

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Portable Normothermic Cardiac Perfusion System in Donation After Cardiocirculatory Death: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Heart failure is a condition in which the heart's ability to pump enough blood to meet the body's needs is reduced. Heart failure can occur as a result of congenital heart defects (problems with the structure of the heart that are present at birth), coronary heart disease (a narrowing of the heart's coronary arteries), or any number of diseases that cause the heart muscle to become thick or rigid or to harden.

Interventions to manage end-stage heart failure include medications and mechanical circulatory support; however, heart transplantation is the most effective treatment for some people with end-stage heart failure. It is considered for people with advanced heart disease who have an unacceptable quality of life and a poor life expectancy despite optimal management. However, there is a chronic shortage of donor hearts. A portable normothermic cardiac perfusion system may increase the availability of donor hearts for transplantation.

This health technology assessment looked at the safety and effectiveness of a portable normothermic cardiac perfusion system for the preservation and transportation of hearts donated after cardiocirculatory death (when the heart has stopped beating and there is no longer blood flow or a pulse). We looked at the budget impact of publicly funding this system for adult heart transplant recipients in Ontario. We also looked at the experiences, preferences, and values of people waiting for a heart transplant, people who had received a heart transplant, and family members of organ donors.

What Did This Health Technology Assessment Find?

Outcomes for people who received hearts donated after cardiocirculatory death using a portable normothermic cardiac perfusion system appear to be similar to those for people who received hearts donated after brain death. However, the quality of this evidence is very low. Given the lack of clinical and economic evidence on long-term outcomes, we were unable to establish the cost-effectiveness of a portable normothermic cardiac perfusion system. We estimate that publicly funding a perfusion system for donor heart preservation after cardiocirculatory death over the next 5 years would cost about \$5.6 million.

Although the people we spoke with had no direct experience with a perfusion system, people waiting for a heart transplant expressed hope that the technology could increase the potential donor pool. Family members of organ donors believed the technology could increase the likelihood of a successful heart transplant.

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

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ABSTRACT

Background

Heart transplantation is the most effective treatment for people experiencing end-stage heart failure whose quality of life and life expectancy are unacceptable. However, there is a chronic shortage of donor hearts to meet the demand, so it is essential to expand the donor pool and increase supply. Heart donation mainly occurs after brain death (neurological determination of death [NDD]), but it may also be feasible after cardiocirculatory death (when the heart has stopped beating and there is no longer blood flow or a pulse), provided specialized preservation techniques are used. An investigational device, a portable normothermic cardiac perfusion system, could make it possible to procure, preserve, and transport hearts donated after cardiocirculatory death (DCD). We conducted a health technology assessment of a portable normothermic cardiac perfusion system for the preservation and transportation of DCD hearts for adult transplantation. This included an evaluation of the effectiveness, safety, value for money, and budget impact of publicly funding this system, as well as an evaluation of patient preferences and values.

Methods

We performed a systematic review of the clinical literature published since 1998 that examined the clinical safety and effectiveness of a portable normothermic cardiac perfusion system for DCD heart transplantation. We assessed the risk of bias of each included study and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We also reviewed the economic evidence published during the same time period for the cost-effectiveness of a portable normothermic cardiac perfusion system for DCD hearts compared with cold storage for NDD hearts. We further estimated the 5-year net budget impact of publicly funding a normothermic cardiac perfusion system for DCD heart transplantation for adults on Ontario's waitlist. To contextualize the potential value of a portable normothermic cardiac perfusion system, we spoke with people waiting for a heart transplant, people who had received a heart transplant, and family members of organ donors.

Results

We screened 2,386 clinical citations. One study and two case reports met the inclusion criteria. The survival of recipients of DCD hearts procured with a portable normothermic cardiac perfusion system did not differ significantly from the survival of recipients of hearts donated after NDD at 30 days or 90 days, nor was there a significant difference in cumulative survival at 1 year post-transplant (GRADE: Very Low). The occurrence of rejection and graft failure also did not significantly differ between the groups (GRADE: Very Low). Cardiac function in the early post-operative period was better in DCD hearts than NDD hearts (GRADE: Very Low). There were no differences in outcomes between DCD procurement techniques.

