South Australian Policy Advisory Committee on Technology (SAPACT)

Health Technology Assessment (HTA) Decision Summary

Government of South Australia

SA Health

Liver Assist™ ex-vivo organ perfusion system to preserve donor livers prior to transplantation

SAPACT MEETING DATES	34th SAPACT Meeting (7 June 2024) – has been considered out-of-session in May 2024 due to applicant's request
APPLICATION #	2403
TECHNOLOGY	Australian Sponsor: Stark Medical Pty Ltd XVIVO* Liver Assist™ Organ Perfusion System, for ex-vivo oxygenated machine perfusion for preservation of donor livers prior to transplantation. The system consists of 5 main modules: (1) Capital: Portal vein pump unit, hepatic artery pump unit, thermos unit, trolley and (2) Consumable: Circuit and solutions disposable single use set. **name of the medical technology company and its stock symbol.*
TECHNOLOGY CLASSIFICATION	TGA class IIa
PATIENT INDICATION (TGA)	TGA intended purpose: Liver Assist is a dedicated device for ex-vivo perfusion of donor livers. Two different pump units provide a pulsatile perfusion of the hepatic artery and continuous flow to the portal vein. The oxygenated perfusion is pressure controlled. Temperature can be set from hypothermic to normothermic conditions thanks to an integrated heater/cooler.

SAPACT DECISION

☐ Recommended for clinical use by the South Australian Liver Transplant Unit (SALTU) with a 24-month follow-up report.

SAPACT Advisory Recommendations

After appraising the international evidence, jurisdictional experiences and expert opinions, SAPACT recommends the use of the Liver Assist Organ Perfusion System in SA Health, under the purview of the SALTU. Specifically, the Dual-HOPE protocol for Liver Assist system is to be used in up to 10 patients per annum in SALTU, according to the donor livers and patient selection criteria as outlined in this HTA Decision Summary. SAPACT notes the sources of funding for the technology, with the annual servicing fee subjected to approval by SAPOM SALHN. The applicant should notify SAPACT on improvements to the application/protocol (e.g. change of device, perfusion technique, perfusionist involvement and ethics). SAPACT would appreciate a 24-month clinical outcomes and costing report, which may also identify whether the process of ex-vivo assessment and resuscitation has led to the implantation of donor livers that would otherwise have been deemed unsuitable.

Evidence Summary

A few good quality, short-term, small randomised controlled trials (RCTs) from Europe formed the primary published evidence base for the Liver Assist perfusion system. The recommended machine perfusion technique is hypothermic oxygenated machine perfusion (HOPE) for donation after brain death (DBD) livers, based on one-year graft survival and serious adverse events. The best available evidence indicated that using the Liver Assist system with HOPE for both DBD and donation after circulatory death (DCD) livers demonstrated improved outcomes after liver transplantation compared with static cold storage (SCS).

The RCT evidence found that HOPE of DBD livers improved one-year graft survival, and perhaps more so for extended criteria DBD livers, compared to SCS. Additionally, the number of serious adverse events was reduced for both DBD and extended criteria DBD livers. No difference in patient survival outcomes were reported.

HOPE for DCD livers resulted in reduced rate of non-anastomotic strictures (NAS). There is insufficient evidence to conclude that end-ischaemic normothermic machine perfusion (NMP) for DBD has the same benefits over SCS, in terms of graft survival, serious adverse events and ischaemic cholangiopathy. Although end-ischaemic NMP for DBD appeared to improve the utilization of grafts that would otherwise be discarded with SCS, the reasons for this and whether this effect is specific to NMP are unclear.

No costing or economics studies have been published for Liver Assist system. However, a cost-utility paper analysing NMP and HOPE machine perfusion techniques found that the HOPE technique is generally cheaper than NMP.

The assumption that the availability of additional livers due to the impact of machine perfusion leads to downstream benefits, such as reduced waiting list time and mortality, and improved donor-recipient matches, is not supported by any RCT evidence.

Understanding longer-term outcomes such as patient survival, downstream benefits, and the costing/economic impact is warranted for the continued use of perfusion machines.

