NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Ex vivo machine perfusion for extracorporeal preservation of livers for transplantation**
Name of Specialist Advisor:	Brian Davidson
Specialist Society:	British Association for the Study of Liver (BASL)

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

☐ 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 2 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 that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☑ I have done this procedure at least once.

☐ I do this procedure regularly.

Comments: PERFORMED THIS TYPE OF PROCEDURE REGULARLY FOR BOTH EXPERIMENTAL & CLINICAL PURPOSES

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: I HAVE BEEN INVOLVED IN CONTRIBUTING PATIENTS & DESIGNING CLINICAL TRIALS.

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

☑ I have done bibliographic research on this procedure.

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

☑ I have done clinical research on this procedure involving patients or healthy volunteers.

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

☐ Other (please comment)

Comments: (1) CLINICAL PROCEDURES
(2) EXPERIMENTAL
(3) TRIAL DESIGN

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 the 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?

STANDARD COLD ORGAN PRESERVATION

3.3 Please estimate the proportion of doctors in your specialty who are doing 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: SOME ACTIVITY IN ALL LIVER TRANSPLANT UNITS.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

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

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

(1) VASCULAR INJURY.

(2) INFECTION RISK.

2. Anecdotal adverse events (known from experience) NIL

3. Theoretical adverse events NIL.

4.2 What are the key efficacy outcomes for this procedure?

CONTROVERSIAL & MAIN LIMITATION OF DEVELOPMENT.
— (1) GRAFT PRESERVATION INJURY (2) ISCHAEMIC BILIARY INJURY.

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

NO CLEAR EVIDENCE OF CLINICAL BENEFIT

4.4 What training and facilities are needed to do this procedure safely?

(1) SURGICAL SKILLS IN PUTTING ON MACHINE
(2) MONITORING OF GRAFT DURING PERFUSION

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

TWO UK TRIALS CO-ORDINATED BY PETER FRIEND, OXFORD.
RECENT UNSUCCESSFUL EU APPLICATIONS.

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, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

UK ORGANOX TRIAL ON POST PRESERVATION PERFUSION PRESENTED BUT NOT YET PUBLISHED.

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

Yes. Underpowered studies & unclear end points.

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

(1) GRAFT INJURY. (2) GRAFT FUNCTION (3) PATIENT OUTCOMES

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

(1) NHSBT feedback (2) Day 3 AST level (3) Complications, deaths, LOS.

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Main measures will have outcomes < 30 days.
Bile duct injury may be > 30 days.

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

Being used in absence of evidence of benefit in most 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.
- ☑ 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: ABOUT 700 LIVER TRANSPLANTS / YR

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?

Need to get. USA & EUROPEAN DATA.

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☑ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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	☐ **YES** ☑ **NO**
Fee-paid work – any work commissioned by the healthcare industry – **this includes income earned in the course of private practice**	☐ **YES** ☑ **NO**

[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).

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 that include investments in the healthcare industry	☐ YES	☑ NO
Do you have a **personal non-pecuniary** interest – for example 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: AN ORGAN PRESERVATION COMPANY, ORS, WAS A partner in a prem NIHR HTA Study.

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

Jan 2016

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

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Ex vivo machine perfusion for extracorporeal preservation of livers for transplantation**
Name of Specialist Advisor:	Mr Colin Wilson
Specialist Society:	British Transplantation Society (BTS)

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:

Organ perfusion preservation is common to all organs currently transplanted- heart, kidney, liver, lung and to a lesser extent pancreas

The next 2 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 that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☒ I have done this procedure at least once.

☒ I do this procedure regularly.

Comments:

The procedure, as described, encompasses both cold perfusion preservation and warm red cell based perfusion preservation. I have more experience in kidney transplantation but am the leader of the liver perfusion program in Newcastle

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 done bibliographic research on this procedure.

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

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

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

☐ Other (please comment)

Comments:

Author of Hepatic Ex Situ Perfusion after Cold Storage (HEPaCS) trial protocol submitted to NIHR EME

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 the procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☒ The first in a new class of procedure.

Comments:

All centres in the United Kingdom perform either cold or warm perfusion preservation and so, in this respect, this is not a new procedure. What is not clear is which patients benefit, when to perform the procedure and which machine/technology is superior.
Perfusion preservation works by circulating an oxygenated solution through the donor liver at temperatures above 4°C. The principle is to sustain metabolism and cellular energy to the point of implantation. For each 10°C rise in temperature cellular metabolism doubles and therefore above 25°C oxygen transportation by haemoglobin is required in the circuit. Addition of red blood cells (NPP) increases the complexity and costs of perfusion, although the therapeutic possibilities to manipulate the organ are also increased. The current standard of care for liver preservation is rapid cooling of the donor organ with University of Wisconsin (UW) solution (an electrolyte solution), surgical removal, then transport to the transplant centre in an ice box. Once arrived, the organ is examined by the implanting surgeon and, if deemed suitable for transplant, the recipient is anaesthetised and their own liver removed. This explanting phase normally takes around 2-6 hours from the time the decision is made.

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

Static cold storage, when the liver is kept in an ice box from donation to implantation

3.3 Please estimate the proportion of doctors in your specialty who are doing 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:

Most centres in the UK have at least one specialist in the field. Around the world this number is much less.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

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

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

One liver, at least, has been lost when the portal vein cannula fell out and the liver perished in transit at warm temperature. Am J Transplant. 2017 Apr;17(4):1071-1080. doi: 10.1111/ajt.14049. Epub 2016 Dec 9. PMID: 27639262 DOI: 10.1111/ajt.14049

2. Anecdotal adverse events (known from experience)

Perfusion at the wrong temperature and pressure can theoretically damage the liver. I am not aware of any specific instances other than the one cited.