The economic literature search yielded 62 citations. One report met the inclusion criteria but was not directly applicable to the Ontario context. Given the lack of clinical and economic evidence on long-term outcomes, we did not conduct a primary economic evaluation. In the budget impact analysis, based on the number of DCD donors under 40 years of age in the last 5 years, we estimated that the increased availability of donor hearts made possible by the technology would result in an additional seven transplants in year 1, increasing to 12 in year 5. The annual net budget impact of publicly funding a normothermic cardiac perfusion system for the transplantation of DCD hearts in Ontario over the next 5 years is about \$2.0 million in the first year and about \$0.9 million in each of years 2 through 5, yielding a total net budget impact

of about \$5.6 million. This number increases to about \$10.3 million if the transplant volume increases to 18 hearts in year 1 (meaning a subsequent increase of up to 21 hearts in year 5). If transplantation were limited to people who do not qualify for a ventricular assistive device or who qualify but do not wish to receive one, the total 5-year net budget impact would be about \$7.9 million.

People waiting for a heart transplant or who had received a heart transplant and family members of organ donors expressed no substantial concerns about the potential use of a portable normothermic cardiac perfusion system. They hope that it may increase the number of donor hearts available for transplant. For family members of organ donors, a perfusion system may provide comfort and value if it can increase the successful procurement of donor hearts.

Conclusions

Based on very low quality of evidence, the outcomes for recipients of DCD hearts preserved using a portable normothermic cardiac perfusion system appear to be similar to outcomes for recipients of NDD hearts. Owing to a lack of evidence relevant to the Ontario context, we were unable to determine whether a portable normothermic perfusion system may be cost-effective. We estimate that publicly funding a portable normothermic cardiac perfusion system for DCD heart transplantation over the next 5 years will cost about \$5.6 million. The people we spoke with believe that the system may increase the number of hearts available for transplant and therefore increase the number of heart transplants that can be done.

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OBJECTIVE

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of a portable normothermic cardiac perfusion system for the preservation and transport of hearts donated after cardiocirculatory death for adult heart transplantation. It also evaluates the budget impact of publicly funding a perfusion system and the experiences, preferences, and values of people with heart failure and family members of organ donors.

BACKGROUND

Health Condition

Heart failure can occur as a result of congenital heart defects, coronary heart disease, and cardiomyopathy of various aetiologies, among other causes.¹ There were 419,551 incident cases of heart failure in Ontario over the period 1997 to 2007.² Interventions to manage end-stage heart failure include medication and mechanical circulatory support, commonly ventricular assist devices, as either a bridge to transplant or destination therapy.³ In February 2016, Health Quality Ontario, under the guidance of the Ontario Health Technology Advisory Committee, recommended left-ventricular assist devices be publicly funded as destination therapy for individuals with heart failure who are ineligible for transplant.⁴⁻⁶ While these technologies have somewhat broadened the field of management options, heart transplantation remains the most effective, life-saving treatment for end-stage heart failure in terms of quality of life and survival.⁷ Heart transplant is considered for people with advanced heart disease who have unacceptable quality of life and life expectancy despite optimal management.⁸

Clinical Need and Target Population

In 2016, 179 adult heart transplants were performed in Canada. An additional 164 people remained on the waitlist.⁹ In Ontario, 93 adult heart transplants were performed in 2017, with 159 people on the waitlist.¹⁰ There is a chronic shortage of donor hearts to meet the need.¹¹⁻¹³ Over the past decade, the number of people listed for cardiac transplant has increased by approximately 25%, while the supply of donor hearts has remained steady.⁸ An estimated 50% of Canadians on the active waitlist for a heart transplant will never receive one; with 20% to 30% dying while waiting and the rest deteriorating until they become ineligible for transplant.⁸

Organ Donation

Neurological Determination of Death

Organ donation occurs most often after death defined by neurological criteria.¹¹ Neurological determination of death (NDD; also known as brain death) is diagnosed according to specific nationally-defined criteria, when there is an absence of neurological function after a known, irreversible cause.¹⁴ In NDD heart donation, the heart continues to beat until planned and controlled cardiac arrest occurs through the infusion of cardioplegia prior to explanting the heart. This permits a more in-depth structural and functional assessment of the heart to be performed (e.g., palpation for cardiac disease, transesophageal echocardiography, angiography).¹⁵ These assessments help to increase confidence in the suitability of a heart for transplant, but they are still rudimentary and do not guarantee good post-transplant heart function or outcomes. Hearts with identified issues may function very well after transplant, and some donor hearts with no signs of problems may fail after transplant.¹⁵

