National Institute for Health and Care Excellence

IP1046 Ex-situ machine perfusion for extracorporeal preservation of lungs for transplantation

IPAC date: 11-03-2021

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Commissioning Specialised Respiratory Clinical Reference Group, NHS England	**General**	NHS England note that the responsibility for the commissioning of machine perfusion to support organ transplantation sits with NHS Blood and Transplant. Although the professional expert notes that EVLP is in use in England practice is not consistent across the country and EVLP is not a substantively commissioned service in any unit.	Thank you for your comments.
2	Consultee 1 Commissioning Specialised Respiratory Clinical Reference Group, NHS England	**General**	We agree that the evidence on the safety and efficacy of ex-situ machine perfusion for extracorporeal preservation of lungs for transplantation is adequate to support consideration of the use of this procedure. It is also worth noting that the technology is highly labour intensive and the cost benefit of use of the technology in the UK would need to be carefully evaluated. Consideration would need to be given to concentration of the use of EVLP in a limited number of centres to develop expertise prior to agreement of wider use. Further evaluation would be needed to determine which devices and protocols are most effective.	Thank you for your comments. Consultee agrees with the recommendation. NICE interventional procedures (IP) guidance assesses only efficacy and safety. It is not within the remit of the IP programme to evaluate cost effectiveness or comment on issues of cost and commissioning. We understand that there are few highly specialized transplant centres that carry out lung transplants in the UK. It is not within the remit of IP or to advise the NHS on issues of commissioning such as the number of centres this procedure should be done prior to wider use.

3	Consultee 2 Cardiothoracic Transplant Committee on behalf of the Society of Cardiac and Thoracic Surgery of Great Britain and Ireland (SCTS)	**General**	Given the shortage of donor lungs and its clinical consequences, we would welcome the availability of EVLP in the UK for improved assessment and more frequent utilisation of donor lungs that are currently declined for transplantation to increase the number of useable donor lungs. However evidence-based organ selection criteria, perfusion protocols and EVLP systems require standardisation. Adequate resources including EVLP equipment and disposables, appropriate surgical, perfusion and theatre staff all need to be made available around the clock to allow this technology to be utilised. These resources do not presently exist. Funding is critically important and centres using this technology currently rely entirely on charitable donations. As such this is not a sustainable process and needs to be centralised and proven to be cost-effective for the NHS in the model of delivery chosen. Consideration needs to be given to where geographically EVLP is best undertaken in the UK to ensure that the necessary resources are made available, a critical volume of EVLP procedures are undertaken to develop and maintain expertise, accompanied by robust evaluation of outcomes and research to further advance the science of this innovative technology.	Thank you for your comments and agreeing with the recommendation. NICE IP advisory committee understands that different devices with technical variations are used for the same procedure and section 2.7 of the guidance clearly states this. NICE IP guidance assesses only efficacy and safety. It is not within the remit of the IP programme to evaluate the cost effectiveness of interventional procedures or stipulate about service provision, resources, and funding.
4	Consultee 2 Cardiothoracic Transplant Committee on behalf of the Society of Cardiac and Thoracic Surgery of Great Britain and Ireland (SCTS).	**General**	Background In selected patients with end stage pulmonary disease and a limited life expectancy, lung transplantation can positively impact on their quality of life and survival. This therapy is currently commissioned at 5 UK centres with 159 lung transplant procedures performed in 2019/20. However, at the end of March 2020, there were still 352 patients on the waiting list and 50 patients had died whilst waiting for suitable donor lungs.	Thank you for your comments. IPAC noted these in their deliberations.

			In Europe, Austria has the highest rate of lung transplants at 11.4 per million population/year (PMP/yr). This contrasts with a rate of just 2.5 PMP/yr in the UK which is the fifth lowest in Europe. The ability to offer lung transplantation to patients accepted onto the waiting list has been limited by a critical shortage of suitable donor lungs. Only 20% of potential deceased donor lungs in the UK are actually used for transplantation and the rest are considered unsuitable as a result of lung injury in the donor, poor function or unfavourable aspects in considering the risk-benefit decisions for individual recipients and donors. As a consequence, approximately 30% of patients will clinically deteriorate and/or die whilst waiting for a lung transplant. Ex-vivo lung perfusion (EVLP), or ex-situ machine perfusion (ESMP), allows for advanced donor lung management through mechanical ventilation and perfusion after removal of the lungs from the donor. There is evidence to suggest that reconditioning of the lungs in this way allows donor lungs that are initially deemed unusable to be improved and become suitable for transplantation, thus increasing donor lung utilisation rate. EVLP was first described 20 years ago and there is significant clinical experience around the world regarding its safety and efficacy to preserve and recondition donor lungs that have been deemed unusable on initial evaluation. However donor lungs reconditioned in this manner represent a very heterogenous group and there is debate as to whether all lungs that have been placed on EVLP actually require it in order to be transplantable. In the UK in particular, there is an established practice in accepting donor lungs that are beyond the standard acceptance criteria, so-called extended criteria donor lungs, as well as lungs from donation after circulatory death (DCD) donors. These are all directly transplanted into recipients without prior EVLP with good outcomes. In some countries, such organs are routinely evaluated with EVLP	