Australian data is limited to experiences from the Victorian Liver Transplantation Unit (LVTU) and Queensland Liver Transplantation Unit (QLTU) in implementing another brand/model, OrganOx metra normothermic perfusion system, which is currently not listed on the TGA Australian Register of Therapeutic Goods (ARTG).

The New Zealand Liver Transplantation Unit (NZLTU) has shared its experience and clinical outcomes in using the Liver Assist system in

routine clinical practice. Staff from the SALTU have attended the NZLTU Liver Assist Dual-HOPE workshop and intends to adopt the NZLTU Dual-HOPE protocol for Liver, if it gets recommended for approval for use in SA Health.

SA Health

In 2019, the UK NICE had conditionally approved the OrganOx metra for preservation of livers donated for transplants, due to the safety and positive benefits. It can only be used with special arrangements for clinical governance, consent, and audit or research. Surgeons undertaking this procedure must inform the patients about the uncertainty of the procedure's efficacy, comply with relevant regulatory and legal requirements of the Human Tissue Authority and should enter details about all patients having this procedure into the NHS Blood and Transplant Registry.

Background

SAPACT received an application from SALTU, Division of Surgery, Flinders Medical Centre, SALHN, via the SALHN New Health Technology & Clinical Practice Innovation (NHT&CPI) Committee, to evaluate the potential use of the Liver Assist system in SA Health. SALTU provides liver transplantation services to the whole of South Australia (SA) and the Northern Territory (NT). SALTU has proposed the use of this technology for 0-10 SALTU patients. The capital equipment will be funded by private donors and the Flinders Foundation, while consumables will be funded through Surgery & Perioperative Medicine (SAPOM), SALHN, as part of the cost of liver transplantation.

REGULATORY APPROVALS

☒ **Australia ARTG**: 27/07/2018; Class IIa; 307528 XVIVO Liver Assist Organ Perfusion System.	☐ **US FDA**: Nil. On 20/09/2022, FDA gave this system a "Breakthrough device designation", where a priority review is given for faster path to market access.	☒ **EU CE mark**: 22/03/2022, with an expiry date of 21/03/2027. MDR CE Certificate from Netherlands, 742864 R000.

QUALITY OF EVIDENCE

Quality of Evidence

A comprehensive search for the best available HTA and policy evidence on the Liver Assist perfusion system was conducted across 7 published and 25 grey literature sources. Other branded perfusion machines, while they may be considered in an overview, are not the focus of SAPACT because only the Liver Assist system is available for use in Australia. In addition to international evidence, SAPACT considered the application of overseas and interstate-jurisdictional experiences, as well as expert opinions, in informing the review. SAPACT also considered the NICE Guidance 2019 (on another system, OrganOx metra) to understand public funding.

The best available evidence (level 1) from two systematic reviews (Tingle 2023 and Parente 2023) informed the SAPACT Review. Tingle 2023 is a Cochrane systematic review that evaluated machine perfusion in liver transplantation. The Cochrane review included seven RCTs (1024 transplant recipients from 1301 randomised/included livers). All trials were RCTs - four compared HOPE versus SCS, and three compared NMP versus SCS. The included studies in the Cochrane review were assessed to be of moderate quality, with low risk of bias for most outcomes. Parente 2023 is a systematic review and meta-analysis of RCTs which evaluated the effect of HOPE and NMP, compared to SCS in liver transplantation.

All trials were conducted in Europe and none of them were funded by the industry. Authors declared no conflicts of interest. There is no published Australian data. The key RCT studies from both systematic reviews which used the Liver Assist system are:

HOPE trial for DBD | Schlegel 2023; RCT; n=170 (85 HOPE; 85 SCS); 12-month follow-up; 6 countries (UK, Netherlands, Belgium, France, Switzerland and Austria) with 10 transplant centres

HOPE trials for DBD-ECD (extended criteria donors, e.g. from older age donors, or fatty livers with more than 30% fat, or liver functions that are not as good) | Czigany 2021; open-label RCT; n=46 (23 HOPE; 23 SCS); 12-month follow-up; Europe (Germany and Czech Republic) with 4 transplant centres.