3. Theoretical adverse events

Microbiological contamination, blood borne virus transmission, inadvertent perfusion with wrong blood type.

4.2 What are the key efficacy outcomes for this procedure?

Day 1 post transplant- serum liver transaminases are the widely accepted outcome measure and recognise the contribution of ischaemia reperfusion injury to early post transplant graft function.
Serum AST in the first 7 days post transplant and the subsequent cumulative morbidity of liver transplantation are intrinsically linked. The risk of dying or losing the liver graft after transplantation is directly related to the peak AST within the first 7 days. If the AST is greater than 2000 iu/l the risk of dying is 18.8% vs. 1.8% (relative risk = 10.7 [95% confidence interval: 3.6, 31.9] $P < 0.0001$, (2)) and the risk of graft loss is 26.1% vs. 3.5% (RR=7.4 (95% CI: 3.4, 16.3), $P < 0.0001$). The risk of developing ischaemic cholangiopathy is increased above 1000 iu/l (15). In a multivariate analysis published by Leithead 2012, only peak AST was able to predict the long term requirement for renal dialysis- surprisingly the incidence of acute kidney injury did not(17).

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

Liver perfusion is effective at reducing the markers of liver injury. What is not clear is whether cold perfusion or warm perfusion are more effective and which livers benefit from perfusion.
Various pre-clinical studies have established that NPP (8, 9) and HPP (10) provide superior organ preservation enabling organs to be transplanted at time periods beyond what would normally be considered acceptable. The "first in man" NPP (11) and HPP (12) series have been published showing the feasibility and safety in clinical application. There is also evidence from the Consortium for Organ Preservation in Europe (COPE) liver-perfusion trial. This randomised controlled efficacy trial recruited 220 livers in 7 European transplant centres, allocating them 1:1 to NPP or SCS from donation to transplantation. 6-month outcomes have now been reported, and demonstrate a significant reduction in the primary endpoint of peak AST during days 1-7 with NPP. Furthermore, the incidence of early allograft dysfunction (EAD) was significantly lower in the NPP group and post-reperfusion syndrome was also lower (12.4% vs. 29.9%, $p<0.001$)(13). These results suggest that NPP, when used from the time of donation, reduces reperfusion injury and improves early function. Longer-term data on biliary complications, histological damage and graft survival have been presented and appear positive but have not been formally published yet. Professor Friend has now performed a small similar series using his OrganOx machine at the recipient centre which is being presented at the British Transplant Society Congress in February. The results appear equivalent.

Hypothermic perfusion preservation (HPP)
There are currently no published RCT's showing efficacy of HPP after cold storage. The technique of providing oxygenated cold perfusion preservation for a short period at the recipient transplant centre was pioneered by Dutkowski et al and published as a series of 25 DCD liver transplants in 2015 (12). The average peak AST was reduced from 2065 to 1239 iu/l with 0% cholangiopathy compared to 22% in a matched retrospective cohort. This experience has been expanded to 50 transplants and presented recently at an international conference. In Newcastle there have been positive experiences with 10 liver transplants (7 DCD and 3 DBD) using a similar technique in 2016-17. The early results in Newcastle confirm 50% reduction in median peak AST/ALT using a matched cohort(1329 reduced to 706, 46.9% reduction). In addition, Newcastle we have had no graft/patient losses or significant cholangiopathy (unpublished data).

Normothermic perfusion preservation (NPP)
There are currently no published RCT's showing efficacy of NPP after cold storage. However, Watson has been developing NPP after cold storage and recently published experience of 12 cases [19]. In a separate publication he has shown that this technology can be used to extend cold ischaemic tolerance by providing a period of NPP between periods of SCS [20]. The Watson standard protocol of oxygenation and perfusate composition will be used as published.

4.4 What training and facilities are needed to do this procedure safely?

A short clinical/ lab based training program is available for the use of all major machines on the market. OrganOx, OrganAssist, Transmedics and ORS Lifeporter

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

The HOPE trial is in progress on the continent. The other trials are either completed or planned. Most of them are industry sponsored or driven.

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, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

1. Leithead, J.A., et al., *The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation.* J Hepatol, 2014. **60**(6): p. 1180-6.
2. Olthoff, K.M., et al., *Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors.* Liver Transpl, 2010. **16**(8): p. 943-9.
3. Ruebner, R.L., P.P. Reese, and P.L. Abt, *Donation after cardiac death liver transplantation is associated with increased risk of end-stage renal disease.* Transpl Int, 2014. **27**(12): p. 1263-71.
4. Sirota, J.C., et al., *Urine IL-18, NGAL, IL-8 and serum IL-8 are biomarkers of acute kidney injury following liver transplantation.* BMC Nephrol, 2013. **14**: p. 17.
5. Wadei, H.M., et al., *Early Allograft Dysfunction After Liver Transplantation Is Associated With Short- and Long-Term Kidney Function Impairment.* Am J Transplant, 2016. **16**(3): p. 850-9.
6. Longworth, L., et al., *Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups.* Liver Transpl, 2003. **9**(12): p. 1295-307.
7. Transplant, N.B.a. *Organ Donation and Transplantation Activity Report 2015/2016*. 2016.
8. Bral, M., et al., *Preliminary Single-Center Canadian Experience of Human Normothermic Ex Vivo Liver Perfusion: Results of a Clinical Trial.* Am J Transplant, 2017. **17**(4): p. 1071-1080.
9. Bradley, C., et al., *The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL.* Qual Life Res, 1999. **8**(1-2): p. 79-91.
10. Glanemann, M., et al., *Clinical implications of hepatic preservation injury after adult liver transplantation.* Am J Transplant, 2003. **3**(8): p. 1003-9.
11. Eisenbach, C., et al., *An early increase in gamma glutamyltranspeptidase and low aspartate aminotransferase peak values are associated with superior*