			before transplantation but with apparently similar clinical outcomes.	
5	Consultee 2 Cardiothoracic Transplant Committee on behalf of the Society of Cardiac and Thoracic Surgery of Great Britain and Ireland.	**3**	The UK undertook the multi-centre DEVELOP-UK study with the objective of evaluating the clinical and cost effectiveness of EVLP in increasing lung transplant activity. This unblinded, non-randomised, non-inferiority observational study compared transplant outcomes between EVLP-assessed and standard donor lungs. During the study period, there were 184 standard donor lung transplants. Lungs from 53 donors that did not meet acceptance criteria for direct transplantation were assessed with EVLP, of which 18 (34%) were subsequently reconditioned and transplanted. This “conversion rate” is low compared with rates of 70-83% reported in other EVLP studies and perhaps supports the notion that UK surgeons accept and directly transplant lungs that centres in other countries would place on EVLP before transplanting. During the DEVELOP-UK study, the extra 18 EVLP donor lungs represented a 10% increase in lung transplant activity. One-year survival in the EVLP arm was lower than in the standard arm, 67% compared to 80%. However, the non-inferiority definition of the study was satisfied. Furthermore patients in the EVLP arm required mechanical ventilation for a longer period and stayed longer in an intensive therapy unit than patients in the standard arm, but duration of overall hospital stay was similar in both groups. There was a higher rate of grade 3 primary graft dysfunction (PGD) in the EVLP arm within 72 hours of transplantation, but rates of PGD did not differ between groups after 72 hours. The requirement for extracorporeal membrane oxygenation (ECMO) support was higher in the EVLP arm (38.8%) than in the standard arm (3.2%). There were no major differences in rates of chest radiograph abnormalities, infection, lung function or rejection	Thank you for your comments. DEVELOP-UK study (Fisher 2016) is an observational study included in the systematic reviews and meta-analyses (Chakos A 2020, Lou 2019, Tian 2019) added to table 2. Therefore, it has been added to the appendix in the overview for consideration by IPAC.

			by 12 months. The DEVELOP-UK Study was terminated early in 2014. The cost of each EVLP lung transplant was approximately £35,000 higher than the cost of standard lung transplants due to the cost of the EVLP procedure, increased ECMO use and longer ITU stay. DEVELOP-UK base-case results suggested that incorporating EVLP would increase the number of donor lungs available for transplantation, but would not currently be considered cost-effective in the UK with the current organisational structure and with present levels of activity. Nevertheless, if a higher conversion rate approaching those observed in other EVLP trials and a lower rate of post-transplant complication could be achieved for EVLP transplants (as seen in other EVLP studies) there is potential for improvement in cost-effectiveness.	
6	Consultee 3 Cystic Fibrosis Trust	**General**	Cystic fibrosis is the most common life-limiting genetic disease affecting children and adults in the United Kingdom. Almost 11,000 people in the UK live with CF and 1 in 25 of the UK population carry one copy of the faulty gene that causes CF. Cystic fibrosis is a multi-system, progressive, and life limiting condition. Over 90% of people with CF will suffer from respiratory failure as a consequence of progressive lung damage necessitating lung transplant to prolong life. The Cystic Fibrosis Trust is pleased to respond to this consultation. Increasing the number of successful lung transplants is vital to our ambition to ensure that everyone living with cystic fibrosis can look forward to a long and healthy life. Cystic fibrosis is the third most common reason for lung transplantation. Research conducted by the Cystic Fibrosis Trust showed people with cystic fibrosis wait on average 412 days, when severely unwell before a suitable donor is found, and then must survive and recover from major surgery. Up to 30% of people are currently dying whilst waiting for a lung transplant.	Thank you for your comments and welcoming the guidance. Issues of service provision and commissioning of services are outside the remit of the IP programme.

