Healthy Blue

Medical Policy

Subject:	Portable Normothermic Organ Perfusion Systems		
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Description/Scope

This document addresses use of a portable normothermic organ machine perfusion and monitoring medical device used to preserve donor organs in a near-normothermic state from retrieval until transplantation. This document *does not* address static cold storage or other forms of solid organ preservation.

Note: Please see the following transplant documents for information related to transplant specific criteria:

- TRANS.00008 Liver Transplantation
- TRANS.00009 Lung and Lobar Transplantation
- TRANS.00033 Heart Transplantation
- CG-TRANS-02 Kidney Transplantation

Position Statement

Medically Necessary:

A. Portable normothermic **lung** perfusion (that is, Organ Care System Lung™) is considered **medically necessary** when used as part of the acquisition, collection and storage of a covered and medically necessary organ transplant involving donor lung pairs initially deemed unacceptable for procurement and transplantation based on limitations of cold storage preservation (that is: age greater than 55, PaO2/FiO2 less than 300 mmHg, donation after cardiac death donors, ischemic time greater than 6 hours).

B. Portable normothermic **liver** perfusion is considered **medically necessary** when used as part of the acquisition, collection and storage of a covered and medically necessary organ transplant when an organ is initially deemed unacceptable and when criteria (1 **or** 2) below are met:

1. *Organ Care System Liver*: liver allografts from donors after circulatory death less than or equal to 55 years old and with less than or equal to 30 minutes of warm ischemic time, macrosteatosis less than or equal to 15%; **or**
2. *OrganOx® metra® System*: liver allografts from donors after circulatory death less than or equal to 40 years of age, with less than or equal to 20 minutes of functional warm ischemic time, and macrosteatosis less than or equal to 15%.

Investigational and Not Medically Necessary:

Portable normothermic portable organ machine perfusion is considered **investigational and not medically necessary** when the above criteria are not met, including but not limited to use as part of the acquisition, collection

and storage of a covered and medically necessary organ transplant involving other solid donor organs, including the heart (that is, OCS Heart System), or donor organs deemed acceptable for transplant according to standard criteria.

Rationale

Static cold storage is currently considered the gold standard for organ preservation of solid organs. Normothermic portable organ machine perfusion is being considered as a potential option to expand organ utilization and improve clinical outcomes.

Portable Normothermic Lung Perfusion System:

The TransMedics® (Andover, MA) Organ Care System (OCS™) (Heart, Lung, and Liver) (Andover, MA) is a portable organ perfusion, ventilation, and monitoring device for the preservation of donor solid organs. The U.S. Food and Drug Administration (FDA) gave premarket approval in March 2018 for the Organ Care System (OCS) Lung System, indicated for the preservation of standard criteria donor lungs in a near physiologic, ventilated, and perfused state for double lung transplantation. The system was also approved for expanded criteria lungs defined as donor lung pairs initially deemed unacceptable for procurement and transplantation based on limitations of cold static preservation. The safety and effectiveness of the OCS Lung System has not been studied in recipients with the following: single lung transplant, prior solid organ or bone marrow transplant, multi-organ transplants, chronic use of hemodialysis or diagnosis of chronic renal failure requiring dialysis. The OCS Lung System was designed to provide a means to allow the transplantation team to evaluate the preservation conditions and the function of the organ during transport. The device monitors lung perfusion flow rates, airway pressure, vascular resistance, temperature, atrial and venous oxygen saturation and hematocrit (HCT) levels. According to the FDA approval letter, two post-approval studies (PAS) are required; the first is a continuation of the INSPIRE study to evaluate long-term outcomes, and the second is a multi-center, prospective, single-arm, observational study to evaluate survival of participants at 12 months.