outcomes after orthotopic liver transplantation. Transplant Proc, 2009. **41**(5): p. 1727-30.
12. Karayalcin, K., et al., *The role of dynamic and morphological studies in the assessment of potential liver donors.* Transplantation, 1994. **57**(9): p. 1323-7.
13. Gaffey, M.J., et al., *Predictive value of intraoperative biopsies and liver function tests for preservation injury in orthotopic liver transplantation.* Hepatology, 1997. **25**(1): p. 184-9.
14. Al-Freah, M.A.B., et al., *Improving the Diagnostic Criteria for Primary Liver Graft Nonfunction in Adults Utilizing Standard and Transportable Laboratory Parameters: An Outcome-Based Analysis.* Am J Transplant, 2017. **17**(5): p. 1255-1266.
15. Dutkowski, P., et al., *First Comparison of Hypothermic Oxygenated PErfusion Versus Static Cold Storage of Human Donation After Cardiac Death Liver Transplants: An International-matched Case Analysis.* Ann Surg, 2015. **262**(5): p. 764-70; discussion 770-1.
16. Abt, P., et al., *Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications.* Transplantation, 2003. **75**(10): p. 1659-63.
17. Gilbo, N., et al., *Reducing Non-Anastomotic Biliary Strictures in Donation After Circulatory Death Liver Transplantation: Cold Ischemia Time Matters!* Ann Surg, 2016.
18. Collett, D., P.J. Friend, and C.J. Watson, *Factors Associated With Short- and Long-term Liver Graft Survival in the United Kingdom: Development of a UK Donor Liver Index.* Transplantation, 2017. **101**(4): p. 786-792.
19. Watson, C.J.E., et al., *Normothermic Perfusion in the Assessment and Preservation of Declined Livers Before Transplantation: Hyperoxia and Vasoplegia-Important Lessons From the First 12 Cases.* Transplantation, 2017. **101**(5): p. 1084-1098.
20. Watson, C.J., et al., *26-hour Storage of a Declined Liver Before Successful Transplantation Using Ex Vivo Normothermic Perfusion.* Ann Surg, 2017. **265**(1): p. e1-e2.

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

Cold vs Warm perfusion remains an area of debate and I submitted a trial application to the NIHR EME program in August 2017 which has not been funded as yet. The major role of perfusion preservation is to reduce the ischaemia reperfusion injury associated with the use of DCD (Donation after Circulatory Death) donors and fatty livers. The COPE trials show it is highly effective in this regard. The controversy centres around which organs benefit the most.
In the United Kingdom, due to logistical challenges, more and more transplants are being done out of hours. Perfusion has the capability to turn transplantation into a daytime speciality. With the right protocol this could dramatically reduce the costs of liver transplantation by turning the speciality into a “daytime only” operating speciality.

5 Audit Criteria

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

Early allograft failure

a. Peak ALT >2000 in first 7 days
b. Bilirubin >170µmol/L on day 7
c. INR >1.6 on day 7

Liver function

a. Lactate change from anhepatic phase to post-reperfusion.
b. ALT- AUC days 1 to 5
c. ALT rate of fall

Reperfusion characteristics

a. Post reperfusion syndrome – MAP in first 5 mins post reperfusion is <70% of MAP in last 5 mins of anhepatic phase
b. Vasoplegia – defined by inotrope usage
c. Change in serum potassium (ΔK^+)

Renal function

a. Need for renal replacement therapy
b. GFR change day 0 to day 7

Ischaemic cholangiopathy

a. MR at 6 months
b. Clinically significant cholangiopathy requiring treatment
c. Need for retransplant

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

Cost effectiveness

a. Length of ITU stay
b. Length of stay
c. OP attendance in the first 6 months
d. Renal replacement therapy costs

Quality of life

a. Health status (SF-12)
b. Quality of life (WBQ16)

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Incidence of primary non function, delayed graft function

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

If the finances are in place, I think all centres would perfuse livers prior to implantation and aim to start the liver transplant in the morning. This could revolutionise the delivery of liver transplantation. 5 years ago no centre offered perfusion, currently all do but limited by financial resources.

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:

Only 7 liver transplant centres

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:

In 2014-2015 the NHS undertook 842 liver transplants with the average cost for each procedure being £70,000 each. It is important that the maximum utility is made of each liver transplant and in most cases of graft failure the only solution is further costly re-transplantation with the attendant extra risks. The clinical role of perfusion preservation in the NHS is unclear. The costs of perfusion using the COPE trial approach from the donor through to implantation (£15k at least) appear prohibitive for universal use in this context. End ischaemic perfusion where the liver is perfused at the recipient centre, using NPP or HPP (<10k), are realistic and feasible for UK transplant centres- if the early positive results can be translated into full scale clinical practice.

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?

See references

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☑ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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

☐ **YES**

☒ **NO**

[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).

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 that include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – for example 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:
No conflicts of interest as far as I am aware

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

Jan 2016

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

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Ex vivo machine perfusion for extracorporeal preservation of livers for transplantation**
Name of Specialist Advisor:	Douglas Thorburn
Specialist Society:	British Association for the Study of Liver (BASL)

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 2 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 that does this procedure, please indicate your experience with it:

X I have never done this procedure.

☐ I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

I am a physician but the patients that undergo liver transplant at my centre have had this and I have looked after them.

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.

