NICE advice

OrganOx metra for liver transplant

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is OrganOx *metra*. It is a device for normothermic machine perfusion to preserve donor livers before transplant. Several alternative devices offering hypothermic and normothermic perfusion exist on the market.
- The **innovative aspects** are that the device preserves organs for longer than standard care. It can also do additional functional testing of the organ that may help increase the use of available donor livers.
- The intended **place in therapy** would be as an alternative or in addition to static cold storage for donor liver preservation for up to 24 hours before implantation for people needing liver transplant.
- The **main points from the evidence** summarised in this briefing are from 6 studies, including 1 randomised trial and 5 non-randomised clinical trials, with a total of 483 livers. One economic evaluation was also found. They show that the OrganOx *metra* may help increase the number of donor livers that can be successfully transplanted compared with static cold storage.
- **Key uncertainties** around the evidence are that sample sizes of the published studies are small and do not compare to alternative devices.

- One field **safety** notice was reported on this device in May 2021. It related to a design flaw that has since been corrected.
- The **cost** of the OrganOx *metra* is £30,000 per device per year on lease (excluding VAT). Additional costs include the use of disposable sets (£6,000 per set), staffing (£500) and associated medicines and solutions used during the procedure (£1,210). The company proposes that 9 *metra* devices would support current transplantation numbers nationally.

The technology

The OrganOx *metra* (OrganOx Limited) is a fully automated transportable normothermic organ perfusion device. It is used for normothermic machine perfusion of livers awaiting transplant to improve organ preservation and reduce the rate of organ discard. The device works by placing the liver in a sterile environment and continuously perfusing the organ with oxygenated blood, medicines and nutrients at normal body temperature to mimic normal physiology. This can be done for up to 24 hours before transplant and aims to minimise liver injury, reducing the number of donor livers discarded. This also means the liver is functional, enabling assessment and evidence-based decisions about whether to transplant. Several alternative preservation devices exist including the Organ Assist Liver Assist (capable of both hypothermic and normothermic perfusion) and the TransMedics Organ Care System Liver System (involving normothermic perfusion).

Innovations

The OrganOx *metra* is reported to offer higher-quality organ preservation to standard care, aiming to reduce the number of organs that cannot be transplanted. It can be used for up to 24 hours, prolonging how long an organ can be preserved. It can also objectively test functionality of the organ, which may increase safe use of available donor livers.

Current care pathway

People identified as needing a liver transplant are placed on a waiting list for a donor liver. The waiting time for a suitable liver can vary quite a lot: the average waiting time for a liver transplant in the UK is reported to be 3 to 4 months for adults (NHS blood and transplant website).

Standard care for liver transplant involves removing the liver of a donor after brainstem death or circulatory death. A donor liver for transplant is usually preserved using static cold storage. This involves the donor liver being flushed with cold organ preservation solution and placed in a sterile bag in a cold storage icebox, aiming to minimise liver degradation. This is done by a specially trained

team before being transferred to the selected hospital for transplant as soon as possible, to minimise ischaemic damage to the organ.

Assessing whether a liver is suitable for transplant is based on the characteristics of the donor before retrieving the organ. It is also based on the appearance of the liver: it is not possible to do a formal functional assessment of the organ after retrieval and as such the function of an organ after transplant is unpredictable.

Currently the use of machine perfusion devices for preservation of livers for transplant is by special arrangement only (NICE interventional procedures guidance on ex-situ machine perfusion for extracorporeal preservation of livers for transplantation). There are several devices on the market offering normothermic and hypothermic machine perfusion. The use of these devices is well recognised in current NHS practice and experts report that the OrganOx *metra* is used across the NHS in different arrangements.

The following publications have been identified as relevant to this care pathway:

- NICE guideline on cirrhosis in over 16s: assessment and management
- NICE interventional procedures guidance on ex-situ machine perfusion for extracorporeal preservation of livers for transplantation
- NICE quality standard on liver disease
- NICE interventional procedures guidance on living-donor liver transplantation
- NICE guideline on non-alcoholic fatty liver disease: assessment and management.

Population, setting and intended user

Adults who need liver transplants are usually those with end-stage liver disease. It may also be indicated in patients with some types of primary liver cancer as well as some metabolic disorders. End-stage liver disease can be caused by a number of factors. It can be either acute (for example, from poisoning) or chronic (for example, because of cirrhosis from alcohol-related liver disease, metabolic, autoimmune or infectious conditions).

Transplants are done by specialist liver transplant surgeons in 7 adult units across the UK.