Neurological determination of death (NDD) donors who are without known risk factors that can impact transplant outcomes are referred to as standard criteria donors (e.g., donors aged < 40 years who have not undergone prior cardiac surgery). Donors with known risk factors are referred to as extended criteria (or marginal) donors.¹⁶ Older donor age and the length of time without blood flow to the donor heart (ischemic time) are two of the most important risk factors for heart transplant recipient survival. Each, when doubled, independently conveys an approximate two-fold risk of death, and the two factors interact to further reduce median survival.¹⁷

Cardiocirculatory Death

Organ donation can also occur after cardiocirculatory death, when the heart has stopped beating, and there is no longer blood flow or a pulse.¹¹ This is referred to as donation after cardiocirculatory death (DCD), occasionally informally called a non-beating heart donor.¹⁸ In Canada, before proceeding with organ donation, the determination of cardiocirculatory death is made by at least two physicians according to accepted medical practice; criteria are the continuous observation of a lack of pulse, blood pressure, and respiration for 5 minutes following the onset of circulatory arrest.¹⁹ By definition, DCD donors do not fulfill the criteria for neurologic (brain) death.¹⁹ Most of this type of organ donation is after controlled DCD (also called Maastricht category III). In these cases, cardiocirculatory death follows withdrawal of life-sustaining therapy (WLST) (e.g., mechanical ventilation, inotropic support) in an intensive care setting only after proper informed consent is obtained from the donor or family.¹⁹ In contrast, uncontrolled DCD can occur after unanticipated cardiac arrest.¹⁹

Donation of organs such as kidneys, lungs, and liver after controlled DCD has become a part of routine practice in the past decade.²⁰ DCD hearts (cardiac grafts) are used clinically in jurisdictions in Sydney, Australia (St. Vincent's Hospital) and at four centres in the United Kingdom (Papworth Hospital, Cambridge; Harefield Hospital, London; Wythenshawe Hospital, Manchester; and the Freeman Hospital, Newcastle, in order of program adoption). More than 80 DCD heart transplants have been performed collectively by these units. DCD heart transplantation presents several clinical challenges: the risk of physiological damage due to warm ischemia (lack of blood flow) during cardiac arrest, the challenge of achieving successful reanimation of the heart, and the need to assess its viability (structure and function) before transplantation.²⁰ For these reasons, DCD hearts are currently not widely used in clinical transplantation in many jurisdictions, including across Canada.

Donor Heart Preservation

Hypothermia has been employed in solid organ preservation since the mid-twentieth century.²¹ Cold static storage involves flushing the heart with a preservation solution to arrest it (i.e., stop beating), and then placing it on ice and is used for the preservation of NDD hearts during transport to the recipient.³ This technique leads to overall good outcomes for recipients, but it has time limitations for maintaining the viability of the organ that in turn confines transport distances and organ sharing.¹² Extended cold ischemic time is associated with heart muscle damage, as well as injury upon reperfusion (ischemic reperfusion injury) that can compromise post-transplant function.¹² This time sensitivity restricts where the heart can be feasibly allocated to, even within a single jurisdiction with vast geography.

The transplantation of DCD hearts is part of clinical practice in select jurisdictions in Australia and in the United Kingdom, but it poses several clinical challenges in terms of organ preservation and transport. The first DCD heart transplant in 1967 was possible because the

recipient and the donor were co-located within the same hospital, thus circumventing the need for preservation techniques.^{21,22} The primary concerns regarding the viability of a DCD heart are potential physiological damage due to warm ischemic time during cardiocirculatory arrest, reanimation of the heart after declaration of cardiocirculatory death, and assessment of its function before transplant.²⁰ Warm ischemic time is unique to DCD and can result in myocardial injury that impedes function.²³ For these reasons, cold static storage presents a potential double-insult to DCD donor heart quality and function due to the heart's exposure to both warm and cold ischemic time, and associated reperfusion injury.

A key for preserving a DCD heart is continuous perfusion, in which substances such as preservation solution, oxygen, nutrient-rich donor blood, or a combination, are circulated through the heart, either in a hypothermic state or normothermic (near body temperature).³ Perfusion can be performed in situ using a technique commonly called normothermic regional reperfusion (NRP). In NRP, after determination of cardiocirculatory death, the donor is connected to mechanical cardiorespiratory support to reperfuse the thoracic and abdominal organs. There is no restoration of cerebral blood flow. This procurement technique, nicknamed the Papworth Protocol, enables assessment of the donor heart in a manner similar to NDD procurement. However, NRP is not widely scalable and raises ethical and legal issues, depending on local laws regarding the definition of death and reperfusion of a cadaver.²⁴ To our knowledge at the time of writing this report, only the centre at Papworth Hospital in the United Kingdom employs the NRP protocol as part of their clinical practice.

