National Institute for Health and Care Excellence

IP1690 Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation

[Comments 1 to 7 had already been discussed at a previous IPAC meeting on 09/08/2018. Comments 8 to 18 from NHS BT were received on 23/08/2018.]

IPAC 11/10/2018

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company Organ Assist b.v.	**1**	"The recommendation made by NICE is that the evidence on ex-vivo machine preservation of livers for transplantation raises no major safety concerns. Ex-vivo machine preservation can be performed under hypothermic and normothermic conditions. Under normothermic conditions, blood is used as a perfusate (perfusion solution). Under hypothermic conditions, an a-cellular solution is used as a perfusate (perfusion solution). Based on the evidence available, both conditions are safe and feasible. NICE correctly does not pronounce a preference in either of the conditions. It is therefore key not to use the wording ""blood"" in the consultation document, but use the wording: ""perfusate"" or ""perfusion solution"". "	Thank you for your comment. The word ‘’blood’’ has been changed to ‘’perfusate’’ throughout the guidance and the overview**.**

2	Consultee 1 Company Organ Assist b.v.	**2.4**	As can be derived from literature and expert interviews, normothermic machine perfusion has the benefit of allowing (near-)physiologic viability assessment of the liver, where hypothermic perfusion tends to recover the liver of preservation injury by re-oxygenation. It would be good to highlight these different applications and their intentions.	Thank you for your comment. Section 2.4 has been changed to: *''Ex-situ machine perfusion preserves the donor liver outside the body under normothermic or hypothermic conditions. A perfusion machine is used to deliver oxygenated perfusate (which may or may not contain blood depending on the technique employed), supplemented with nutrients and metabolic substrates. The intention is to:* • *reduce the rate of tissue deterioration that occurs after the liver has been removed from the donor compared with that seen with conventional static cold storage* • *extend how long the liver can be stored to allow more flexibility in the timing of the transplant operation.* *Normothermic machine perfusion also allows assessment of donor liver viability and function during preservation. The aim is to improve clinical outcomes for the recipient and to enable otherwise marginal organs (such as those donated after circulatory death, steatotic livers and livers from older people) to be transplanted safely, so increasing the number of livers available for transplantation.''*

3	Consultee 1 Company Organ Assist b.v.	**Lay description**	Abstract box: please replace blood with perfusate/perfusion solution.	Thank you for your comment. Please refer to comment 1.
4	Consultee 1 Company Organ Assist b.v.	**2.4**	please replace blood with perfusate/perfusion solution.	Thank you for your comment. Please refer to comment 1.
5	Consultee 1 Company Organ Assist b.v..	**2.5**	please remove 'blood' from 'blood reservoir'. please remove 'blood' from 'blood oxygenator'. please remove 'blood' from 'blood warming unit'. please replace 'effluent blood' with 'effluent perfusate/perfusion solution'.	Thank you for your comment. Please refer to comment 1.
6	Consultee 1 Company Organ Assist b.v.	**2.5**	In the last sentence of this section it is stated that this procedure has been used to store a liver for 24 hours. This is purely speculative. There is no clinical evidence that 24 hours is a safe and feasible. This statement should therefore be left out of this document. It has a high risk of being a misleading recommendation to the clinicians in defining their protocols. Please leave it out or limit the recommended period to the mean as found in evidence literature.	Thank you for your comment. Section 2.5 has been changed to: *'' In this procedure, the donor liver is placed in a perfusion machine. The precise configuration of the machine depends on whether normothermic or hypothermic perfusion is being used. Typically, it comprises a reservoir, a pump, an oxygenator, a warming or cooling unit and, for normothermic machine perfusion only, monitoring equipment. Both the hepatic artery and portal vein of the liver may be perfused. For normothermic perfusion, the effluent perfusate is collected and recirculated through the liver. A donor liver can be perfused for several hours,*