The OrganOx *metra* is for all adults having a liver transplant from deceased donors. It may be used in 'transport mode', which involves continuous normothermic perfusion; or in 'back-to-base mode',

which consists of normothermic perfusion on arrival at the hospital of the person having the transplant, after initial static cold storage. These options offer flexibility of use across specialist transplant units. The aim is to improve clinical outcomes for the person having the transplant and to enable otherwise marginal organs to be transplanted safely, increasing the number of livers available for transplant.

Costs

Technology costs

The OrganOx *metra* is available for lease at a cost of £30,000 per year per device. Costs per perfusion also include the cost of disposables (£6,000), staff (£500) and associated medicines and solutions used during the procedure (£1,210). The company reports that the incremental cost of the device compared with current standard care is £9,341 per transplant.

Costs of standard care

Static cold storage is currently used for donor liver preservation in the NHS. The cost of cold storing organs includes the cost of disposable consumables and the solutions in which organs are stored.

Standard care of static cold storage totals £710.80, including the cost of an icebox at £45.80 (Bond et al. 2009) and cold storage solution (per case) at £665.00 (Javanbakht et al. 2020).

Resource consequences

In the UK, 922 liver transplants were done between 1 April 2019 and 31 March 2020 (NHS Blood and Transplant data). The number of transplants has been increasing in recent years and is likely to rise further after the change in law to an 'opt-out' system in 2020 (organ donation law in England, NHS Blood and Transplant).

The company proposes that 9 OrganOx *metra* devices would support current transplant numbers nationally. The cost of this device would be in addition to current standard care. However, the company claims that the *metra* may reduce the number of livers that are discarded, helping effective functional assessment of donor livers and increasing transplants. The cost increase with OrganOx also includes the additional operational and post-operative care costs for people having a transplant. Normothermic perfusion may also increase flexibility around transplant surgery, which could allow for better use of resources, in particular, staffing in busy surgical departments.

One economic evaluation was found that related to the cost of the OrganOx *metra* (Javanbakht et al. 2020). This examined the cost effectiveness of the device including discard rates, renal replacement therapy rates, adverse events, length of stay and 5-year mortality rates. The evaluation reported that the OrganOx *metra* costs more and is more effective than static cold storage.

Implementation of the device into the pathway is supported by a training package for device users and surgeons which is provided by the company and included in the purchase. The company also currently provides yearly refresher courses to UK customers free of charge. A trained device operator is needed to monitor the device during perfusion and check the perfusion parameters at regular intervals. This staff member should be appropriately trained for any troubleshooting issues. No changes were identified for the pathway after transplant.

Regulatory information

OrganOx *metra* is a CE-marked class IIa medical device.

The following manufacturer field safety notices for this device have been identified:

Field Safety Notice Reference 2021/006/016/291/001. OrganOx Ltd issued a Field Safety Corrective Action for the OrganOx *metra* Retained Unit (P/N D0003), affecting all serial numbers in the fleet. An erroneous electrical noise caused battery discharge and recharge issues with a risk of premature device failure. Because of this a design change was implemented and field corrections arranged.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

OrganOx *metra* is used for liver transplants for adults with liver disease. There are different types of liver diseases that can be associated with alcohol, obesity, viral infection, and genetic factors. Many liver diseases do not cause any symptoms in the early stages, and develop over the course of time, leading to long-term conditions. It may mean that someone is disabled if their liver disease has a substantial and long-term effect on their ability to do daily activities. Disability is a protected characteristic under the Equality Act.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 6 studies summarised in this briefing, including 483 livers. Five studies were prospective non-randomised clinical studies and 1 was a randomised controlled trial.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence base for the technology is of moderate methodological quality.

Three of these studies are based in the UK NHS. All clinical studies suggest that the device may help increase the number of donor livers that can be successfully transplanted.

Further evidence would benefit from sufficiently powered sample sizes, use of high-risk organs, randomisation at time of organ donation and appropriate long-term follow ups to improve the evidence base. No studies were found that showed the benefit of the OrganOx *metra* compared with other machine perfusion devices.

Nasralla et al. (2018)

Study size, design and location

Randomised multinational controlled trial across 7 centres including the UK, Belgium, Spain and Germany (n=334).

Intervention and comparator

OrganOx *metra* and static cold storage.

Key outcomes

Livers were randomised into 2 arms: normothermic machine perfusion (NMP) using the OrganOx *metra*, and static cold storage (SCS). The results showed that the organ discard rate was statistically significant between groups. The SCS group had a 24.1% discard rate and NMP had a 11.7% discard rate. There was a significant reduction in peak aspartate aminotransferase and early allograft dysfunction rates in NMP livers compared with the SCS group.

