[GID-HTE10084] Ex-situ machine perfusion devices for lung transplants

Final Protocol

Produced by: York Health Economics Consortium

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1. Decision problem

Ex-situ lung perfusion technologies have been identified by NICE for early use assessment. As described in the NICE scope, the aim of this early use assessment is to evaluate whether ex-situ machine perfusion technologies for deceased donor lung transplants are a clinical and cost-effective use of NHS resources, and to identify gaps in the evidence base. This document was prepared in response to the NICE scope and presents the methods that the external assessment group (EAG) commissioned by NICE will undertake to produce the assessment.

This assessment will consider the use of ex-situ machine perfusion devices for lung transplants in addition to standard care for the preservation and functional assessment of marginal donor lungs.

Table 1 summarises the decision problem to be addressed in this assessment. Further detail on each element can be found in the published scope for the assessment.

Table 1. Summary table of the decision problem

Proposed type of assessment	Early use
Population	People active on the lung transplant waiting list
Intervention	XVIVO Perfusion System XPS (XVIVO Perfusion AB)
Comparators	• Static cold storage (SCS) • Storage at 8 to 12ºC
Outcomes and costs (may include but are not limited to)	System outcomes: • Proportion of donor lungs that proceed to transplant rather than being discarded (utilisation rate) • Proportion of donor lungs having machine perfusion that proceed to transplant (conversion rate) • Size and duration of lung transplant waiting list • Number of people who die on the transplant waiting list (mortality) • Number of people removed from the waiting list because they are too unwell for surgery • Length of and type of organ storage • Length of perfusion Clinical outcomes: • Recipient survival post-transplant

	• Graft survival post-transplant • Primary lung graft dysfunction (PGD) • Graft injuries • Use and duration of life support, including ECMO or mechanical ventilation • Measures of lung function • Serious adverse events Patient-reported outcomes: • Health-related quality of life (including impact on mental health and social functioning) Costs and resource use: • Cost of the technology (for example, purchase or lease costs, consumable costs and cost of training, including costs for procedures that do not result in transplantation) • Cost of organ retrieval and transplant surgery, post operative care, management of complications & hospital length of stay (including use of life support) • Cost of managing the condition on the transplant waiting list, including hospitalisation episodes • Staff time and cost according to specialism and level of pay, including theatre staff • Proportion and cost of daytime procedures compared with night-time procedures
Economic analysis	A health economic model will be developed comprising a cost utility or cost-comparison analysis. Costs will be considered from an NHS and Personal Social Services perspective. Sensitivity and scenario analyses will be undertaken to address the relative effect of parameter and structural uncertainty on results. The time horizon will be long enough to reflect all important differences in costs and outcomes between the technologies being compared.

1.1 Objectives

The purpose of this assessment is to address the following key decision questions:

- What is the clinical effectiveness of using ex-situ machine perfusion technologies for deceased donor lung transplants?
- What is the cost effectiveness of using ex-situ machine perfusion technologies for deceased donor lung transplants?

- What evidence is available to support the value proposition of ex-situ machine perfusion devices outlined in the scope, i.e.:
    - improving access to donor lungs for people on the waiting list
    - reducing the number of people who die on waiting list or become too unwell to receive a transplant
    - increasing the number of donor lungs that are transplanted
    - extending the period during which the lung can be stored, allowing more flexibility when arranging transplant.
- Are there gaps in the evidence base and what are the key gaps?

2. Evidence review methods

We will conduct an evidence review to identify the clinical and economic evidence that is available on the selected technology and explore if the technology addresses the unmet need, using methods that conform to the NICE HealthTech programme manual [1] and with reference to guidance from the NICE Decision Support Unit [2]. The review methods, search approach, and synthesis will be conducted in a transparent manner. We will conduct a systematic search for relevant published evidence and incorporate any relevant evidence submitted by manufacturers through the NICE request for company evidence. Retrieved evidence will be screened according to the eligibility criteria described in Section 2.1. We will extract and synthesise relevant data from the eligible documents. Relevant clinical and health-related quality of life (HRQoL) data will inform the parameters of an Excel-based economic model.