				after which it can be implanted into a recipient in the conventional way." Section 3.5 also states: ‘*'The literature described different methods used for this procedure including: variation in the temperature used for machine perfusion (hypo- or normothermic); the point at which machine perfusion was started after donor liver explantation; and the duration of machine perfusion."*
7	Consultee 2 Patient organisation The Liver Patients' Transplant Consortium (LPTC)		Thank you for extending the consultation period to allow us to contribute to your project. The Liver Patients' Transplant Consortium (LPTC) is a group of patient groups from liver transplant centres (Cambridge, Kings and Liver North) and specialist liver charities including the Child Liver Disease Foundation, PSC Support and the British Liver Trust amongst others. The LPTC is represented at the Liver Advisory Group and has two votes. The LPTC agrees with the draft recommendations 1.1 to 1.5 and believes these to be sensible and proportionate. The LPTC supports the development of perfusion and encourages research into ways of safely increasing the number of organs available to patient.	Thank you for your comment. The consultee agrees with main recommendation. The committee considered your comment but decided not to change the guidance.

			In addition we believe there are two other advantages. Firstly, the potential increase in transplants could lead to changes in listing criteria to include patients who are currently not eligible due to their unlikelihood of becoming a recipient in a reasonable period of time. Secondly, ground breaking research and development into clinical settings benefits not only patients in the United Kingdom but elsewhere in the world; this research is vital to ensure the UK maintains its position as an innovator in medical science and care.	
8	Consultee 3 NHS Blood and Transplant	**General**	Date: 23rd August 2018 Dear Mr Clutton-Brock On behalf of NHS Blood & Transplant we welcome the opportunity to comment on the NICE Interventional Procedure Consultation document concerning the use of ex-vivo machine perfusion for extracorporeal preservation of livers for transplantation. This is a very important topic currently in liver transplantation. Several approaches are explored in clinical trials to evaluate their benefit with	Thank you for your comment.

			regards to liver utilisation, transplant function and long-term outcome. The current NICE consultation focuses on the ex-vivo machine perfusion for liver preservation. As suggested by the committee in the document we would like to comment on the draft recommendation and factual inaccuracies.	
9	Consultee 3 NHS Blood and Transplant	**Title**	The title of the document describes the procedure as ex-vivo. However, a more appropriate term would be ex-situ, given that several preservation approaches that happen in the donor (in situ) are currently explored in clinical practice. This would be in keeping with the proposed terminology for machine perfusion indices donation in the UK and globally. Please click below to review the draft report of the Novel Technologies in Organ Transplantation working party.  Final NTOT report	Thank you for your comment. The committee decided to change the title of the guidance to: ‘’*Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation*.’’
10	Consultee 3 NHS Blood and Transplant	**2.5**	On page 3, the document describes what the procedure involves and mentions the normothermic and hypothermic conditions for liver perfusion on several devices. However further on it goes on to describe the components of the machine which include a	Thank you for your comment. The word ‘’blood’’ has been changed to ‘’perfusate’’ throughout the guidance and the overview.

			blood warming unit as well as describing the re-circulation of blood on the machine. Although this description is accurate it is only pertinent to the normothermic conditions. In hypothermic conditions the liver is perfused with University of Wisconsin solution on the machine which contains a reservoir, pump, oxygenator and a warming/cooling unit.	The committee decided to change section 2.5 as follows: *2.5 In this procedure, the donor liver is placed in a perfusion machine. The precise configuration of the machine depends on whether normothermic or hypothermic perfusion is being used. Typically, it comprises a reservoir, a pump, an oxygenator, a warming or cooling unit and, for normothermic machine perfusion only, monitoring equipment. Both the hepatic artery and portal vein of the liver may be perfused. For normothermic perfusion, the effluent perfusate is collected and recirculated through the liver. A donor liver can be perfused for several hours, after which it can be implanted into a recipient in the conventional way.*
11	Consultee 3 NHS Blood and Transplant	**1.1**	With regards to the draft recommendations, we agree that current evidence is limited and therefore we feel that the timing for issuing such recommendations by NICE is premature, particularly when several clinical trials are ongoing and will report soon.	Thank you for your comment. The consultee agree that the current evidence is limited in quantity. It is within the remit of the NICE IP programme to issue recommendations on novel procedures as long as there is some evidence on which to assess these. Guidance on procedures with 'special' arrangements is proactively reviewed after 3 years, and the guidance is updated if important new evidence is available. This may be done sooner if there is significant new evidence or emerging new safety concerns.