Dual HOPE trial for DCD | Van Rijn 2021; RCT; n=156 (78 DHOPE; 78 SCS); 12-month follow-up; Europe with 6 transplant centres

End-ischamic NMP trial for DBD | Ghinolfi 2019; open-label RCT; n=20 (10 NMP; 10 SCS), 6-month follow-up; Italy

Dual controlled oxygenated rewarming (COR) trial for DBD (presumed as donor graft type not specified) | Minor 2022; RCT single centre; n=40 (20 COR; 20 SCS); 3-month follow-up; Germany

CLINICAL NEED

Burden of Illness

The 34th Annual Report of the Australian and New Zealand Liver and Intestinal Transplant Registry (ANZLITR) provided data on liver and intestinal transplantation activity up to the end of 2022. In that year, a total of 314 liver transplants were conducted in 306 patients across the nation. The annual waiting list mortality rate has shown a notable decrease, dropping from a peak of 12.3% in 2007 to 5.7% in 2022. Specifically in 2022, one out of 17 patients listed as category 1 and one out of 13 patients listed as category 2 died while waiting for transplantation.

	In South Australia, according to the Australian Donation and Transplantation Activity Report 2023, approximately 50 liver transplants were performed each year between 2021 and 2023. SALTU conducts roughly [redacted] liver transplants annually. With the implementation of the Liver Assist perfusion system, SALTU anticipates an increase in liver transplant numbers by [redacted] per year.
Need	Patients with advanced liver disease often succumb while awaiting a transplant. Donor livers vary in quality, with some being marginal, leading to poorer outcomes. Machine perfusion offers a solution by enabling assessment and 'resuscitation' of marginal liver grafts before transplantation, thereby increasing the pool of viable organs that would otherwise be discarded. SCS or cold preservation fluid has long been the standard for preserving donor livers due to its cost-effectiveness and simplicity. While effective for high-quality organs with short cold ischemic times, SCS has limitations, particularly when dealing with marginal livers from donation after circulatory death (DCD) or other sources. These limitations include: (a) inability to reverse sustained organ injury; (b) risk of further injury during storage; (c) inability to assess organ viability; and (d) limited storage time. Machine perfusion systems offer an alternative for liver preservation. They have the potential to reduce ischemic injury during procurement, enable viability testing, extend storage time, and minimize further injury during storage (Croome 2023). Currently, only one machine perfusion system, Liver Assist, is registered with the Therapeutic Goods Administration (TGA) for market access in Australia. The OrganOx metra, available in the UK, is in the process of obtaining TGA approval. The Liver Assist perfusion system offers various perfusion protocols: • HOPE (cold; 4-12°C): HOPE is used as a "resuscitative" measure, in the sense that the marginal liver graft has already been selected as suitable to be transplanted (after HOPE). HOPE restores mitochondrial function and reduces the damage due to production of oxygen radicles. This reduces the ischaemia-reperfusion injury and subsequent development of biliary strictures and therefore improves outcomes after transplantation. • Dual (perfused via both portal vein and hepatic artery) HOPE (Dual-HOPE) • NMP (warm; 34-38°C): NMP enables assessment of graft function as the graft is perfused with circulating blood and nutrients at 37 degrees, and the graft function is able to be "assessed" in terms of lactate clearance, bile production and AST/ALT measurements. • Sub-normothermic, or a combination. As SALTU has proposed the use of the Liver Assist system, particularly via the Dual-HOPE protocol, primarily on DBD livers (with the remainder being DCD), SAPACT will concentrate on evidence pertaining to Liver Assist via the HOPE/Dual-HOPE method for both DBD and DCD livers.
CLINICAL BENEFITS	
Safety	HOPE for DBD livers resulted in a statistically significant decrease in major complications like ischaemic cholangiopathy (Parente 2023), and reduction in serious adverse events (graft-related) compared to SCS (Tingle 2023). These subsequently led to decreased mortality and decreased the need of re-transplantation due to these complications. There was a statistically significant reduction in NAS at 12 months in DBD donors (Schlegel 2023). Dual HOPE for DCD resulted in a statistically and clinically significant reduction in ischaemic cholangiopathy in livers preserved with Dual HOPE compared to SCS at 6 months (van Rijn 2021). van Rijn 2021 reported no statistically significant difference observed in the rate of serious adverse events (Clavien-Dindo ≥IIIb), noting that the number of people experiencing serious adverse events was not reported (Tingle 2023). van Rijn 2021 reported 101 serious adverse events across 78 recipients of HOPE livers, and 132 serious adverse events across 78 recipients of SCS livers. End-ischaemic NMP for DBD As Ghinolfi 2019 lacks statistical power to detect any difference in serious adverse events, there is no good evidence from this small pilot trial that NMP has the same benefits over SCS in terms of reduction in serious adverse events (Tingle 2023, Ghinolfi 2019).
Effectiveness	**Best perfusion technique** Tingle 2023 meta-analysis results (of Czigany 2021, Ravaioli 2022, and Schlegel 2023) favoured HOPE for DBD livers, as they found statistically significant differences were found between preservation methods, based on one-year graft survival and serious adverse events. **Clinical outcomes** Machine perfusion using HOPE and NMP techniques can reduce the incidence of early allograft dysfunction in the first week after liver transplantation, compared to SCS. It was uncertain whether overall participant survival was