The heart can also be perfused by a machine after recovery from the donor.³ Mechanical perfusion most often occurs immediately after organ explantation, (direct procurement and perfusion [DPP], also known as the Sydney Protocol) and continues for the duration of organ transport.³ The DPP technique is used at all DCD heart transplant centres in the United Kingdom and Australia, including Papworth Hospital, which makes use of the DPP protocol as dictated by local procurement logistics. The portable normothermic mechanical cardiac perfusion system under review in this health technology assessment has the potential to monitor donor hearts, including DCD hearts, and thus expand the donor pool beyond NDD, potentially increasing the number of donor hearts available for transplant.^{12,13}

Health Technology Under Review

The Organ Care System Heart (TransMedics, Inc.) preserves donor hearts in a warm functional state during transport after recovery. This portable normothermic cardiac perfusion system is composed of an organ-specific perfusion system and a wireless monitor (the console).²⁵ The reusable console houses the hardware containing the components that drive and monitor the heart perfusion set. The heart perfusion set is composed of a single-use biocompatible device to perfuse and monitor the donor heart.¹ The Organ Care System Heart employs retrograde perfusion, whereby warm, nutrient-rich, oxygenated blood is pumped into the aorta to the coronary arteries. From the coronary sinus, it is ejected from the right ventricle, which is having to eject blood into the pulmonary artery and out into the reservoir.²⁶ Thus, during perfusion the donor heart is beating but the left ventricle is entirely unloaded and therefore in a non-ejecting resting state. In this condition, it is not possible to assess its working function.²⁷

Donor blood (≥ 1.1 L, drawn before organ recovery) is passed through a leukocyte filter, and then proprietary solutions containing buffered electrolytes, mannitol, vitamins, and steroids are circulated to prime the circuit. Once the donor heart is instrumented (installed) on the perfusion system, ventricular pacing wires are placed. In the absence of spontaneous sinus rhythm, the heart may require defibrillation or pacing at 80 to 90 beats per minute, unless the intrinsic

rhythm is faster.²⁸ During perfusion, a proprietary solution of isotonic electrolytes, amino acids, dextrose-insulin, and low-dose adenosine is circulated to keep coronary flow within the target range. An internal gas supply with pulsing system provides oxygenation.^{25,26} Measurements of heart rate, coronary flow, aortic pressure, cardiac electrical activity and arterial blood gas, electrolytes, and glucose are taken regularly during transport.²⁶ Lactic acid levels in the venous sample (blood draining from the pulmonary artery) and arterial sample (blood flowing into the ascending aorta and coronary arteries) are both monitored throughout perfusion as a biochemical surrogate for heart function. Arterial lactate levels should be greater than that of the venous perfusate, with both levels recommended to be less than 5 mmol/L in order to proceed with transplant.²⁸ The technology costs approximately \$275,000 USD for the console and \$55,000 USD per case for single-use components (TransMedics Inc., written communication, June 27, 2018). The system also requires a maintenance service that costs about \$20,000 AUD (2016 dollars) over 10 years.⁴

A prospective randomized controlled trial (PROCEED II) demonstrated the Organ Care System Heart to be noninferior to cold static storage, yielding similar short-term clinical outcomes for transplant recipients for NDD hearts.¹² After a 2-year follow-up of participants,²⁹ there were no significant differences in important post-transplant outcomes, including recipient survival, cardiac allograft vasculopathy, incidence of non-fatal major cardiac events, or rejection. In 2016, the National Institute for Health and Care Excellence (NICE) released guidance on the basis of these seminal trials. They recommended the technology to preserve standard criteria NDD hearts to permit extended preservation time compared to cold storage (IPG 549).³⁰ NICE also encouraged further research into safety outcomes.³⁰ There is presently an ongoing clinical trial to evaluate the effectiveness of the Organ Care System Heart in extended criteria NDD hearts (EXPANDHeart Trial, NCT02323321). This trial expected to be completed in early 2019.