Warnecke and colleagues (2018) reported findings from the INSPIRE clinical study (NCT01630434), a randomized, controlled, multi-center, international, prospective clinical trial to investigate the OCS Lung System, compared to the current cold storage standard of care (SOC) for preservation of donor lungs. The study randomly assigned 370 participants, and 320 (86%) subjects underwent transplantation, with 151 participants assigned to the OCS Lung System group and 169 participants to the control group. The primary endpoint was met in 79.4% (n=112) of participants in the OCS group compared with 70.3% (n=116) of the control group. The 30-day survival was lower in the OCS Arm compared to the control group with 11 deaths in the OCS arm and 1 death in the control group within 30 days post transplantation. Freedom from acute primary graft dysfunction (PGD3) within 72 hours post-transplantation was comparable between the two arms. In conclusion the authors found that both the primary effectiveness and safety endpoints were met. “Although no short-term survival benefit was reported, further research is needed to see whether the reduction in PGD3 within 72 h of a transplant might translate into earlier recovery and improve long-term outcomes after lung transplantation.”

On May 31, 2019 the FDA granted expanded approval for the OCS Lung System indicated for use in the preservation of standard criteria donor lung pairs and for preservation of donor lung pairs initially deemed unacceptable for procurement and transplantation based on the limitations of cold static preservation. This device

allows for ex vivo assessment of donor lungs prior to transplantation (OCS Lung System; Product Label Information, 2019). The FDA expanded approval was based on review of data from the EXPAND study (NCT01963780) (Loor, 2019). The prespecified primary efficacy endpoint of 65% was not met, with only 54% (n=43) of participants meeting the composite endpoint of 30-day survival post-transplant and no PGD3 within 72 hours. Loor and colleagues concluded that:

> Longer follow-up of the EXPAND trial patients is underway to assess the long-term survival and prevalence of bronchiolitis obliterans syndrome. In addition, a prospective OCS Thoracic Organ Perfusion registry has been developed to further expand prospective clinical evidence with the OCS Lung technology in the postmarket setting. Advances in portable ex-vivo lung perfusion technology, along with evolving strategies for reducing PGD, could usher a new era in lung transplantation marked by greater use and improved quality of lung allografts.

The EXPAND Continuation PAS is a single-arm, prospective, observational study designed to evaluate long-term outcomes in EXPAND trial participants. All 79 United States participants and OCS EXPAND participants will be approached for enrollment. The primary effectiveness endpoint is bronchiolitis obliterans syndrome (BOS)-free survival through 5 years after transplantation; other endpoints include 5-year survival and 5-year freedom of BOS. The OCS Lung System EXPAND II trial (NCT03343535) is an intervention trial designed to evaluate the safety and effectiveness of the portable OCS Lung System for recruiting, preserving and assessing non-ideal donor lungs for transplantation. The ongoing study is estimated to enroll 46 participants with study completion date in June 2022.

Portable Normothermic Liver Perfusion Systems:

On September 21, 2021 the FDA granted premarket approval for the OCS Liver System, a portable extracorporeal liver perfusion and monitoring system. The device is indicated for preservation and monitoring of hemodynamics and metabolic function which allows for ex-vivo assessment of liver allografts from donors after brain death (DBD) or liver allografts from donors after circulatory death (DCD) ≤ 55 years old and with ≤ 30 mins of warm ischemic time, macrosteatosis ≤ 15% in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient (OCS Liver System; Product Label Information, 2021).

The FDA approval of the OCS Liver System was primarily based on the PROTECT trial, a prospective, multicenter, unblinded trial with randomization 1:1 to the OCS Liver or Control (ischemic cold storage). The clinical objective of the trial was to compare the safety and the effectiveness of the OCS Liver System vs. cold storage (control) to preserve and access donor livers intended for transplantation that may benefit from warm oxygenation perfusion compared to cold static storage. A total of 300 initial screenings were considered (OCS 153 and Control 147). The primary effectiveness endpoint of early liver allograft dysfunction (EAD) was met, with use of OCS liver resulting in lower incidence of early liver allograft dysfunction (EAD) (17.3% OCS vs. 30.5% Control, p=0.009) across both the DBD and DCD cohorts in the trial. The three secondary effectiveness endpoints were met. The OCS Liver system was able to maintain a near physiologic functioning state and monitor the condition of the liver outside of the human body; participant survival at 30-days post-transplant was high and non-inferior to control (99.3% OCS vs. 99.3% Control, p=0.0004). In addition, the use of OCS Liver resulted in a significantly lower incidence of ischemic cholangiopathy complications at 6 months post-transplantation (1.4% OCS vs. 8.5% Control, p=0.005), a leading cause of late graft failure after liver transplantation. The safety endpoint

of graft-related serious adverse events per participant observed using the OCS Liver was non-inferior to Control (0.046 OCS vs. 0.075 Control, p<0.0001).

