Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER431
Topic:	Ex-vivo lung perfusion for advanced pulmonary disease
Summary of findings:	The number of patients with advanced pulmonary disease who are eligible for a lung transplant currently outweighs the number of available suitable donor organs, where the current utilisation rate is around 20%. This is associated with increased mortality and significant deterioration of health. Ex-vivo lung perfusion (EVLP) may increase the number of donor lungs suitable for transplant by assessing and treating the lungs before they are transplanted. One piece of relevant guidance, four systematic reviews/meta-analyses and an economic evaluation were identified. Results show that EVLP allows for greater access to transplants by widening the number of available donor organs. EVLP transplants are comparable to standard practice with regard to acute rejection, mid to long-term survival and primary graft dysfunction. Health economic data suggests that EVLP may have a quality-adjusted life year incremental cost-effectiveness ratio of £73,000 in the UK.

Introduction and aims

Lung transplantation is an effective and potentially life-saving measure for patients with advanced pulmonary disease, and may improve both quality of life and life expectancy outcomes. Currently, the number of waitlisted lung transplant candidates far exceeds the availability of suitable organs for transplantation, where the utilisation rate is around 20%. The limited availability of donor lungs that meet the standard criteria to be eligible for transplant results in up to 30% of eligible patients deteriorating whilst awaiting transplant, and is associated with increased mortality.

Ex-vivo lung perfusion (EVLP) technology may increase the number of donor lungs eligible for transplant by extending donor criteria and allowing for the donation of lungs after circulatory death. EVLP allows donor lungs to be evaluated in a closed circuit outside of the body, and allows for assessment prior to final acceptance for transplantation. Developments in EVLP technology have effectively eliminated the need to keep donor lungs in static cold storage prior to transplantation, reducing the cold ischemic time. EVLP also provides a mechanism for improving the quality of donor lungs, as lung segments affected by atelectasis are able to be mechanically repaired. Similarly, mechanical bronchoscopies and intravascular administration of anti-inflammatory and antibiotic therapies is possible.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of EVLP technology for lung transplantation.

Evidence overview

One piece of guidance, three systematic reviews, one meta-analysis and two individual studies were identified.

Guidance

This TER is informed by NICE IPG695 *'Ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant*'. Which supports that the evidence on the safety and efficacy of ex-situ machine perfusion is adequate to support the use of this procedure. This TER aims to assess the evidence available for clinical and cost effectiveness of the technology.

Systematic reviews and meta-analyses

Three systematic reviews and one meta-analysis were identified by IPG695. Further evidence was searched for, but no results were found.

Tian et al. (2020) identified eight individual studies with 1911 participants with a total of 1911 participants. The study concluded that there is no significant difference in outcomes with respect to intubation, life support, length of ICU/hospital stay, primary graft dysfunction, 30 day and 1-year survival rates between EVLP-treated Lung transplantation and standard Lung transplantation practice. The review also identified that all post-transplant outcomes were similar between groups, despite the quality of EVLP donor lungs being worse overall. The review suggests that EVLP technology may serve to improve donor lung use for successful transplantation.

Chakos et al. (2020) identified thirteen individual studies, comparing 407 EVLP-treated transplants and 1765 standard practice transplants. The review identifies that for EVLP, donor lungs come primarily from brain death donors and have a significantly worse PaO2/FiO ratio and a greater rate of abnormal chest X-ray. The review concludes that there is no significant difference in mid to long-

term survival of EVLP lung transplant patients compared to standard practice, as the incidence of 30-day mortality and primary graft dysfunction (grade 3) at 72 hours did not differ significantly between groups. The review concludes that EVLP offers the potential to increase lung donor utilisation with similar short-term outcomes and mid to long-term survival as standard practice.

Tsuang et al. (2020) identified 12 reviews, and concludes that when compared to standard practice, EVLP may result in little to no difference in acute rejection (relative risk 0.95) or primary graft dysfunction (grade 3) at 72 hours (relative risk 0.99). The review identifies that acute rejection and PGF outcomes are similar for both groups, with little difference in regard to airway complications and survival at one year post transplant. Though the overall body of evidence is identified as having low certainty, the review concludes that EVLP may be a promising intervention with the potential to increase patient access to transplants.

Lou et al. (2019) conducted a meta-analysis of 20 published articles, and concluded that EVLP improved the function of high-risk donor lungs as well as a lower incidence of primary graft dysfunction (grade 3) at 72 hours, but was associated with a longer hospital stay overall. Other clinical outcomes between the two groups were similar. Pooled results from the analysis indicated that EVLP can be used to access and improve high-risk donor lungs with non-interior postoperative outcomes compared with standard practice – increasing the utilisation of marginal donors and extending preservation time by reducing the total ischemia time for donor lungs.