	improved with either HOPE or NMP (Tingle 2023). HOPE led to lower "re-transplantation" rates (Parente 2023). HOPE for DBD livers resulted in a statistically significant improvement (HR 0.45, 95% CI 0.23 to 0.87; P = 0.02, I^2 = 0%) in graft survival at one year (from 4 trials, 482 recipients), and more so for extended criteria DBD livers (HR 0.30, 95% CI 0.11 to 0.82; P = 0.02, I^2 = 0%) (Tingle 2023). Dual-HOPE for DCD livers resulted in a clinically significant reduction in ischaemic cholangiopathy (specifically NAS), compared to SCS (van Rijn 2021, Tingle 2023). No statistically significant differences were found between preservation methods for primary non-function (resulting in liver-related graft loss), re-transplantation, graft survival at one year or patient survival at one year. The authors noted larger trials would be required to detect an effect on graft and patient survival, given the current high survival rates after liver transplantation. (van Rijn 2021). End-ischaemic NMP for DBD As Ghinolfi 2019 lacks statistical power to detect any difference in patient and graft survival , there is no good evidence from this small pilot trial that NMP has the same benefits over SCS in terms of graft survival and ischaemic cholangiopathy (Tingle 2023, Ghinolfi 2019). Patient survival at six months was investigated and found that 10/10 participants in the NMP group were alive and 9/10 in the SCS group were alive. Overall risk of bias for this outcome was low and hazard ratio cannot be calculated (Ghinolfi 2019). Dual controlled oxygenated rewarming (COR) for DBD is feasible and can be regarded as a safe and easily implementable novel tool in liver preservation, likely to improve early functional outcome after transplantation (Minor 2022). **Retrieval outcomes** End-ischaemic NMP for DBD appeared to improve utilization of grafts which would otherwise be discarded with SCS, however the reasons for this, and whether this effect is specific to NMP, is not clear. More research is needed to understand why (Tingle 2023, Ghinolfi 2019). The availability of additional livers due to the impact of machine perfusion is assumed to lead to downstream benefits, however, these purported benefits as outlined below, have not been demonstrated from the RCTs: • reduced time on the transplant waiting list, therefore reduced costs • reduced mortality on the transplant waiting list • improved donor-recipient matches
Suitability of Patient Group	Number of SALTU patients proposed per year: 0-10 patients (includes SA and NT) Patient selection: Patients with end-stage liver disease and liver malignancies requiring liver transplantation who are on the active South Australian Liver Transplant waiting list for standard liver transplantation. Eligibility for liver transplantation is determined through a thorough assessment, and patients are extensively discussed in the Liver Transplant multidisciplinary team (MDT) before placement on the waiting list. Patient exclusion: At the initial stages of using machine perfusion, SALTU will avoid high-risk patients with potentially complex operations, such as re-transplantation or anticipated longer operative times. Patients in need of multiple organ transplants (e.g. simultaneous liver and kidney) or split liver transplants are generally at higher risk of complications Therefore, SALTU would not initially consider using the Liver Assist system in such cases, as it is unlikely that they would use marginal DBD grafts or DCD grafts in these high-risk patients. However, as SALTU gains confidence and familiarity with the perfusion machine, these patients may later be considered appropriate recipients of machine-perfused liver grafts. Donor liver selection: Extended criteria DBD and DCD liver grafts will be prioritised for use with the Liver Assist perfusion machine, to "resuscitate" these grafts. The majority of SALTU's suitable liver donors are DBD donors. Strict selection criteria for DCD donors have led to very low numbers of DCD liver grafts being deemed suitable for transplantation.