The PROTECT CAP is a single-arm study but otherwise the study design was the same as the OCS Liver PROTECT Trial approved by the FDA. This trial was approved by the FDA for 74 subjects; the study is ongoing, and data are still being collected, monitored, verified, and adjudicated for all transplanted participants.

On December 9, 2021, OrganOx received premarket approval by the FDA for use of OrganOx® metra® System (OrganOx Limited, Minneapolis, MN), a transportable device intended to sustain donor livers for transplantation in a functioning state for a total preservation time of up to 12 hours. The device is indicated for liver grafts from DBD, or liver grafts from DCD less than or equal to 40 years of age, with ≤ 20 mins of functional warm ischemic time (time from donor systolic blood pressure < 50 mmHg), and macrosteatosis ≤ 15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient (Product Label Information, 2021).

The FDA approval was based on unpublished data from the pivotal WP01 – Normothermic Liver Preservation study (IDE trial; NCT02775162) to support the safety and efficacy of ex-vivo normothermic machine perfusion using the OrganOx metra device with static cold storage in human liver transplantation. A total of 267 participants were enrolled; 266 transplanted livers in the study were followed up to 12 months post-transplant procedure (follow-up examinations at 30 days, 3 months, 6 months, and 12 months). Donor livers were randomly assigned with a 1:1 computer-generated randomization schedule to the normothermic machine perfusion group (n=136) or static cold storage group (n=131). The 12-month graft survival rates were 97.0% for the normothermic machine perfusion arm and 97.7% for static cold storage arm. The number of serious adverse events was similar between the two groups. Subject survival rates at 12 months were 92.5% and 96.6% in the normothermic machine perfusion group and static cold storage arm, respectively. There was a clinically important difference in the preservation time between the two arms; in the normothermic group the mean preservation time was 9.2 hours versus 5.3 hours for the static cold storage arm (OrganOx metra device, Product Label Information, 2021).

Other Considerations:

On September 3, 2021 the FDA granted premarket approval for the OCS Heart System, indicated for the preservation of hearts from donors after brain death (DBD), initially deemed unsuitable for procurement and transplantation at initial evaluation due to limitations of prolonged cold static cardioplegic preservation (for example, greater than 4 hours of cross-clamp time). Contraindications are for any of the following: moderate to severe aortic valve incompetence in donor heart, observed myocardial contusion on donor heart, known unrepaired interatrial or interventricular defects including patent foramen ovale. (OCS Heart System; Product Label Information, 2021)

The FDA approval of the OCS Heart System is based on results from the historical PROCEED II trial conducted between 2008-2013, which studied standard donor hearts suitable for cold static cardioplegic preservation. Overall survival was lower in individuals transplanted with donor hearts preserved with the OCS Heart system compared to those transplanted with donor hearts preserved with cold static preservation. The incidence of serious adverse events related to the heart graft in the OCS arm was shown to be non-inferior to the control group. Through the national database established by UNOS, 5-year follow-up data is available. The data show lower overall survival for the OCS participants compared to the control group with 19 individuals dying through 5 years after transplant in

the OCS group versus 11 individuals in the cold storage control group. The number of participants that died related to heart graft was the same for the two groups.