Individual studies

One individual study was identified in IPG695. Further studies were searched for, but no results were found**.**

Divithotawela et al. (2019) performed a retrospective cohort single-centre study between August 2008 and February 2017 comparing the long-term outcomes of 706 standard practice LTx patients and 230 EVLP Lung transplantation patients. The study identified that more recipients in the EVLP group received single-lung transplants, with no significant difference in time to chronic lung allograft dysfunction between groups, or allograft survival between groups at 5 years. At 9 years, allograft survival was 50%/44% to standard practice and EVLP, respectively. All secondary outcomes were similar between groups. The study concludes that use of EVLP led to an increase in the number of patients undergoing transplantation, with comparable long-term outcomes to standard practice.

Economic evidence

Two economic studies were identified - these were included in the systematic reviews identified by IPG695.

Fisher et al (2016) performed a cost-effectiveness analysis of EVLP technology using an exploratory economic model. The study concluded that the incremental cost of the EVLP service was £4,496, while the number of incremental life-years gained and number of QALYs gained was 0.03 and 0.06 respectively, stating that the life-year ICER was £147,000 and the QALY ICER was £73,000. The same study also performed a within-study assessment of costs based on a regression model, and identified a significant variation in the cost associated with the transplant of each individual regardless of whether EVLP or standard practice was used. Based on the calculations made in this assessment, the average total cost per recipient for the standard donor lung transplantation is equal to £59,608 (SD £42, 664), and the total cost per recipient for EVLP is £139,081 (SD £39,561) primarily due to the increased cost of the EVLP procedure and the cost of post-operative care.

Ahmad et al (2022) noted that cost is a significant barrier to the widespread adoption of EVLP, and identifies that the matter of cost effectiveness is an area of ongoing study. However, there is

evidence to suggest that EVLP is profitable at the institutional level through increased transplant volumes, but each individual EVLP case costs approximately $40,000-50,000USD more than a traditional transplant.

Areas of uncertainty

If this topic were to proceed to appraisal, further clarification is required in the following areas:

- There are multiple conditions that would lead to advanced/end stage pulmonary disease, such as cystic fibrosis or severe pulmonary fibrosis. It is also unclear how people are selected to receive a lung transplant, i.e. what, if any, criteria are used. Consideration is needed as to which populations would be appropriate for inclusion in an appraisal and how evidence from different populations would be presented, if needed.
- Whether addition of EVLP into the lung transplantation pathway would impact on the criteria used to assess lung suitability for donation.
- One study that prevents conflicting evidence was terminated early. Further clarification should be sought on the reasons for this termination.
- A multicentre UK study was identified as treating Welsh patients with EVLP at clinics in England. It is therefore unclear whether EVLP is being used in Wales, and how many Welsh patients currently receive treatment.

Literature search results

Health technology assessments and guidance

NICE. (2021). [IPG695]: Ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant. Available at: https://www.nice.org.uk/guidance/ipg695 [accessed 24/01/23]

Evidence reviews and economic evaluations

Chakos A, Ferret P, Muston B, et al. (2020). Ex-vivo lung perfusion versus standard protocol lung transplantation mid-term survival and meta-analysis. Ann Cardiothorac Surg. 9(1): 1-9. doi: 10.21037/acs.2020.01.02

Luo Q, Zhu L, Wang Y, et al. (2019). The Conversional Efficacy of Ex Vivo Lung Perfusion and Clinical Outcomes in Patients Undergoing Transplantation of Donor Lungs by Ex Vivo Lung Perfusion: A Meta-Analysis. Ann Transplant. 24: 647-60. doi: 10.12659/AOT.919242

Tian D, Wang Y, Shiiya H, et al. (2020). Outcomes of marginal donors for lung transplantation after ex vivo lung perfusion: A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 159(2): 720-30 e6. doi: 10.1016/j.jtcvs.2019.07.087

Tsuang WM, Okamoto T, Morgan RL, et al. (2020). Ex Vivo Lung Perfusion Resuscitated Donor Lungs and Subsequent Acute Rejection and Airway Complications: A Systematic Review and Meta-Analysis. The Journal of Heart and Lung Transplantation. 39(4). doi: 10.1016/j.healun.2020.01.463

Individual studies

Ahmad K, Pluhacek JL, Brown AW. (2022). Ex Vivo Lung Perfusion: A Review of Current and Future Application in Lung Transplantation. Pulm Ther. 8(2): 149-65. doi: 10.1007/s41030-022-00185-w

Divithotawela C, Cypel M, Martinu T, et al. (2019). Long-term Outcomes of Lung Transplant With Ex Vivo Lung Perfusion. JAMA Surg. 154(12): 1143-50. doi: 10.1001/jamasurg.2019.4079

Fisher A, Andreasson A, Chrysos A, et al. (2016). An observational study of Donor Ex Vivo Lung Perfusion in UK lung transplantation: DEVELOP-UK. Health Technol Assess. 20(85): 1-276. doi: 10.3310/hta20850

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Concepts used:	EVLP, Ex-vivo lung perfusion, Lung perfusion, Lung transplantation, Lung transplantation