2.1 Inclusion criteria

The eligibility criteria for included studies are summarised in Table 2 and reflect the decision problem set out in the NICE scope.

Table 2. Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria

Population	People active on the lung transplant waiting list	Non-lung and heart-lung transplant recipients
Intervention	Ex-situ machine perfusion devices for marginal donor lungs initiated on arrival at the hospital of the recipient after the lungs have been transported using conventional static cold storage or refrigeration. The following ex-situ machine perfusion devices will be considered: • XVIVO Perfusion System XPS (XVIVO Perfusion AB)	Ex-situ machine perfusion devices other than those listed as eligible.
Comparators	• Static cold storage • Storage at 8 to 12ºC	Any comparator not listed.
Outcomes	**System outcomes:** • Proportion of donor lungs that proceed to transplant rather than being discarded (utilisation rate) • Proportion of donor lungs having machine perfusion that proceed to transplant (conversion rate) • Size and duration of lung transplant waiting list • Number of people who die on the transplant waiting list (mortality) • Number of people removed from the waiting list because they are too unwell for surgery • Length of and type of organ storage • Length of perfusion **Clinical outcomes:** • Survival post-transplant • Graft survival post-transplant • Graft injuries • Use and duration of life support, including ECMO or mechanical ventilation • Primary lung graft dysfunction (PGD) • Measures of lung function • Serious adverse events **Patient-reported outcomes:** • Health-related quality of life	Studies not reporting outcomes relevant to the NICE final scope.

	For the economic review: • Total costs • Effectiveness outcomes (e.g. quality adjusted life-years (QALYs), disability adjusted life-years (DALYs)) • Incremental analyses or other economic evaluation outcomes (e.g. incremental cost-effectiveness ratios (ICERs))	

Study design	**For the clinical review:**
	• RCTs.
	• Non-randomised comparative studies, including:
	  • Non-randomised comparative trials.
	  • Cohort studies.
	  • Case-control studies.
	• Single arm studies.
	• Case reports.
	Real-world evidence will be considered for the meta-analysis if applicable.
	For the economic review:
	• Cost-effectiveness analyses (including cost-utility analyses).
	• Cost-benefit analyses.
	• Cost-consequence analyses.
	• Cost-comparison analyses.
	• HTA reports investigating the cost-effectiveness of treatments.
		• Bench studies.
		• Reviews, both systematic and non-systematic.

Limits	• Studies in English language only. • Studies published from 2000 onwards. • Conference abstracts published from 2023 onwards.	• Studies not in the English language. • Studies published in 1999 or earlier. • News items, opinion pieces and editorials.

Key: HTA – health technology assessment, RCT – randomised controlled trial.

Initial scoping searches indicate that the first in-human studies in machine perfusion for lung transplants were published from 2001 [3]. This is reflected in the eligibility criteria.

If we identify a large number of studies we will prioritise those that provide the most relevant and rigorous evidence.

For the review of clinical evidence, we will prioritise:

- Randomised controlled trials
- Prospective studies reporting comparative evidence

Single arm studies may be included if there is limited comparative evidence for the technology. Inclusion criteria may be expanded if no evidence directly relevant to the evaluation is available, for example, including studies that report on relevant information, but do not include the intervention technologies.

For the economic review, we will prioritise:

- Studies reporting full economic evaluations over partial economic evaluations, on an intervention-by-intervention basis, taking the use case into account.
- Studies conducted in the UK, or if not in the UK, Europe, or Canada.

2.2 Search strategy

A MEDLINE (OvidSP) search strategy designed to identify clinical and economic evidence on the eligible technology is presented in Appendix 1.

The strategy comprises search terms for lung transplants (search lines 1 to 4), perfusion devices (search lines 5 to 8), and terms associated with the eligible technology (search line 10). The search is structured: (lung transplants AND perfusion devices) OR eligible technology.