The International EXPAND Heart Pivotal Trial (EXPANDHeart) (NCT02323321) between 2015 and 2022 enrolled 75 participants that were transplanted with donor hearts preserved on OCS Heart System. The study evaluated the effectiveness of the OCS Heart System in donor hearts that may not meet current standard donor heart acceptance criteria for transplantation to potentially improve donor heart utilization for transplantation. A second study of these same type of donor hearts (that have seldom been used today without the OCS Heart System), called the OCS Heart EXPAND Continued Access Protocol (CAP) (NCT03835754), was performed to provide additional data evaluation the safety and effectiveness of the OCS Heart system and enrolled non-standard DBD donor hearts. The study showed a 94.6% survival in participants at 30 days post-transplant and 89.3% freedom from severe PGD (left or right ventricle) in the first 24 hours post-transplant (OCS Heart System; Product Label Information, 2021).

Based on the FDA approval letter the PMA is based on the post-approval requirements, continued follow-up of the premarket cohort of the OCS Heart EXPAND + CAP "Continued follow-up Post-Approval Study" (OCS-HEART-02-PAS; NCT05096299). The study consists of living participants enrolled in the IDE study, including those enrolled under the CAP investigation. The study objective is to observe clinical outcomes annually through 5 years post-transplant, evaluate the safety and effectiveness endpoints including patient survival, cardiac-related survival, and heart graft survival 5 years post-transplant. This study is ongoing with estimated enrollment of 150 participants, and estimated study completion in August 2026.

In 2021, Madan and colleagues publish results of preliminary analysis from United Network of Sharing (UNOS) registry study of 136 DCD adult heart donors, normally considered off-limits for transplantation showing no difference in early (30-day) outcomes as compared DBD donors for heart transplantation. The important details on the procedures used for DCD heart procurement (that is, direct procurement with ex vivo perfusion vs in vivo normothermic regional perfusion) were absent from the UNOS data. Madan and colleagues concluded that confirmation of clinical outcomes from ongoing trials should assist in identifying the potential use of DCD donors in heart transplantation.

In March 2022, XVIVO Perfusion was awarded EU Medical Device Regulation (MDR) certification for its Kidney Assist Transport device in Europe, XVIVO has submitted a 510(k) application with the FDA, but has not received final clearance for use in the United States.

Summary:

Portable normothermic organ machine perfusion is an advancing technology that hold promise for improving preservation, assessment and transport of donor organs, with the demand of transplantation exceeding the supply and the rising waitlist mortality. There is currently insufficient published evidence to assess the risks and benefits of portable normothermic organ machine perfusion over standard cold storage techniques for preservation of standard criteria donor organs, including cardiac allografts. Normothermic organ machine perfusion for the preservation of extended criteria donor lung pairs and liver allografts, that is, organs initially deemed unacceptable for procurement and transplantation based on limitations of cold storage preservation, has the potential to expand donor organ supply.

Background/Overview

According to the Organ Procurement and Transplantation Network (2021) there are more than 107,000 individuals on the national transplant waiting list for a solid organ transplant, with nearly 17 deaths reported daily from individuals awaiting an organ transplant. The limiting factor for solid organ transplantation is the short supply of donor organs available in the United States. There is a currently an unmet need of currently available donor organs available in the United States with individuals dying while on the waitlist.

Static cold storage has been used successfully for decades as a donor preservation method in standard criteria donor organs. Presently, normothermic machine perfusion technologies are being evaluated for use in donor preservation and transportation of marginal or expanded criteria donor organs in donation after cardiac death and after brain death.

Definitions

Normothermic machine perfusion: A method of preservation to recreate the physiological environment by maintaining normal temperature and providing the essential substrates for cellular metabolism, oxygen and nutrition.

Static cold storage: Solid organ is stored on ice after removal from the donor and then removed from ice at the time of implantation.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:
For the following procedure codes or when the code describes a service using a normothermic organ perfusion system for lung or liver transplantation

CPT

32999	Unlisted procedure, lungs and pleura [when specified as use of a portable normothermic organ perfusion system for lung transplantation]
47399	Unlisted procedure, liver [when specified as use of a portable normothermic organ perfusion system for liver transplantation]

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary:
For the services listed above when criteria are not met.