			The UK has a chronic shortage of donor lungs, and amongst the lowest rates of organ utilisation in Europe. Effective measures to address this are urgently needed. It is essential that EVLP is not viewed in isolation, and rather as a part of a suite of measures needed to increase the rates of donor lung utilisation leading to transplants. EVLP is a welcome addition to increase lung transplantation and will offer some individuals a lifeline in their wait for an organ. On average, only 20% of potential deceased donor lungs in the UK are used for transplantation, but this varies significantly between cardiothoracic transplant centres. EVLP must be seen as a way of providing an increased pool of donor lungs at every centre, so that patients have equality of opportunity wherever they are listed. It is essential that through this recommendation all patients can access this increased pool of donor lungs, whether through each centre directly having access to the technology or through a system of co-operation. Centres must be supported to inform patients of the provision available to enable an informed choice and the realistic hope of a successful lung transplant. The reality is, however, centres regularly decline donor offers for reasons other than the function of the lung. The NHSBT Lung Summit Report referenced a shocking 245 organ declines, over a 12-month period, purely due to a lack of resource/ logistics. Given that actual lung transplants in the same period were just 158, with 331 people on the waiting list, the magnitude of current capacity issues cannot be overstated. Introducing technologies such as EVLP must be done hand in hand with increased resources to deal with any predicted increase in rates of transplants. Expert evidence given by [redacted] stated that at Harefield Hospital, about 10-20% of their 50- 60 lung transplants are done using EVLP. If this was replicated across the transplant centres it has the potential for a significant increase of up to 20% more lung transplants, and the potential	

			to massively reduce mortality on the lung transplant waiting list. We know international studies have shown that use of EVLP can increase the number of lung transplants by 15-30%. Given the stark reality facing patients waiting for a lung transplant, such an increase in hope of a future would be huge. It is vital to ensure patients, such as those with cystic fibrosis, a genuine chance of a future. "It's not right that one in three people are still dying waiting for lungs, especially if people have been kind enough to donate them in the first place." [redacted], who has cystic fibrosis.	
7	Consultee 4 Lung Transplant Working Group of Cystic Fibrosis Medical Association	**General**	We thank the National Institute For Health And Care Excellence for the opportunity to comment on this important topic. The UK Cystic Fibrosis Medical Association is a profession body representing doctors who care for people (adults and children) with Cystic Fibrosis (pwCF) in the UK. 1. We generally view ex-situ machine perfusion for extracorporeal preservation (EVLP) for lung transplantation favourably, as we believe that it has the potential to increase organ availability to pwCF on the lung transplant waiting list who would otherwise die without suitable organs. The current situation is that far too many people (including many pwCF) are dying due to lack of suitable organs. We are aware that the UK has some of the lowest lung utilisation rates in the world. The implementation of EVLP will improve this situation, but will not make up for other systemic problems, such as those outlined in the report from the Lung Utilisation Summit (BTS/NHSBT) held on 31st October 2019.	Thank you for your comments and welcoming the guidance. Issues of implementation are outside the remit of the IP programme.
8	Consultee 4 Lung Transplant Working Group of Cystic Fibrosis Medical Association	**General**	2. The CFMA members are physicians, not surgeons, and are thus not experts in the surgical techniques involved in EVLP. However, we are aware that there are at least three different techniques/methods available: Lund, OCS and Toronto. We would like reassurance on the generalisability of findings that	Thank you for your comments. NICE IP advisory committee understands that different devices with technical variations are used for the same procedure and section 2.7 of the guidance clearly states this.

			use different methods. We are aware of the results of the Fisher et al (HTA 2016) study which used the Lund method. Will any comment be made on which method(s) should be adopted?	NICE IP guidance does not generally name or relate to specific devices/technical variations. The Committee makes recommendations based on the available evidence, while bearing in mind that it is evaluating the procedure rather than a specific device/technical variation.
9	Consultee 4 Lung Transplant Working Group of Cystic Fibrosis Medical Association	**General**	3. Whichever method/methods are recommended, we would like reassurance that potential recipients are not disadvantaged, neither due to where they live nor which lung transplant centre they attend, by the uptake of EVLP by some centres and not others.	Thank you for your comments. It is the role of commissioners of health services to decide on clinical facilities, and service provision.
10	Consultee 4 Lung Transplant Working Group of Cystic Fibrosis Medical Association	**General**	4. Given that some studies of EVLP suggest worse outcomes for pwCF than standard techniques, we would like reassurance that regular ongoing audit of activity and outcomes, including reporting by disease group, will be made public.	Thank you for your comments. NICE IP guidance recommends that *Clinicians and centres doing this procedure must follow the **relevant regulatory and legal requirements of the Human Tissue Authority.*** *Clinicians should enter details about all patients having this procedure and details about the device used into the **NHS blood and transplant organ donation and transplantation registry**.*

"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."