The strategy excludes animal studies from MEDLINE using a standard algorithm (search line 12). The strategy also excludes some ineligible publication types which are unlikely to yield relevant study reports (editorials, news items and case reports) and records with the phrase 'case report' in the title (search line 13).

Reflecting the eligibility criteria, the strategy is restricted to studies published in the English language (search line 15) since 2000 (search line 16).

The final Ovid MEDLINE strategy will be peer-reviewed before execution by a second Information Specialist. Peer review will consider the appropriateness of the

strategy for the review scope and eligibility criteria, inclusion of key search terms, errors in spelling, syntax and line combinations, and application of exclusions.

2.2.1 Resources to be searched

We will conduct the literature search in the databases and information sources shown in Table 3.

Table 3. Databases and information sources to be searched

Resource	Interface / URL
Databases	
MEDLINE(R) ALL	OvidSP
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley
HTA database	https://database.inahta.org/
Conference Proceedings Citation Index – Science (CPCI-S)	Web of Science
NHS Economic Evaluation Database (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
EconLit	OvidSP
Trials Registers	
ClinicalTrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform (ICTRP)	https://trialsearch.who.int/
Reference list checking	n/a
Evidence from companies and NHS Blood and Transplant	n/a

The resources include sources of both clinical and economic studies. The trials register sources listed above (ClinicalTrials.gov and ICTRP) will be searched to identify information on studies in progress.

The CPCI-S search results and records indexed in Embase as conference abstracts will be restricted to studies published from 2023 to date.

We will also check included studies lists from the company request for evidence to NICE, and evidence received from NHS Blood and Transplant, as well as retrieved

relevant systematic reviews or meta-analyses published in the last 3 years, for additional eligible studies.

2.2.2 Running the search strategies and downloading results

We will conduct searches using each database or resource listed in the protocol, translating the agreed Ovid MEDLINE strategy appropriately. Translation includes consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri. The final translated database strategies will be peer-reviewed by a second Information Specialist. Peer review will consider the appropriateness of the translation for the database being searched, errors in syntax and line combinations, and application of exclusions.

We will document all search strategies and search results, and we will provide this in the final report to meet standard requirements for clear formal reporting of the search process. The report of search methods will be informed by the PRISMA-S (Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension) checklist [4] and the PRISMA 2020 statement [5, 6].

Where possible, we will download the results of searches in a tagged format and load them into bibliographic management software (EndNote) [7]. The results will be deduplicated using several algorithms and the deduplicated references held in a duplicates EndNote database for checking if required. Results from resources which do not allow export in a format compatible with EndNote will be saved in Word or Excel documents as appropriate and manually deduplicated.

2.3 Study selection

Record assessment will be undertaken as follows:

- A single researcher will remove obviously irrelevant records such as those ineligible conditions.
- The titles and abstracts of remaining records will be assessed in detail for relevance against the protocol eligibility criteria by a single experienced reviewer, with a 10% sample checked by a second reviewer and any queries regarding eligibility addressed in discussion with the second reviewer.

- The full text of potentially relevant studies will be obtained and assessed for relevance against the protocol criteria by a single experienced reviewer, with a 10% sample checked by a second reviewer and any queries regarding eligibility addressed in discussion with the second reviewer.

We will list studies excluded after assessment of the full document in an excluded studies table, with the reasons for exclusion.

2.4 Data extraction strategy

A bespoke data extraction template will be developed in Word and piloted on 10% of the included studies. One researcher will extract data and a second researcher will check all data points. Any discrepancies will be resolved by discussion, and by involvement of a third researcher when required. Data extraction will be targeted, involving the limited extraction of key details describing the study reference (bibliographic details), study design, key patient characteristics, key intervention / comparator characteristics and outcomes.

2.5 Quality assessment strategy

Formal risk of bias assessment is not required in the early use assessment process and so will not be conducted. However, the report will include discussion of any concerns regarding the reliability of the key included studies, due to study designs used and consequently how the risk of bias might have affected key outcomes. The report will comment on the generalisability of the results to clinical practice in the NHS.