When services are also Investigational and Not Medically Necessary:
For the following procedure codes or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
33999	Unlisted procedure, cardiac surgery [when specified as use of a portable normothermic organ perfusion system for heart transplantation]
53899	Unlisted procedure, urinary system [when specified as use of a portable normothermic organ perfusion system for kidney transplantation]
ICD-10 Diagnosis	
	All diagnoses

References

Peer Reviewed Publications:

1. Ardehali, A, Esmailian F, Deng M, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicenter, randomized non-inferiority trial. Lancet. 2015; 385:2577-2584.
2. Loor G, Warnecke G, Villavicencio MA, et al. Portable normothermic ex-vivo lung perfusion, ventilation, and functional assessment with the Organ Care System on donor lung use for transplantation from extended-criteria donors (EXPAND): A single-arm, pivotal trial. Lancet Respir Med. 2019; 7(11):975-984.
3. Madan S, Saeed O, Forest SJ, et al. Feasibility and potential impact of heart transplantation from adult donors after circulatory death. J Am Coll Cardiol. 2022; 79:148-162.
4. Markman J, Abouljoud MS, Ghobrial RM, et al. Impact of portable normothermic blood-based machine perfusion on outcomes of liver transplant. JAMA. 2022; 157(3):189-198.
5. Markman J, Ghobrial M, Magliocca J, et al. Results of the initial phase of the portable organ care system (OCS™) Liver PROTECT Pivotal trial. Abstract 279. Am J Transplant. 2017; 17(suppl 3).
6. Miguel M Leiva-Juárez 1, Andreacarola Urso , Elisabet Arango Tomás, et al. Extended post-ex vivo lung perfusion cold preservation predicts primary graft dysfunction and mortality: Results from a multicentric study. Clinical Trial J Heart Lung Transplant. 2020; 39(9):954-961.
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8. Schiavon M, Faggi G, Rebusso A, et al. Extended criteria donor lung reconditioning with the organ care system lung: a single institution experience. Transplant International. 2019; 32:131-140.
9. Selzner M, Goldaracena N, Echeverri J, et al. Normothermic ex vivo liver perfusion using steen solution as perfusate for human liver transplantation: first North American results. Liver Transplantation. 2016; 22(11):1501-1508.
10. Van Fijn R, Schurink IJ, de Vries Y, et al. Hypothermic machine perfusion in liver transplantation – a randomized trial. N Eng J Med. 2021; 384(15):1391-1401.
11. Warnecke G, Moradiellos J, Tudorache I, et al. Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: A pilot study of 12 patients. Lancet. 2012; 380(9856):1851-1858.

12. Warnecke G, Van Raemdonck D, Smith MA, et al. Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): A randomised, open-label, non-inferiority, phase 3 study. Lancet Respir Med. 2018; 6(5):357-367.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Copeland H, Hayanga A, Neyrinck a, et al. Donor heart and lung procurement: a consensus statement. J Heart Lung Transplant. 2020; 39(6):501-517.
2. Health Resources & Services Administration. Organ donation statistics. Last reviewed October 2021. Available at: https://www.organdonor.gov/learn/organ-donation-statistics. Accessed on December 23, 2021.
3. TransMedics. OCS Liver PROTECT Trial: preserving and assessing donor livers for transplantation (PROTECT). NLM Identifier: NCT02522871. Last updated October 8, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02522871. Accessed on December 22, 2021.
4. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). Summary of Safety and Effectiveness and labeling: Premarket Approval (PMA). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. Accessed on January 4, 2022.
   - OrganOx metra System. Premarket approval application No. P200035. December 9, 2021.
   - TransMedics Organ Care System (OCS) Heart System. Premarket approval application No. P180051. September 3, 2021.
   - TransMedics Organ Care System (OCS) Liver System. Premarket approval application No. P20031. September 28, 2021.
   - TransMedics Lung Organ Care System (OCS) Lung System. Premarket approval application No. P160013/S002. May 31, 2019.

Websites for Additional Information

1. Organ Procurement and Transplantation Network (OPTN). Available at: https://optn.transplant.hrsa.gov/. Accessed on January 7, 2022.

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action

New	05/12/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.