The large studies of the Organ Care System Heart to date mainly assess its potential to improve existing NDD heart transplantation. However, the proposed uses for the technology aim to increase the availability of donor hearts and address the shortage by extending NDD heart preservation time (e.g., across greater distances), assessing and restoring marginal NDD hearts, and enabling the use of DCD hearts for transplant. Owing to the damage to the heart during cardiocirculatory arrest (warm ischemic time) and the need to assess and preserve heart function, the effectiveness of a perfusion system for DCD hearts and recipient outcomes is of particular interest.

Regulatory Information

The TransMedics Organ Care System Heart does not currently hold an active license from Health Canada. A device to monitor and perfuse the heart is considered a Class II device (Health Canada, written communication, February 2, 2018), and requires a declaration from the manufacturer of data on effectiveness and safety in any application for license (see Medical Devices Regulations, Part 1, Sections 10–20 for full details).³¹ In the United States, use of the Organ Care System Heart is limited by Federal law to investigational circumstances.²⁵ The Organ Care System Heart received a CE mark in Europe in 2006 (updated in 2015) as a class IIa device.¹

Ontario Context

Ontario has seen an overall increase in organ transplantation volume since 2006, when DCD donation of lungs, livers, pancreases, and kidneys was introduced.¹³ DCD now accounts for approximately 30% of these solid organ donations in Ontario;⁹ however, DCD hearts have not

been transplanted. Technological advancements such as a portable normothermic cardiac perfusion system may present an opportunity to do so.

In 2006, a Canadian national, multidisciplinary forum was held to define the principles and practices for DCD organ donation in a sound ethical and legal framework to protect and serve the Canadian public and professional standards.¹⁹ The guiding principles for ethical implementation detailed in the national recommendations are respect for the lives and dignity of all individuals, optimal end-of-life care that respects the holistic well-being of the dying patient, respect for patient autonomy with regard to known values and preferences for a meaningful life and death, support for the grieving family and loved ones through all phases of dying, public trust and avoidance of actual or perceived conflicts of interest in care provision, and respect for professional integrity.¹⁹ These core values and ethics provide the framework for existing DCD organ donation in Canada and are expected to apply also to a DCD heart donation program.

Expert Consultation

We solicited expert feedback on organ donation, portable normothermic cardiac perfusion systems, cardiac transplantation, and donation after cardiocirculatory death. The consultations included local, national, and international clinical and technical experts in organ transplantation, transplant cardiology, and cardiac surgery as well as ethicists and clinicians with relevant expertise, including industry representatives (see Acknowledgments, page 2). The role of the expert advisors was to contextualize the evidence and assist in understanding the use and technical aspects of a perfusion system in the context of donation after cardiocirculatory death. The statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42018095927), available at <https://www.crd.york.ac.uk/PROSPERO>.

CLINICAL EVIDENCE

Research Question

What are the clinical effectiveness and safety of a portable normothermic cardiac perfusion system for donor heart preservation in the context of donation after cardiocirculatory death?

Methods

Clinical Literature Search

We performed a clinical literature search on April 3, 2018, to retrieve studies published from January 1, 1998, until the search date. We used the Ovid interface to search the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the CRD Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.³²

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 1998
- Comparative randomized and non-randomized studies or non-comparative studies for effectiveness outcomes; case reports for adverse events/effects outcomes
- De novo adult heart transplant recipients of donation after cardiocirculatory death (DCD)
- Portable normothermic cardiac perfusion system (e.g., TransMedics, Inc. Organ Care System Heart) used in DCD heart procurement, including direct procurement and perfusion (DPP) or normothermic regional reperfusion (NRP)
- Compared with DCD donation with direct procurement and perfusion (DPP), DCD donation with NRP, or neurological determination of death (NDD) donation, or no comparator
- Clinical transplant setting

Exclusion Criteria

- Animal, laboratory, or in vitro studies of viability of hearts (biologic parameters)
- Editorials, letters or commentaries, conference proceedings, abstracts, or posters
- Adolescent or pediatric donors or recipients
- Recipients of heart transplant from NDD donors

- Re-transplant recipients
- Other experimental or commercial perfusion systems (including, but not limited to hypothermic perfusion systems such as the Paragonix SherpaPak Cardiac Transport System, Organ Transport Systems Inc.'s LifeCradle Heart Perfusion System, and stationary normothermic cardiac perfusion systems)
- Portable normothermic perfusion systems for other solid organs

Outcomes of Interest

- Survival
- Symptoms
- Quality of Life
- Acute rejection
- Graft failure
- Graft survival/primary graft function
- Adverse events, effects
- Long-term graft survival/function
- Infection, malignancies, etc.
- Detection of hidden pathology
- Device-related complications
- Occurrence of hearts declined for transplants due to functional or technical issues
- Number of deaths on waitlist pre- and postimplantation
- Number of heart transplants pre- and postimplantation
- Length of stay in intensive care unit (ICU), hospital
- Ischemic time

We did not detect potential health inequities related to the effectiveness of a portable normothermic cardiac perfusion systems in DCD during scoping. Relevant equity issues related to the effect of a perfusion system in DCD heart transplant across different populations defined by the PROGRESS-Plus categories³³ were not identified.