2.6 Methods of synthesis and analysis

The data will be summarised in tables and synthesised in a narrative review.

3. Economic analysis methods

We propose the development of an economic model to estimate the clinical and economic outcomes associated with the use of ex-situ machine perfusion devices in patients undergoing lung transplantation from deceased adult donors.

The model will address the decision problem outlined in the final scope (see Section 1 for the draft decision problem).

The primary aim of this economic analysis is to estimate the costs and clinical outcomes for ex-situ machine perfusion devices initiated at recipient specialised lung transplant centres when compared with SCS and storage temperatures ranging 8 to 12ºC. The model will also identify key drivers of costs and clinical outcomes. Changes to the transplant pathway as informed by NHSBT will also be considered, such as the Assessment and Recovery Centre (ARC) pathway.

We will also consider the costs and clinical outcomes in specific sub-groups, where data allows. Sub-groups may include those registered as super-urgent, urgent and non-urgent on the transplantation waiting list or where other clinically meaningful characteristics are identified.

The secondary aim of this economic analysis is to assess the health equity implications for machine perfusion. This secondary analysis will primarily look at the impact that using the technology may have upon specific groups. We anticipate that there may be limited evidence to inform this analysis and, therefore, in its absence it may be commented qualitatively within the report. The economic evaluation will adopt an NHS and Personal Social Services (PSS) perspective, in line with the NICE reference case [8].

3.1 Model development

This evaluation will include analysis for the patient population, and where possible, and conditional on evidence, disaggregated analyses will also be conducted to examine costs and clinical outcomes for relevant subgroups and scenarios. We anticipate there will be differences in the level and quality of evidence available across subgroups. Where this is identified, we will reference and interpret this in the final report. Where appropriate, this will be used to inform recommendations for future data collection.

Expert clinical opinion will be used to guide the model design, use of subgroups, and to ensure that key clinical events and outcomes are appropriately captured. We will aim to include all outcomes listed in the NICE scope that either have suitable evidence to inform them, or where assumptions can be used. Outcomes with the highest level of evidence will be prioritised and those with greater uncertainty may be included in additional scenario analyses. For example, where outcomes such as

length of time required on mechanical ventilation are supported by evidence with notable uncertainty, these may be included in the base case model with the option to switch their inclusion on or off in scenario analysis.

Costs associated with the use of ex-situ machine perfusion may include cost of the technology to a department / NHS site, staff time for organ transport, procedure time, and any training or ongoing equipment maintenance costs. Where company-supplied evidence is available, the model will aim to explore different intervention cost structures such as leasing, annualised capital investment and free loan with consumable contracts, as applicable. Clinical outcomes which influence costs may include conversion rate from ex-situ machine perfusion for lungs to transplant, waiting list times, hospital length of stay, adverse events rates and other relevant interventions.

Model inputs will be informed by published literature, company submissions, NHS data sources, and expert opinion. To identify appropriate evidence for costs and resource use, we will conduct targeted searches of the economic literature, supplemented by data from the NHS Cost Collection data, the Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU), and the British National Formulary (BNF). All costs will be inflated to the 2023/24 price year.

The model will include health-related quality of life outcomes (HRQoL) where available. However, it may not be possible to fully reflect the impact of different patient pathways or additional time spent on the transplant waiting list, particularly over the long-term. Where we are unable to quantify this, these issues will be discussed qualitatively in the final report. Equally, we acknowledge that broader societal outcomes, including personal and family costs and potential impacts on quality of life for family and caregivers, may not be captured in the model. These outcomes will also be discussed qualitatively in the final report.

Deterministic sensitivity analysis (DSA) will be used to test the impact of uncertainty in key model parameters. A tornado diagram will be included to display the parameters with the greatest impact on model outcomes. Additional scenario analyses may also

be conducted on key drivers of the model, or as exploratory analysis on uncertain parameters. Probabilistic sensitivity analysis (PSA) will also be conducted, though it is worth noting that, if there is a significant lack of data for some parameters, the results of the PSA may not be fully accurate, as the underlying probability distributions may be less robust.