Strengths and limitations

Two authors are co-founders of OrganOx Limited, but their roles in this study did not involve selection, recruitment or transplant.

Reiling et al. (2020)

Study size, design and location

Prospective non-randomised non-comparative study in Australia (n=10).

Intervention and comparator

OrganOx *metra*. No comparator.

Key outcomes

Ten donor livers that were considered unsuitable for transplant had 4 hours of perfusion using OrganOx *metra*. Graft viability was reassessed using haemodynamic, metabolic and synthetic parameters. All 10 were then considered acceptable and since transplant they all function satisfactorily.

Strengths and limitations

No competing interests were declared.

Bral et al. (2019)

Study size, design and location

Prospective non-randomised comparative study in Canada (n=43).

Intervention and comparator

OrganOx *metra* using back-to-base approach compared with immediate NMP.

Key outcomes

The primary outcome measure was safety as defined by 30-day patient and graft survival. Secondary outcomes included 90-day graft survival; incidence of early allograft dysfunction; and biliary and arterial complications at 6 months. Results showed no difference in graft function, incidence of complications or graft and patient survival in back-to-base approach compared with immediate NMP.

Strengths and limitations

Excluding 3 livers from the statistical analysis may have introduced bias into the results. The limited sample size is not adequately powered to support definitive conclusions for non-inferiority of a back-to-base approach compared with local NMP.

Ceresa et al. (2019)

Study size, design and location

Prospective multicentre study across 3 UK transplant centres (n=31).

Intervention and comparator

OrganOx *metra* used with post-SCS.

Key outcomes

The primary end point was to test the safety and feasibility of the post-SCS normothermic perfusion approach. Results showed a 94% 30-day graft survival rate, supporting safety and feasibility of the device. Secondary end points included early allograft dysfunction, need for renal replacement therapy and adverse events.

Strengths and limitations

The study is not sufficiently powered to detect small differences between the 2 different approaches of OrganOx *metra* usage. The small sample size also precludes subgroup analyses. Retrospective comparison with historical cohorts is a recognised limitation by the authors.

Cardini et al. (2020)

Study size, design and location

Prospective non-randomised single site study in Austria (n=34).

Intervention and comparator

OrganOx *metra*.

Key outcomes

From 34 donor livers, 9 were discarded because of poor performance during NMP. There were 25 organs successfully transplanted after preservation of up to 38 hours. Extended criteria donor rates were 100% and 92% in discarded and transplanted livers. Graft and patient survival at 20 months was 88%.

Strengths and limitations

The sample size is not large enough for statistical significance.

Mergental et al. (2020)

Study size, design and location

Prospective non-randomised single site phase III trial in the UK (n=31).

Intervention and comparator

OrganOx *metra* and standard SCS.

Key outcomes

There were 31 discarded livers assessed using OrganOx *metra*, and 22 (71%) were found to meet viability criteria and were transplanted. Viability testing with NMP allowed successful transplantation of 71% of discarded livers, with 100% 90-day patient and graft survival. There were 4 individuals who developed biliary structures that needed re-transplantation.

Strengths and limitations

The study did not include people who were at higher risk with marginal organs. Three authors

declared involvement in OrganOx in various capacities.

Sustainability

The company did not report any sustainability benefits.

Recent and ongoing studies

- Using ex-vivo normothermic machine perfusion with the OrganOx metra device to store human livers for transplantation. ClinicalTrials identifier: NCT02478151. Status: enrolling by invitation. Indication: end-stage liver disease. Device: OrganOx *metra*. Estimated study completion date: September 2021. Country: Canada.
- RESTORE declined livers study. Trial identifier: NCT04483102. Status: recruiting. Indication: liver diseases, surgery, and transplant; failure, liver. Device: OrganOx *metra*. Estimated study completion date: September 2022. Country: US.
- Normothermic liver preservation trial. Trial identifier: NCT03089840. Status: recruiting. Indication: end-stage liver disease or liver diseases. Device: OrganOx *metra*. Estimated study completion date: June 2022. Country: Canada.
- Hypothermic oxygenated (HOPE) versus NMP in human liver transplantation (HOPE-NMP). Trial identifier: NCT04644744. Status: recruiting. Indication: hepatocellular injury or liver transplant disorder. Devices: HOPE or NMP. Estimated study completion date: December 2024. Country: Germany.
- WP01 - normothermic liver preservation. Trial identifier: NCT02775162. Status: completed. Indication: liver transplantation. Device: NMP. Completion date: February 2021. Country: US.
- NAPLES study (normothermic machine perfusion of the liver to enable the sickest first). Status: preliminary results, ongoing study. Indication: liver transplant. Device: NMP. Country: UK.