X 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 done bibliographic research on this procedure.

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

X I have done 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):

☐ Established practice and no longer new.

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

X 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?

Organ retrieval with cold storage

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

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

X 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 is the potential harm of the procedure?

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

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

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

4.2 What are the key efficacy outcomes for this procedure?

T`ransplant survival, graft survival, primary non function, early graft dysfunction

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

What do they add to cold storage ie improved outcomes and resource utilsatrion v increasd organ utilisation with improved outcomes

4.4 What training and facilities are needed to do this procedure safely?

Transplant surgical and perfusion teams experienced with the device in question

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

COPE has closed and 'Back to base' studies of organox completed

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, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

BASL meeting in September 2017, NHSBT research meeting 2018

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 are a range of technologies and it is unclear whether any one is superior. Furthermore question as to whether it neads to be undertaken at the donor hospital or at the implantating hospital after a period of cold storage.

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). Please suggest the most appropriate method of measurement for each:

Organ utilisation machine v cold storage
Measure of early graft dysfunction
Need for renal support post OLT
Length of ITU stay after transplant
Length of hospital stay after transplant
90 day transplant survival (graft and patient survival) by donor risk
1, 3 year graft survival
Cholangiopathy rates

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

above

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

Quickly if it can be funded but would be restricted to the 7 liver transplant centres in the UK

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:

☐ Major.

X Moderate.

☐ Minor.

Comments:
Major impact within the domain of liver transplantation but this equates to only approx. 1000 patients per annum

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?

Just clinical trials and audit information

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☐ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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 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 that include investments in the healthcare industry	☐	**YES**
	x	**NO**
Do you have a **personal non-pecuniary** interest – for example 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**
	X	**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:
Occasional speaking fees for industry (Falk and Intercept). Ad boards (Intercept and Astellas)

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

Jan 2016

[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).

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

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Ex vivo machine perfusion for extracorporeal preservation of livers for transplantation**
Name of Specialist Advisor:	Mr Michael Silva
Specialist Society:	Royal College of Surgeons

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:

I am a specialist liver and pancreatic surgeon. My primary work is therefore surgery for liver and pancreatic cancer. I am however a trained liver transplant surgeon and am currently also active as a lead surgeon for the National Organ Retrieval Service (NORS), which is provided by NHSBT.

The next 2 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 that does this procedure, please indicate your experience with it:

☒ I have never done this procedure.

☐ I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

I have been present when liver grafts I have retrieved were placed on the ex vivo perfusion machine in the context of a concluded clinical trial. I have however personally not carried out the placement of a liver on the machine myself.

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:

Please see comment for 2.2.1. Selection of liver grafts I have retrieved from donors were place on the ex vivo perfusion machine based on a randomised basis that I had no part to play and was in the context of a clinical trial.

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

☐ I have done bibliographic research on this procedure.

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

☐ I have done 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 background training in liver transplantation also included a higher degree on ischemia reperfusion injury of liver grafts during the process of transplantation. I am therefore well versed in the issues at hand.

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 the procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

None of the above statements describes the current status of ex vivo machine perfusion of liver grafts adequately. Ex vivo perfusion is currently being evaluated, mostly in trial settings in the UK and elsewhere. Its use is becoming widespread and the likelihood is that it will be established as standard practice in the near future, but it is not there yet.

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

Non perfused (static) cold organ preservation

3.3 Please estimate the proportion of doctors in your specialty who are doing 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:

This is largely due to non-availability, inadequate funding and results being awaited from on going trials. All the liver transplant centres in the UK (Edinburgh, Newcastle, Leeds, Birmingham, Cambridge, Kings College and Royal Free London) have experience using ex vivo perfusion machines in the context of on going and concluded clinical trials. It is likely therefore that most liver transplant surgeons in the UK have exposure or have limited experience using the system.

I am also aware of 15 centres in the US, 2 centres in Canada (Edmonton and Toronto), centres in the Netherlands, Belgium, Spain, Italy and Germany trialling the system.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

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

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

No major adverse events reported

2. Anecdotal adverse events (known from experience)

It is reported that 1 liver was lost due to device error out of > 300 to date.

This resulted from possible arterial hypo-perfusion of the liver due to an error of the recorded arterial pressure by the perfusion system used. The liver transplant surgeon when informed of this potential problem chose not to use the organ and it was discarded.

A recently concluded randomised controlled clinical trial however has shown that the use of ex vivo perfusion storage results in approximately 50% reduction in organ discard rate after retrieval from donors.

Abstract; **http://atcmeetingabstracts.com/abstract/outcomes-from-a-multinational-randomised-controlled-trial-comparing-normothermic-machine-perfusion-with-static-cold-storage-in-human-liver-transplantation/**

Also published in Transplant International 2017 Vol 30 supplement 2 Pages 6

3. Theoretical adverse events

Normothermic ex vivo perfusion could theoretically result in immediate warm ischaemic injury to the organ if for any reason the perfusion system fails and the process is interrupted. This risk is less for hypothermic and sub-normothermic perfused devices. The general acceptance is that normothermic perfusion however offers the best physiologic preservation and organ resuscitation.

Organ loss could also occur due to device or operator error.

Additionally, there is potential for warm ischemic injury when the organ comes off normothermic perfusion until circulation established in the recipient, unlike in cold static storage where the organ remains cooled down until reperfusion. This risk is theoretical since results thus far have shown better outcomes with machine perfused normothermic preservation.