	Donor liver exclusion: DBD liver grafts meeting standard criteria (and suitable for transplantation) will be stored in SCS and will not be used with the Liver Assist system. SA Health Machine perfusion technique: SALTU plans to utilize the Dual-HOPE perfusion technique with the Liver Assist system. They have noted emerging evidence suggesting that liver grafts treated initially with sequential hypothermic perfusion followed by subsequent normothermic perfusion prior to implantation into the transplant recipient may improve graft function post-transplantation. The Liver Assist machine will allow for this option to be used in the future pending further emerging literature.
FINANCIAL CONSIDERATIONS	
Device costs	Capital: Liver Assist Organ Perfusion System, quoted $[redacted] Consumables: Liver Assist circuit and solutions disposable/single use set: $[redacted] Annual servicing fee: [redacted] Number of SALTU patients per year: 0-10 patients Total costs to SALHN per year: [redacted] (excluding capital equipment)
Value for Money	No costing or economics studies have been published for Liver Assist Organ Perfusion System. According to the Tingle 2023 Cochrane review, the Zimmermann 2022 study is a cost-utility paper that analyzed NMP and HOPE techniques. The study found that hypothermic techniques are generally less expensive due to their inherent simplicity, both in terms of the circuit and perfusate constituents/infusions. Additionally, hypothermic techniques typically do not require blood products, which alleviates pressure on blood donation services and avoids logistical issues.
Australian and Overseas Funding approvals	**Australia** The Liver Assist perfusion system has not undergone review by the Australian Organ and Tissue Authority (OTA), Commonwealth Medical Services Advisory Committee (MSAC), or Prosthesis List Advisory Committee (PLAC). Consequently, it is not listed on the Medical Benefits Schedule (MBS) nor on the Prescribed List (PL). In Victoria, the VLTU at Austin Health has received public funding from VicHealth since 2019 to access the OrganOx metra, a non-TGA registered liver perfusion system, through the TGA Special Access Scheme. This funding is not allocated as part of a clinical trial but rather as a standard clinical activity. In Queensland, the OrganOx metra is funded through the Queensland Health Department New Technology Funding and Evaluation Program (NTFEP) and has been used by the QLTU since 2018 in the Princess Alexandra Hospital and Queensland Children's Hospital. **Overseas** United Kingdom (UK): The National Institute for Health and Care Excellence (NICE) did not conduct an evaluation of the Liver Assist system. However, in 2019, NICE developed Guidance IPG636 for the OrganOx metra, a NMP system. The OrganOx metra was created by two UK Professors from the spinout company, OrganOx Ltd, under the University of Oxford. NICE conditionally approved the OrganOx metra for the preservation of livers donated for transplants within the National Health Service (NHS) due to its positive benefits and safety profile. However, given the limited quantity of evidence on efficacy at the time, this procedure should only be conducted under special arrangements for clinical governance, consent, and audit or research. Surgeons performing this procedure are required to inform patients about the uncertainty surrounding its efficacy and must comply with relevant regulatory and legal requirements of the Human Tissue Authority. Additionally, details about all patients undergoing this procedure should be entered into the NHS Blood and Transplant Registry.
Experiences and consultations	**SA advice** Local advice has been sought from the (1) State Medical Director of DonateLife SA and the (2) Chair of the South Australian Transplantation and Organ Donation Advisory Council (SATODAC). [redacted] **National and interstate advice** The Australian Organ and Tissue Authority (OTA) does not provide guidance on machine perfusion for livers. SAPACT appreciated advice and experiences from Victoria, Queensland and New South Wales.