Literature Screening

A single reviewer screened titles and abstracts using DistillerSR citation management software and then obtained the full texts of studies that appeared eligible according to the inclusion criteria. The reviewer then examined the full text articles and selected studies that were eligible for inclusion. We also examined reference lists of included studies for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant information from the published article(s) on study context, methods, population, intervention, comparators, outcomes, results, and risk-of-bias items into a data form.

We contacted the authors of two studies^{34,35} by email to clarify if the heart donor was DCD to assess eligibility. We contacted the author of one included study³⁶ to provide clarification on the published analysis. None of the authors responded to our inquiries.

Statistical Analysis

We describe the findings of the included studies. We did not conduct a meta-analysis because there was only one comparative study identified.

Critical Appraisal of Evidence

We assessed risk of bias of nonrandomized studies using the Newcastle-Ottawa Scale for Cohort Studies³⁷ (Appendix 2). Publication bias could not be assessed because of the small number of studies.

We evaluated the quality of the body of comparative evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook*.³⁸ The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality reflects our certainty in the evidence. As planned a priori, we did not critically appraise case reports or case series but included them in the interest of comprehensiveness and to identify future areas of inquiry with more systematic research methods.

Results

Literature Search

The clinical literature search yielded 2,386 citations published between January 1, 1998, and April 3, 2018, after removing duplicates. We identified two studies (one comparative cohort study and one report of three cases) that met our inclusion criteria.^{36,39} We identified one additional study⁴⁰ (a report on two cases) after identification at full-text screening as a conference abstract, but which had subsequently been published as a full text article (reported in Figure 1, “other sources”). We identified a health technology assessment conducted for the New South Wales Ministry of Health in Australia during expert consultations. This study searched for clinical literature published before June 2016 and was excluded because it did not answer our research question and we were aware of DCD studies published since. Therefore, a total of three studies (one comparative cohort and two case series) were included. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