4.2 What are the key efficacy outcomes for this procedure?

- Better organ preservation with optimal organ function at reperfusion in recipient
- Reduced risk of non anastomotic biliary strictures (ischaemic cholangiopathy) in graft post transplant
- Better post transplant organ function, graft survival and recipient survival
- Objective evaluation of marginal grafts
- Ability to resuscitate some marginal grafts
- Increase in donor pool and thus number of liver transplants (this is in the context of nearly 20% mortality of patients waiting for a suitable liver transplant)
- Longer period of organ preservation, therefore grafts can be transported longer distances
- Possible reduction in immunological insult ischemia reperfusion causes and therefore improved graft function and recipient survival

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

No major uncertainties
It is claimed that normothermic organ preservation reduces ischemic cholangiopathy and graft dysfunction. However this has not played out in clinical trials thus far with the incidence of reduced cholangiopathy not reaching statistical significance.

4.4 What training and facilities are needed to do this procedure safely?

The process will need start up training for each team. This will include technical aspects of connecting graft to machine plus maintenance on ex vivo perfusion and usage of the perfusion machine along with trouble shooting ability. Additionally, initial investment of multiple perfusion machines plus storage will have to be built in to each unit.

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

Please see attached Excel spread sheet regarding on going and concluded trials

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, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

See link below

http://atcmeetingabstracts.com/abstract/outcomes-from-a-multinational-randomised-controlled-trial-comparing-normothermic-machine-perfusion-with-static-cold-storage-in-human-liver-transplantation/

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

No

5 Audit Criteria

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

- Number of grafts (donors) considered marginal
- Number of marginal grafts utilised (static cold preserved vs machine perfused)
- Peak AST levels post transplant
- Duration of post transplant ITU stay
- Requirement of post transplant renal support
- Graft survival and patient survival
- Incidence of non anastomotic biliary strictures (ischaemic cholangiopathy)

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

- Organ utilisation
- Mortality rates on waiting list for liver transplantation
- Graft survival
- Recipient survival post transplant
- QoL post transplantation

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Organ loss;

- Due to device error
- Due to user error

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

There is widespread acceptance among the liver transplant community that normothermic organ preservation will improve outcomes, graft utilisation and reduce waiting times for liver transplantation.
However availability of ex vivo perfusion machines, restricted funding, acceptance of the procedure (Eg NICE recommendations), outcome of on going clinical trials all will contribute towards approximately 2- 5 year before the procedure being widespread.

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:

Organ retrieval happens in all (most) hospitals in the UK. Liver transplantation occurs in 7 centres in the UK. Therefore use will be initiated in retrieval centres and completed in the transplant centre.

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 is likely to be an increase in number of liver transplants in the UK, but this could be counterbalanced by a reduction of patients waiting for a transplant and the impact morbidity and mortality has on this cohort of patients.

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?

None at present

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE

publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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	☐	**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 that include investments in the healthcare industry	☐	**YES**
	☒	**NO**

[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).

Do you have a **personal non-pecuniary** interest – for example 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:

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

Jan 2016

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

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Ex vivo machine perfusion for extracorporeal preservation of livers for transplantation**
Name of Specialist Advisor:	Prof Peter Friend
Specialist Society:	British transplantation society (BTS)

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 procedure of normothermic liver perfusion is not standard of care currently and has been used largely in the context of clinical trials to date. However, the CE-marked devices now available are beginning to be used outside the context of trials in the UK and elsewhere.

The next 2 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 that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☒ I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

I am not currently carrying out liver transplantation, but have a close understanding of the field, having been an active liver transplant surgeon in the past, and an intimate knowledge of normothermic perfusion as a clinical academic transplant surgeon with involvement in this specialist area of research; I have been the lead investigator in clinical trials of this technology. Also, I am a co-founder of one of the companies active in this field, as declared in my conflict of interests.

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 done bibliographic research on this procedure.

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

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

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

☐ Other (please comment)

Comments:

Please see answer to 2.2.1

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 the procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☒ The first in a new class of procedure.

Comments:

This procedure has been subjected to Phase 1 testing, confirming safety, and Phase 3 testing (220 liver transplants in 7 European liver transplant centres), confirming efficacy. The technology reduces the level of transplant-related liver injury by 50% (as measured by peak transaminase levels in the 7 days postoperatively), despite longer preservation times and improved organ utilisation rates.

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

The standard of care is static cold storage – infusing specialist preservation solution into the organ and storage in an ice box.

3.3 Please estimate the proportion of doctors in your specialty who are doing 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:

This technology is very new and has been used in a small number of cases in the UK outside the context of trials, although there is increasing use in liver transplant units in other European countries and elsewhere.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

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

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

I am aware of a single report of a liver of marginal quality being discarded because of a technical complication on the perfusion system: however, this was an operator error (twisting of a cannula in the portal vein, correctly identified by the error message displayed on the device) and was not reported as a device malfunction

Please see reference: Bral M, Gala-Lopez B, Bigam D, Kneteman N, Malcolm A, Livingstone S, Andres A, Emamaullee J, Russell L, Coussios C, West LJ, Friend PJ, Shapiro AM. Preliminary Single-Center Canadian Experience of Human Normothermic Ex Vivo Liver Perfusion: Results of a Clinical Trial. Am J Transplant. 2017 Apr;17(4):1071-1080

2. Anecdotal adverse events (known from experience)

I am aware of a single donor liver, of marginal quality, which was discarded because of a period of hypoperfusion during preservation.

3. Theoretical adverse events

Device malfunction is a risk to the liver, mainly because the liver is preserved in the warm, functioning state and any interruption to the flow of oxygenated blood would be rapidly deleterious. The perfusion systems in use have been designed to minimise the risk of this occurring.