	Victoria Austin Health does not have experience using the Liver Assist perfusion system, but has experience with the OrganOx metra since late 2019 [redacted] Queensland The Queensland Liver Transplant Service, located at Princess Alexandra Hospital and Queensland Children's Hospital, uses the OrganOx Metra for normothermic perfusion but not the Liver Assist system. They began using the OrganOx metra in 2018 and are [redacted] New South Wales The New South Wales Health Department commissioned evidence reviews in 2023 on organ perfusion systems, including for livers. The liver perfusion system developed by the Royal Prince Alfred Hospital will not be included in the review. The New Health Technologies and Specialised Services Committee of NSW will soon make its recommendations based on the review. **Overseas advice** NZLTU has been using the Liver Assist system in routine clinical practice since September 2022. They have shared with SAPACT their experiences, clinical outcomes and advice. [redacted]
FEASIBILITY OF ADOPTION	
Organizational Feasibility	The application outlined the following: Service impact • Operating theatres: An expected increase of [redacted] liver transplant cases per year, with some impact on Theatre 2 utilization, though not anticipated to be significant. • Biomedical engineering: Required for service and maintenance of the perfusion machine. • Staffing: Additional time for Transplant Surgeons, approximately 2-4 hours per case, covered by SAPOM SALHN. Patient consent: • Machine perfusion of extended criteria organs will be considered accepted practice and will be incorporated into the SALTU normal liver transplant consenting process. • Potential recipients will be informed of the risks and benefits of using a range of organs (split liver, DCD, DBD, machine perfused, and older donors) for transplantation, in accordance with usual guidelines. Clinical outcomes reporting: • Usual parameters for transplanted liver functions, graft, and patient survival will be reported. • Additional fields for machine-perfused cases will be added to the existing database. • Liver transplant data collection in normal practice is comprehensive. • Reports will be submitted to SAPACT and SALHN NHT&CPI Committee. National data collection: • The Australia & New Zealand Liver and Intestinal Transplant Registry (ANZLITR), funded by the Australian OTA, contains data on all liver and intestinal transplants performed in Australia and New Zealand. • ANZLITR produces an annual report containing information on transplant numbers, waiting list flows, and patient and graft outcomes.
Credentialing and Competency	Training and competency • There is a learning curve associated with operating the Liver Assist system, and operators need to gain experience using machine-perfused liver grafts. Training is provided by the supplier. • At this stage, the Liver Transplant Surgeons in SALTU will be the operators, and they have received training recently at the Auckland workshop. With the approval of this technology, SALTU will monitor and consider its operators for Liver Assist. [redacted]

	[redacted] • SALTU intends to use the Liver Assist HOPE protocol developed by the New Zealand Liver Transplantation Unit (NZLTU) in conjunction with the company's Liver Assist 'Instructions for use.' • SALTU recently visited the NZLTU in Auckland and attended the Liver Assist Dual-HOPE workshop, gaining hands-on experience with the machine. SALTU will adopt the NZLTU Dual-HOPE protocol for Liver Assist. Severe graft dysfunction or significant ischemic cholangiopathy are the stopping criteria for the procedure. • The operator must be a medical practitioner registered in South Australia, appointed as a senior medical officer in SALHN, hold relevant credentialing and scope of practice, and develop competence through supervised proctored 2-3 cases (under an external clinician) before independent practice. <u>Credentialing</u> • If approved for use, the Liver Assist Organ Perfusion System should only be operated by clinicians with specific training and accreditation. • Clinicians must be appropriately credentialed and approved by the SA Health Credentialing and Scope of Practice Committee to use the Liver Assist Organ Perfusion System, following the SA Health Credentialing Policy Directive's guidelines on New Clinical Procedures, Technologies, and Treatments.
CONSISTENCY WITH EXPECTED SOCIETAL/ ETHICAL/ LEGAL VALUES	
Values	Consistent with expected societal, ethical and legal values at this time.
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