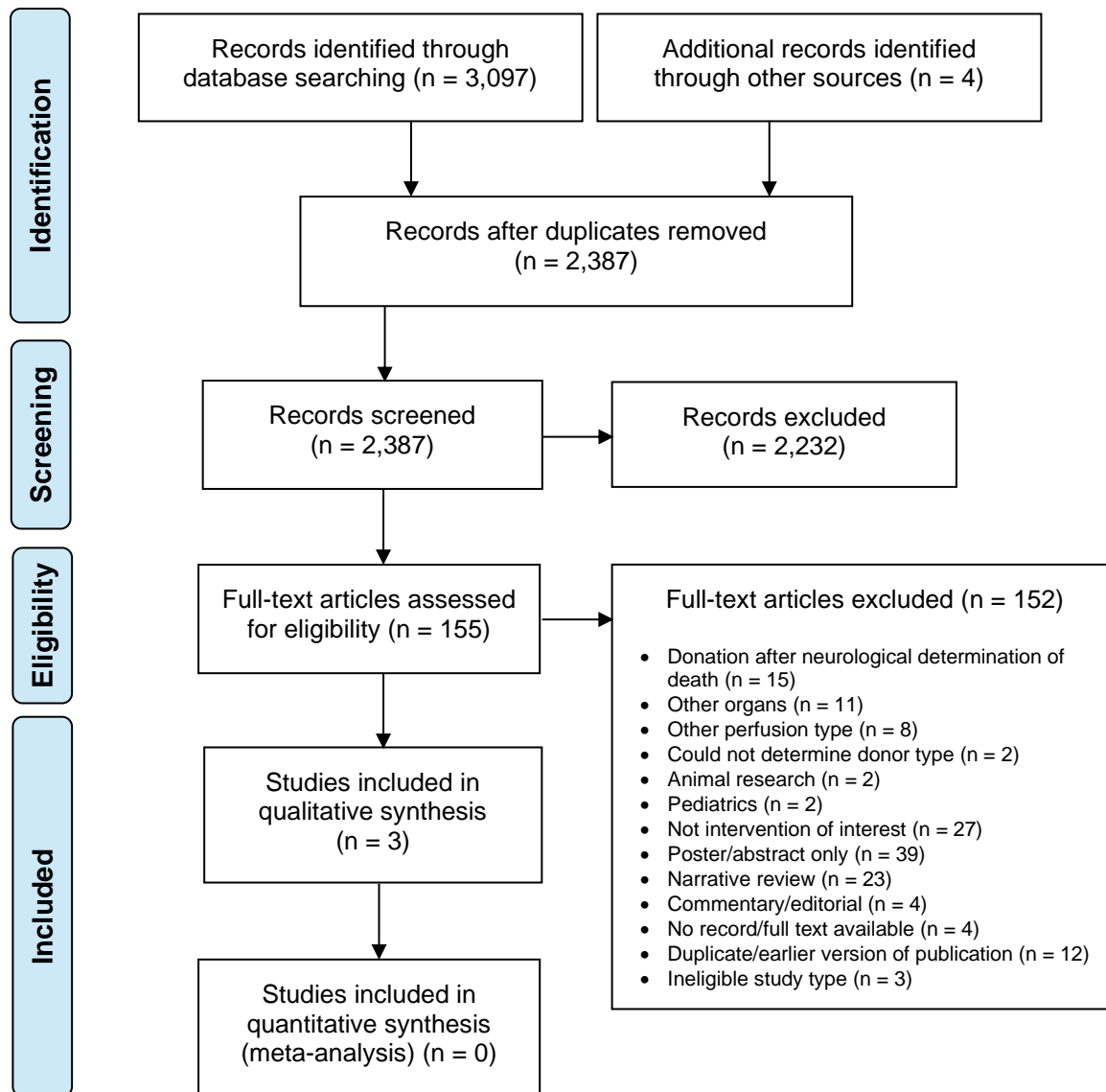


Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Source: Adapted from Moher et al, 2009⁴¹

Characteristics of Included Studies

The comparative study³⁶ and case series^{39,40} all involved Maastricht category III (controlled) donations after cardiocirculatory death (i.e., death expected following withdrawal of life-sustaining therapy [WLST]) for which consent for donation was obtained from next of kin (Table 1). Across the studies, donors were excluded if they had a history of cardiac disease or surgery, communicable diseases or infections (e.g., human immunodeficiency virus [HIV], hepatitis, Creutzfeldt–Jacob disease), or cancer. Recipients were eligible if they were listed for cardiac transplant, provided consent for DCD heart transplant, and did not have high pulmonary vascular resistance. All procedures and protocols related to consent, WLST, determination of death, and organ procurement were approved by the applicable regulatory authorities for organ donation and retrieval and each centre’s research ethics body.

Table 1: Characteristics of Included Studies

Author, Year	Location (Centre)	Study Design	N	Recipient(s) of	DCD Donor Eligibility Criteria	Outcomes
Messer et al, 2017 ³⁶	United Kingdom (Papworth Hospital)	Matched cohort study	52	DCD hearts procured and preserved via either NRP + OCS or DPP + OCS or NDD hearts preserved with cold static storage	Maastricht category III DCD Age: 18–57 years Consent provided by next of kin Death expected within 4 h after WLST No valvular abnormalities on ECG Ejection fraction > 50% before WLST	Primary: 90-day survival Secondary: Cardiac performance Need for support (inotropic, mechanical, or ventilator) Rejection episodes Length of stay: ICU and hospital
García-Sáez et al, 2016 ⁴⁰	United Kingdom (Harefield Hospital)	Case series	2 ^a	DCD hearts procured via NRP + OCS	Maastricht category III DCD Age: 16–50 years Consent: provided by next of kin or is on organ donation register	Description of clinical course
Dhital et al, 2015 ³⁹	Australia (St. Vincent's Hospital)	Case series	3	DCD hearts procured via DPP + OCS	Maastricht category III DCD Age: < 40 years < 30 min WIT (from WLST to cardioplegia)	Description of clinical course

Abbreviations: DCD, donation after cardiocirculatory death; DPP, direct procurement and perfusion; ECG, echocardiogram; ICU, intensive care unit; LVAD, left ventricular assist device; N, number of transplant recipients; NDD, donation after neurological determination of death; NRP, normothermic regional reperfusion; OCS, Organ Care System Heart portable normothermic cardiac perfusion system; WIT, warm ischemic time; WLST, withdrawal of life-sustaining therapy.