4.2 What are the key efficacy outcomes for this procedure?

The primary outcomes measures in trials to data have been: graft survival (Phase 1 study) and peak aspartate transaminase (AST) days 1-7 in Phase 3. The composite endpoint of 'Early Allograft Dysfunction' (comprising peak transaminase during days 1-7, bilirubin on day 7and INR on day 7) is being used as the primary endpoint in the 2 trials currently underway in the USA.

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

The results of the European Phase 3 study (head-to-head comparison with current practice cold storage) were unequivocal. The trial was designed and powered to show a 33% reduction in peak AST in the first 7 days postoperatively (selected as

being a clinically relevant difference), and the results showed a 50% reduction. This was in the context of a significantly higher level of organ utilisation (significantly fewer organs were discarded as unsuitable to transplant after randomisation, ie after retrieval) and significantly longer preservation times (an important factor in organ allocation as well as the overall logistics of transplantation).

4.4 What training and facilities are needed to do this procedure safely?

The technology requires specific training of transplant surgical team members for the cannulation of the liver, and also of technical staff for the setting up and priming of the device.

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

There are 2 randomised trials in progress in the USA (of different normothermic perfusion devices), but neither is likely to complete recruitment until 2019 at the earliest and therefore will not report until 2020 at the earliest.

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, for example PUBMED? (This can include your own work). If yes, please list.

Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

A number of presentations have been made at the American Transplant Congress, International Transplantation Society, British Transplantation Society, European Society of Organ Transplantation, International Society of Liver Transplantation. There have been no very recent presentations (the most recent of these was September 2017).

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

I am not aware of any controversy regarding the implementation of this procedure. There is a great deal of interest and enthusiasm, because the technology is widely seen as a potential means to increase the number of transplantable organs without compromising the outcome.

5 Audit Criteria

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

The data set needs to include donor and recipient parameters (allowing the risk associated with the individual donor organs to be quantified). It needs to include graft and patient survival, longer-term outcomes (12 months), including biliary complications. Data to allow a rigorous health economic analysis will be important.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

Short-term: patient and graft survival, renal replacement, ICU length of stay, hospital length of stay
Longer-term: graft and patient survival at 12 months; biliary complications and interventions; biochemical liver function tests
Heath-economic: data to conduct a full health-economic analysis. This should include the overall contribution of the technology to the costs of running a liver transplant service (eg one of the purported benefits is the shift to daytime working and the more efficient use of the staff, being able to conduct sequential transplants even if donor organs arrive simultaneous, and the ability to bring both organs and patients from longer distances)

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

As a surgical procedure, the Clavien-Dindo classification would be appropriate to the quantification of post-procedure morbidity.

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

In the UK there is a very high level of interest in all 7 of the NHS-designated liver transplant programmes, and 5 of these have had direct experience in one of the clinical trials. Because of the increasing prevalence of liver failure, and the 20% waiting list mortality in patients listed for a transplant, the use of sub-optimal organs is widely practiced in UK liver transplantation. It is in this context that the uptake of new technology that allows improved preservation, viability assessment and longer preservation is very likely to proceed rapidly.

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:
The current annual liver transplant rate in the UK is slightly less that 1000, but this number is artificially low, because of deliberate restriction to waiting list access based on donor availability. The number of deceased organ donors approximately 1500. It is the latter that constitutes the limiting factor to the number of liver transplants that can take place.

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. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☐ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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	☒	**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 that include investments in the healthcare industry	☒	**YES**
	☐	**NO**
Do you have a **personal non-pecuniary** interest – for example 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 a co-founder, Chief Medical Officer and stockholder of OrganOx Ltd, a spinout company from the University of Oxford that was established to commercialise the normothermic perfusion research carried out under my supervision in the University.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

[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).

Jan 2016

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

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**NHS Blood and Transplant**
Name of Specialist Advisor:	Professor Chris Watson,
Specialist Society:	NHS Blood and Transplant

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 procedure is done by/in liver transplant centres

The next 2 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 that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☐ I have done this procedure at least once.

☒ I do 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.

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

Comments:

This is not a procedure you refer patients for, since it is done on a liver by itself at some stage between removal from the donor and implantation in the recipient.

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

☒ I have done bibliographic research on this procedure.

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

☒ I have done 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):

☐ Established practice and no longer new.

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

☒ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

You can divide machine perfusion into two categories, normothermic and hypothermic, and also by whether the liver is subject to it for the entire preservation period, or just a part (typically just before implantation).

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

"Static cold storage" of a liver on ice, flushed with University of Wisconsin solution (Belzer UW, ViaSpan, KPS1) at the time of retrieval and sitting in a bag of the same suspended in an ice box

3.3 Please estimate the proportion of doctors in your specialty who are doing 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:

In the UK, Cambridge and Birmingham have active research programmes and clinical programmes with normothermic liver perfusion. Kings College Hospital, the Royal Free Hospital and St James Leeds have been part of clinical trials organised by one of the companies with a normothermic machine, along with Cambridge and Birmingham. Newcastle is doing research on hypothermic machine perfusion. The only other liver transplant centre in the UK is Edinburgh and they are not currently researching in this area, but are keen to be involved.

Of the liver transplant surgeons, very few are actually involved in managing machine perfusion of the liver, hence the figure of <10%
There are studies of hypothermic machine perfusion been run from Zurich (Dutkowski et al) and Groningen (Porte et al).
Machine perfusion of the liver is not an area where the USA is leading – they did report the first hypothermic perfusion but thereafter the hypothermic work has come from Zurich initially. The normothermic work has initially been pushed by the UK, since the first trials were run by OrganOx, and Oxford based company.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

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

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

The field is really very new. I have seen the data for the first two trials of the OrganOx metra machine and to date I have not seen a difference in adverse events between normothermic and perfused livers – some of these data are yet to be published.