3.2 Conceptual Modelling

A conceptual model will be developed to address the decision problem. The proposed model structure will likely be a Markov model with a lifetime horizon and monthly cycle length. Whilst it is not possible at this point to provide a definitive outline, it is anticipated the model would consist of six health states: super-urgent waitlist, urgent waitlist and non-urgent waitlist, transplant surgery, post-transplant and death. This approach would capture the impact of machine perfusion on increased organ utilisation as well as the impact on clinical outcomes in both surgery and post-transplant.

The final model structure will be finalised following further exploration of the clinical pathways and the evidence assessment.

The base case model is expected to focus primarily on the short-term change in lung transplant utilisation, alongside other important clinical and resource use outcomes such as hospital length of stay and patient survival while on the waiting list. The lifetime model will aim to assess the long-term consequences of how increasing utilisation of donor lungs may increase access and, therefore, reduce average time spent on the waiting list. Where possible, this will include any consequences of remaining without a transplant, including the possibility of condition deterioration and/or death. This analysis will consider the lifetime impacts on patient outcomes including survival and any other relevant impacts where available.

Costs and health outcomes in the model will be discounted at 3.5% per annum, in line with the NICE reference case [8]. Due to the paucity of data in the literature detailing long-term clinical outcomes, it may not be possible to model some outcomes. Therefore, exploratory assumptions may be necessary to investigate the range of potential impacts on model results.

This outlined approach enables us to balance the use of existing evidence, capture both short-term events and select long-term cost and health outcomes, while limiting the structural uncertainty that may arise from the use of more complex modelling structures.

Due to a variety of sub-populations, as well as specific workflows and preferences of speciality departments, there will be a range of additional long-term outcomes, which will not be possible to capture. YHEC will take expert advice into account to consider long-term outcomes, where feasible. Model results will be reported disaggregated by short- and long-term outcomes; commentary will be provided on the relative robustness of each of these outcomes in the final report.

Once the model structure and key assumptions have been refined based on the final scope and evidence review, we will validate the approach with clinical experts. This will be done through dedicated meetings or email correspondence. Expert feedback will be used to test the face validity of the conceptual model, inform subgroup analysis, and ensure that key events and outcomes are appropriately captured.

4. Handling information from the companies and other stakeholders

All data submitted by the companies in evidence and information requests by NICE, or data submitted by other stakeholders will be considered by the EAG if received by 24th March 2026. Information arriving after this date may not be considered. If the data included in the information provided meets the inclusion criteria for the review, they will be extracted and quality assessed following the procedures outlined in this protocol. The EAG will handle confidential data in line with NICE's standard process. The EAG may seek clarification or additional information from companies and other stakeholders where necessary. All correspondence between the EAG and companies will happen through NICE.

5. Additional information sources

NICE will recruit clinical and patient experts for this assessment. Experts are selected from those nominated by consultee organisations or by NICE, taking into

account NICE's policy on declaring and managing interests for NICE advisory committees.

6. Competing interests of authors

There are no competing interests of authors.

7. References

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Appendix A: Draft search strategy

1 exp lung transplantation/ (20453)

2 ((lung* or pulmonary) adj5 (transplant* or allotransplant* or allograft* or graft* or replac*)).ti,ab,kf. (35719)

3 ((lung* or pulmonary) adj5 (donat* or donor*)).ti,ab,kf. (4788)

4 or/1-3 (39906)

5 organ preservation/ (10789)

6 perfusion/ (54660)

7 (perfus* or evlp).ti,ab,kf. (252134)

8 or/5-7 (272181)

9 4 and 8 (2853)

10 (xvivo or (xps and (lung* or pulmonary)) or xpstm or xpsr).ti,ab,kf. (174)

11 9 or 10 (3018)

12 exp animals/ not humans/ (5427969)

13 (news or editorial).pt. (985132)

14 11 not (12 or 13) (1859)

15 limit 14 to (english language and yr="2000 -Current") (1395)