12	Consultee 3 NHS Blood and Transplant	**1.2**	Based on the current evidence provided for the NICE committee it appears there are no major safety concerns, and this should be strengthened in the recommendations, given the level of current evidence. Therefore, the statement in 1.2 which advises clinicians to ensure that patients understand the uncertainty about the safety of the procedure should be removed given that the statement made in 1.1: “no major safety concerns”.	Thank you for your comment. The committee considered your comment but decided not to change the guidance. The committee confirmed that “no major safety concerns had been identified” but felt this statement was not inconsistent with the requirement to explain to the patient any uncertainties about the procedure’s safety.
13	Consultee 3 NHS Blood and Transplant	**1.3**	At 1.3: We discussed with the HTA and their current position is unchanged in relation to consent when organs for transplant are machine perfused – that consent for the procedure is not required from the donor family – if the perfusion is considered integral to the safe and effective transplant of the organ (obviously this is different for research).	Thank you for your comment. The committee considered your comment but decided not to change the guidance.
14	Consultee 3 NHS Blood and Transplant	**1.3**	The Regulations in relation to use of the machines themselves will fall under MHRA but there is a requirement that any equipment used is appropriately CE marked on the retrieval and transplant side of the regulations.	Thank you for your comment. The committee considered your comment but decided not to change the guidance. It is explicit in our programme manual that any device used in a procedure on which we produce guidance must have a CE mark specific for the notified indication.
15	Consultee 3 NHS Blood and Transplant	**1.4**	The NHSBT transplant registry captures the details of all patients transplanted in the UK and we are in the process of re-structuring the data collected to reflect the usage of in-situ or	Thank you for your comment. Data collected in the registry will be very useful when the guidance is updated and the

			ex-situ machine perfusion. Therefore 1.4 is already addressed at a national level.	committee wanted to re-inforce this requirement in its guidance.
16	Consultee 3 NHS Blood and Transplant	**1.4**	NHS Blood & Transplant through its Research Innovation and Novel Technology Advisory Group (RINTAG) is already monitoring the current research and clinical activity involving the utilisation of machine perfusion and collecting the relevant data in the registry.	Thank you for your comment. Data collected in the registry will be very useful when the guidance is updated.
17	Consultee 3 NHS Blood and Transplant	**1.5**	Finally, 1.5 is rather limited in the suggestions for data collection which should be more comprehensive and compliment what is currently collected in the National Transplant Registry. We would suggest that this recommendation is changed to reflect that these data should be collected irrespective of the type of ex-situ perfusion device utilised (normothermic or hypothermic) to allow subsequent comparison between various techniques.	Thank you for your comment. Section 1.5 of the guidance has been changed to: *''1.5 Further research should report the exact method of perfusion used (such as hypothermic or normothermic), graft survival and the use of marginal grafts.''*
18	Consultee 3 NHS Blood and Transplant	**General**	In summary this is a very important topic currently in transplantation, given the increase utilisation of marginal grafts and the overall shortage of available organs for transplantation. However, given the current level of our clinical activity and research in the area, we feel that the recommendations are rather premature and have the potential to stifle further developments and innovation in the field. It is also likely that within the next 2-5 years this document, should it be	Thank you for your comment. Guidance on procedures with 'special' arrangements is proactively reviewed after 3 years, and the guidance is updated if important new evidence is available. This may be done sooner if there is significant new evidence or emerging new safety concerns.

			considered further at this stage, is very likely to require a revision and a complete re-haul of the proposed recommendations. Yours sincerely [redacted] [redacted]	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."