In my own study we used the Liver Assist machine and noted a high incidence of post reperfusion syndrome and vasoplegia in recipients when high levels of oxygen were administered to the liver ex situ; once this was adjusted and lower levels were given, as is also the case with the OrganOx metra machine, there have been no such effects.

Normothermic perfusion also runs the risk of losing a liver if the machine fails for some reason, since the liver is warm and will deteriorate quickly. This is not going to be the case with hypothermic perfusion where the colder temperature is protective.

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

   Risks:

   - Damage to artery or vein during cannulation or perfusion
   - Warm ischaemic damage to liver if normothermic machine fails
   - Microbiological infection – more likely if normothermic preserved (we do see this in static cold stored livers)
   - Non function or poor function of a liver - happens with static cold storage, may happen with machine perfusion
   - Cholangiopathy – ischaemic injury to the bile ducts – happens with cold storage, may happen with machine perfusion
   - Machine failure and loss of liver

4.2 What are the key efficacy outcomes for this procedure?

Perfusion has two roles:

a) Hypothermic and normothermic perfusion can be used to improve preservation – the outcomes there are long term graft function. However, the trials have focussed on short term outcomes, namely peak AST or ALT in the first week.

b) Normothermic perfusion can also be used to test function to see whether the liver will work post transplant, so called viability testing. This has potentially the biggest benefit, in that it will give clinicians confidence to use livers that would otherwise be discarded. There are a number of predictive scoring systems to estimate graft survival, so an ideal trial would look at a subgroup of livers predicted to be high risk of failure to see whether outcomes can be improved, and whether more livers can be transplanted.

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

Normothermic perfusion has been shown to work in a large multicentre trial run by OrganOx but yet to be published. The technique is efficacious.
Hypothermic perfusion is subject to two ongoing studies in Europe, still to finish recruiting. This technique cannot offer the same level of confidence as normothermic perfusion since the viability of the liver cannot be tested in the cold

4.4 What training and facilities are needed to do this procedure safely?

Training in preparing the liver and setting up the machine are required. In addition there is a need for experience in interpreting the results of viability tests, which is still a bit of an art with no clear criteria available
Facilities – it can be set up in an operating theatre, which is the environment in which it will be running

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

HOPE
D-HOPE
VITAL
COPE

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, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

I will attach our recent ones. There is a manuscript for the OrganOx multicentre study in submission at the moment

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

Hypothermic:

- How do you know the liver will work – you are still somewhat blinded.
- Uncertainty how long a liver can be stored in hypothermic perfusion

Normothermic:

- Criteria for deciding marginal livers will work after transplantation are debatable
- The optimal perfusion fluid remains to be determined
- Livers can be preserved for 24 hours underoing normothermic perfusion, but it is not proven that it is as safe to keep them for 24 hours as it is for 12 hours, for example; intuition would say it cannot be as good

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). Please suggest the most appropriate method of measurement for each:

Incidence of ischaemic type biliary strictures (=ischaemic cholangiopathy) – MRCP at 6 months
Incidence of post reperfusion syndrome – fall in mean arterial pressure of 30% compared to baseline during hepatectomy
Incidence of early allograft dysfunction – Olthoff criteria (Liver J Transplant 2010;16:943)
Incidence of acute kidney injury post transplant
ITU stay post transplant
Graft survival at 90 days and 1 year

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Early (first month):

- Primary non function resulting in death or retransplant
- Hepatic artery or portal vein thrombosis
- Biliary anastomotic leak
- Mycotic aneurysm of graft vessels (implies infected preservation solution/perfusate)

Late:

- Ischaemic cholangiopathy
-

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

I think every liver transplant centre in the UK will have a machine in the next 5 years, and will use it selectively to determine viability of a liver, or to facilitate timing of a transplant (e.g. by storing one liver while you do another liver transplant).

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 Edinburgh, Newcastle, Leeds, Cambridge, Birmingham, Kings and Royal Free hospitals with liver transplant programes

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:
We do around 800 liver transplants a year in the UK. I would estimate this machine may facilitate another 100 at most, but would be used on 100 to 200 of the currently transplanted ones for the indications mentioned above, hence 300 cases per year

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?

I think it's a couple of years too soon to be looking at this. Cost will determine whether it isi used, and will stop it being used on every liver

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☒ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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	☐	**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**

[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).

Investments – any funds that include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – for example 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:
Expenses or hospitality. I was paid travel expenses and accommodation to attend a conference in Groningen and present my results with the Liver Assist machine

Non-pecuniary interest: I have a research programme looking at normothermic liver perfusion. I have published on the subject. I have also been part of the data safety monitoring committees for two of the OrganOx studies, and an investigator in another OrganOx study

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

Jan 2016

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

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**NHS Blood and Transplant**
Name of Specialist Advisor:	Professor Steve Wigmore,
Specialist Society:	NHS Blood and Transplant

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:

This title effectively excludes consideration of normothermic regional perfusion in the donor which is a competing technology but is in vivo rather than ex situ.

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:

There is a complete lack of consencus in the UK over which machine to use or whether to perform in vivo normothermic regional perfusion of donor abdominal organs or ex situ machine perfusion. This is compounded by a number of individuals having competing academic or commercial interests. I have just been to the RINTAG Research Innovation Novel Technologies Advisory Group of NHS Blood and Transplant and there remains no resolution over approach or research into these technologies.

The next 2 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 that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☐ I have done this procedure at least once.

☒ I do 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.

☒ 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 done bibliographic research on this procedure.

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

☐ I have done 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):

☐ Established practice and no longer new.