Expert comments

Comments on this technology were invited from clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

All 4 experts were familiar with and had used this technology before.

Level of innovation

One expert advised that there are 3 devices on the market that provide normothermic machine perfusion (NMP). All experts reported that this device is in use in all UK liver transplant centres. It is established practice at some sites and more novel at others. There are also a range of uses of the device across these sites, depending on the financial support in place. The technology can be used either as an addition to, or instead of, existing standard care, depending on its use in back-to-base mode or continuous perfusion. One expert felt that its role was in addition to standard care and would not be needed for good quality livers with straightforward logistics.

Experts reported that the technology could replace current standard care to varying extents. This included assessing less than ideal livers to support optimum outcomes, after standard care on arrival at the site where the person having the transplant is, and potentially throughout the process, given the increased number of extended criteria grafts and organ use possible.

Potential patient impact

Three experts reported that the ability to assess the function of the organs may reduce discarded livers, increasing available organs for people on the waiting list. They highlighted that the increased use of livers would result in shorter waiting times and reduced waiting list mortality. One expert reported that this opportunity for functional assessment also means the livers that are appropriate may have improved outcomes and reduced complications for people after transplant.

Three experts reported multiple benefits to the extended preservation time that the OrganOx *metra* offers. The flexibility in arranging the transplant allowed a more prolonged donor assessment. Experts reported that this may result in reduced call ups and cancellations for patients, improving their experience. Two experts highlighted that this flexibility in timings could also reduce inequalities in access to machine perfusion technologies, with particular benefit to people who live further away from transplant centres.

Three experts reported that the technology could benefit viability of donor organs from older donors, donors with steatotic (fatty) livers, donors with concerning histories, or after circulatory death. All experts highlighted that it would particularly benefit people with complexities, including those with fulfilment liver failure, those who were very unwell (such as those with haemodynamic instability) and people having re-transplant.

Potential system impact

Experts agreed that the technology could change the current pathway and improve clinical outcomes. Three experts highlighted the increased upfront costs needed to set the device up in the system, including support, training and staffing for organ perfusion and monitoring on the machine. Also, 1 expert highlighted the need for formal training protocols to be in place. This is particularly important when considering prolonged preservation (up to and beyond 24 hours) and the supervision and troubleshooting that may be needed with this.

One expert reported that the increased flexibility meant that the logistics of transplants were improved and provided the option of elective surgeries to be arranged. One expert highlighted the benefit, in particular during the pandemic, of allowing livers to be stored for longer while testing and admission is arranged for people.

All experts emphasised the system benefit of increased donor liver rates. One expert reported that using the device means that livers can be offered to people who may otherwise have had long hospital stays without transplant, as well as better early function being reported, which may reduce length of inpatient stays and re-transplantation rates.

General comments

Three experts highlighted that a full cost economic analysis is still needed to see the true effect on the pathway, summarising how much the existing healthcare burden is offset by adopting this technology. This should include the reduction in hospital costs of those on waiting lists, the increased number of transplants done, the impact on waiting list mortality, the development of complications and the follow-up costs.

Experts described various gaps in knowledge that they reported would benefit from further data. These included having information to reduce uncertainty in safety and efficacy, in particular highlighting some noted effects with the use of the device, as reported in Richards et al. (2021) and Hann et al. (2020). Data to inform the optimum perfusate on the machine is yet to be identified, as is further data to inform the accepted criteria for viable livers, clarifying which organs may benefit from functional assessment. Another expert felt they would benefit from a better understanding of quality of life after transplant.

Experts also highlighted that the analysis of its use alongside, and compared with, other evolving techniques would be beneficial. This should include regional perfusion (in donation after circulatory death) and understanding the risks and benefits of hypothermic oxygenated machine perfusion

(HOPE) in relation to normothermic perfusion of the OrganOx *metra*.

Expert commentators

The following clinicians contributed to this briefing:

- Professor Christopher Watson, professor of transplantation, University of Cambridge, and Cambridge University Hospitals NHS Foundation Trust. Received honorarium for delivering a talk about normothermic perfusion at OrganOx sponsored symposium, European Society of Organ Transplantation, 2019.
- Mr Thamara Perera, consultant liver transplant surgeon, Queen Elizabeth Hospital, Birmingham. No declarations of interest declared.
- Mr Gabriel Oniscu, consultant transplant surgeon, Edinburgh Transplant Centre, Royal Infirmary of Edinburgh. No declarations of interest were declared.
- Mr Abdul Rahman Hakeem, consultant hepatobiliary and liver transplant surgeon, St James's University Hospital, Leeds Teaching Hospitals NHS Trust. No declarations of interest were declared.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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