.

3.3 Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

☒ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

Due to the very high cost and the uncertain added benefit of normothermic ex-vivo preservation of donor hearts, only a tiny number of centres have adopted this technique as their standard practice.

4 Safety and efficacy

4.1 What are the adverse effects of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

The donor heart may be under perfused leading to myocardial damage. The donor heart may be overperfused leading to myocardial oedema. Donor hearts may have to be discarded after a period of normothermic ex-vivo preservation.

2. Anecdotal adverse events (known from experience)

Inadequate perfusion leading to donor heart ischemia. If transplanted, this can result in primary graft dysfunction or primary graft failure. Some patients who have suffered these complications have required a period of support including inotropes, balloon pump, ECMO and /or VAD. If donor heart function does not recover after a period of support, the recipient would either die or require re-transplantation.

There have also been cases in which the donor heart becomes detached from the machine during normothermic ex-vivo preservation. As a result, the heart could not be transplanted.

3. Adverse events reported in the literature (if possible please cite literature)

As above.

4.2 What are the key efficacy outcomes for this procedure?

Donor heart function; primary graft failure, 30-day recipient survival

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

Currently, there is no evidence that this technique is superior to cold static preservation for DBD donor hearts that are selected for transplantation

4.4 What training and facilities are required to undertake this procedure safely?

The surgeon needs to be trained to retrieve the donor heart and instrument the heart so that it can be attached to the machine for normothermic ex-vivo preservation. The surgeon has to learn about managing the machine in terms of flow rate, aortic pressure, and various infusions into the circuit including epinephrine solution and a nutrient solution which contains adenosine.

A technician needs to trained to set up the machine and prime the circuit.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

PROCEED II was a global clinical trial that compared standard cold storage of donor hearts to warm oxygenated blood perfusion using the Organ Care System.

Ex-vivo perfusion of donor hearts for human heart transplantation (**PROCEED** II): a prospective, open-label, multicentre, randomised non-inferiority trial.

Ardehali A, Esmailian F, Deng M, Soltesz E, Hsich E, Naka Y, Mancini D, Camacho M, Zucker M, Leprince P, Padera R, Kobashigawa J; PROCEED II trial investigators.

Lancet. 2015 Jun 27;385(9987):2577-84. doi: 10.1016/S0140-6736(15)60261-6. Epub 2015 Apr 14.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

The original circuit comprise a “working mode” which loads the left ventricle during machine preservation. This feature has been removed from the current device. There is debate about the value of the feature.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

Primary graft failure rate, use of IABP/ECMO support, duration of inotrope use post-transplant, measurement of cardiac function in donor and in recipient following transplantation. ICU length of stay, hospital length of stay, 30-day survival, 1-year survival.

5.2 Adverse outcomes (including potential early and late complications):

Primary graft failure, right ventricular failure, cardiac allograft vasculopathy (late)

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

With the device at the current cost, it is highly unlikely that it will adopted in any scale soon

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☒ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

There are only 6 adult heart transplant units and 2 paediatric heart transplant units in the UK. Only 2 units have had experience of this procedure.

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☒ Minor.

Comments:

There were some 180 heart transplants in the UK during 2014-15. Even if used in 20% of these, the numbers will be small.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

This procedure may have more value in marginal donor heart and in DCD hearts.

8 Data protection and conflicts of interest

8.1 Data protection statement

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	☒	**NO**
Fee-paid work – any work commissioned by the healthcare	☒	**YES**

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industry **– this includes income earned in the course of private practice**	☐	**NO**
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	☒	**NO**
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	☒	**NO**

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Fellowships endowed by the healthcare industry	☐	**YES**
	☒	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	☒	**NO**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

I am an investigator, a proctor and I am on the speaker panel for HeartWare Ltd.

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

February 2010

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- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

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