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

☒ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

Doesn't fit easily inot any of these classifications. NRP normothermic regional perfusion and ex situ perfusion have been around and used clinically for several years but are still quite new and not well established. The other problem is that there are no agreed criteria for defining successful organ perfusion and determining which organs are suitable for transplant and which are not. Assessment of organ suitability is a priority for research and to help the introduction of these technologies.

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

Standard practice is donor cold perfusion and static cold perfusion for donation after brainstem death donrs and some donation after cardiac death donors. Normothermic regional perfusion is established practice in Edinburgh and Cambridge for DCD donors.

3.3 Please estimate the proportion of doctors in your specialty who are doing 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 is the potential harm of the procedure?

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

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

Potential loss of organs, failure to improve organ function, making organ function worse.

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

4.2 What are the key efficacy outcomes for this procedure?

Organ utilisation is probably the most important so specifically use of organs that would otherwise be discarded. Organ function and avoidance of complications such as ischemic cholangiopathy and primary non-function

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

There is evidence of benefit in certain donors but the criteria for organ selection for treatment is not agreed or evidenced

4.4 What training and facilities are needed to do this procedure safely?

Needs capital investment in machine and each use costs of disposables which can be very expensive depending on which machine is used. Most programmes currently running have required additional consultant surgeon level support and often also perfusionist or research nurse support. Organ retrieval teams are likely to need additional training and support to deliver as a service.

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

Angelico R, Perera MT, Ravikumar R, Holroyd D, Coussios C, Mergental H, Isaac JR, Iqbal A, Cilliers H, Muiesan P, Friend PJ, Mirza DF. Normothermic Machine Perfusion of Deceased Donor Liver Grafts Is Associated With Improved

Postreperfusion Hemodynamics. Transplant Direct. 2016 Aug 5;2(9):e97. eCollection 2016 Sep. PubMed PMID: 27795989; PubMed Central PMCID: PMC5068202.

Bral M, Gala-Lopez B, Bigam D, Kneteman N, Malcolm A, Livingstone S, Andres A, Emamaullee J, Russell L, Coussios C, West LJ, Friend PJ, Shapiro AM. Preliminary Single-Center Canadian Experience of Human Normothermic Ex Vivo Liver Perfusion:
Results of a Clinical Trial. Am J Transplant. 2017 Apr;17(4):1071-1080. doi: 10.1111/ajt.14049. Epub 2016 Dec 9. PubMed PMID: 27639262.

Selzner M, Goldaracena N, Echeverri J, Kaths JM, Linares I, Selzner N, Serrick C, Marquez M, Sapisochin G, Renner EL, Bhat M, McGilvray ID, Lilly L, Greig PD, Tsien C, Cattral MS, Ghanekar A, Grant DR. Normothermic ex vivo liver perfusion using steen solution as perfusate for human liver transplantation: First North American results. Liver Transpl. 2016 Nov;22(11):1501-1508. doi: 10.1002/lt.24499. PubMed PMID: 27339754.

Ravikumar R, Jassem W, Mergental H, Heaton N, Mirza D, Perera MT, Quaglia A, Holroyd D, Vogel T, Coussios CC, Friend PJ. Liver Transplantation After Ex Vivo Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial. Am J Transplant. 2016 Jun;16(6):1779-87. doi: 10.1111/ajt.13708. Epub 2016 Mar 7. PubMed PMID: 26752191.

No registry agreed yet for UK although some progress made to establishing one.

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, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

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

Yes there are no good trials and the pragmatic proposal to run a head to head trial of normothermic machine perfusion in DCD donors versus initial static perfusion and then any method of ex vivo machine perfusion with organ utilisation as the primary outcome was not well received by the individuals who have specific interests in particular technologies.

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). Please suggest the most appropriate method of measurement for each:

Organ utilisation
COST (written in capitals deliberately as this is an important consideration and NRP is very cheap by comparison)

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Ischemic cholangiopathy rate
Primary non function rate
1 year graft and patient survival
retransplant rate in 3 years.

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

Yes I think there will be rapid uptake

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:
Could affect many liver transplant recipients but this is a small number compared with many other procedures performed in the NHS

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. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☐ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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 that include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – for example 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 vice president and President Elect of the British Transplantation Society I don't think that this constitutes a COI but has to be declared as per your terms above.

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

Jan 2016

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

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name: Ex Vivo Machine Perfusion for Extra-corporeal preservation of livers for transplantation

Name of Specialist Advisor: Dr Charlie Millson

Specialist Society: British Society of Gastroenterology

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 2 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 that does this procedure, please indicate your experience with it:

☑ I have never done this procedure.

☐ I have done this procedure at least once.

☐ I do 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.

☐ 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 done bibliographic research on this procedure.

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

☐ I have done 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):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter the 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 doing 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 is the potential harm of the procedure?

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

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

This procedure is only carried out on organs that have been removed from donors *before* implantation into the potential recipient. This technique is a promising strategy to expand the donor pool by reconditioning and assessing viability during the preservation period of liver grafts that are traditionally considered to be unusable or borderline.

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

4.2 What are the key efficacy outcomes for this procedure?

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

4.4 What training and facilities are needed to do this procedure safely?

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

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, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

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

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). Please suggest the most appropriate method of measurement for each:

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

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?

Could increase done post, reducing patients on waiting list.

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☑ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed 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	☐ **YES** ☑ **NO**
Fee-paid work – any work commissioned by the healthcare industry – **this includes income earned in the course of private practice**	☐ **YES** ☑ **NO**

[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).

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 that include investments in the healthcare industry

☐ YES
☒ NO

Do you have a **personal non-pecuniary** interest – for example 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:

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

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

Jan 2016