^aBoth recipients were high-risk because they were bridged to transplant with implantable LVAD.

Heart Transplant Outcomes With Hearts Donated After Cardiocirculatory Death Using a Portable Normothermic Cardiac Perfusion System Versus Hearts Donated After Neurological Determination of Death

Messer et al (2017)³⁶ evaluated the outcomes of transplant recipients of DCD hearts that were preserved and transported using a portable normothermic cardiac perfusion system, compared with recipients of NDD hearts. They studied a cohort of consecutive people who received a DCD heart procured via either DPP or NRP, followed by preservation using the Organ Care System Heart portable normothermic cardiac perfusion system, between February 1, 2015, and March 31, 2017.³⁶ The cohort of DCD recipients was matched to non-contemporaneous recipients of NDD hearts at the same centre. Matching was performed by an independent, blinded reviewer for important prognostic factors: donor age, sex, and height, as well as recipient sex, heart failure etiology, pre-transplant ventricular assist device (VAD), transpulmonary gradient, and pulmonary vascular resistance.³⁶ The immunosuppressant medication regimen and heart implantation technique were the same for all heart transplants.

There were 40 potential donors of DCD hearts during the study period. Five did not experience cardiac arrest after WLST and were therefore excluded. Of the 35 DCD hearts, 17 were procured using the NRP technique, including 12 that were instrumented on a perfusion system and subsequently transplanted.³⁶ The other 18 hearts were procured using the DPP technique and then instrumented on a perfusion system, which led to three being declined. One additional DPP recipient was excluded from the study because they underwent a combined heart-kidney transplant. Ultimately, 26 DCD hearts transported using a portable normothermic cardiac perfusion system (12 NRP and 14 DPP) and 26 matched NDD hearts were included in the analysis.³⁶ For secondary outcomes, analyses were also performed with statistical adjustment for multiple comparisons to control Type I error (i.e., false discovery rate). Unless otherwise stated, *P* values reported are from unadjusted analysis. Messer et al's³⁶ matched-cohort study was judged to be at low risk of bias (Appendix 2, Table A1).

We rated the certainty of the evidence for all outcomes as very low (Appendix 2, Table A2), downgrading for serious limitations related to imprecision.

Survival

Table 2 shows the results for survival between recipients of DCD hearts using a perfusion system and matched NDD recipients at 30 days, 90 days (the primary outcome), and 1 year. Non-parametric Kaplan-Meier survival analysis was used to compare the groups' survival over time. Causes and timing of reported deaths are also described.³⁶

Table 2: Survival and Deaths Following Cardiac Transplants With Donation After Cardiocirculatory Death Hearts Versus Donation After Neurological Determination of Death Hearts

Outcome	Type of Donor Heart		P
	NDD n (%)	DCD n (%)	
Survival at 30 days	26 (100)	26 (100)	1.00
Survival at 90 days	25 (96)	24 (92)	1.00
Cumulative survival at 1 year	88%	86%	.98
Deaths	1	3 ^a	—
Causes (timing)	Primary graft dysfunction requiring ECMO Multi-organ failure POD 34	<ul style="list-style-type: none"> Primary graft dysfunction requiring ECMO; catastrophic intracerebral hemorrhage POD 31 Opportunistic infection POD 88 Antibody-mediated rejection on post-operative POD 291 	—

Abbreviations: DCD, donation after cardiocirculatory death; ECMO, extracorporeal membrane oxygenation; n, number; NDD, donation after neurological determination of death; POD, post-operative day;

^aA third DCD heart recipient died on POD 291 despite having been discharged from hospital 23 days after transplant. This death was not captured in the analysis of survival at 30 or 90 days.

Source: Messer et al, 2017.³⁶

There was no significant difference in survival at 30 or 90 days post-transplant ($P = 1.00$ for both).³⁶ More than 90% of recipients of DCD hearts using a portable normothermic cardiac perfusion system were alive and well at POD 90, compared with 100% of NDD recipients. In each group, all recipients survived to POD 30. At POD 90, one participant in the NDD group died from primary graft dysfunction. Two participants in the DCD group had died by POD 90, one also from primary graft dysfunction and the other resulted from an opportunistic fungal infection that required re-hospitalization.³⁶

The 1-year cumulative survival probability was not significantly different between groups, at 88% for NDD recipients and 86% for DCD recipients ($P = .98$). However, there were 10 individuals in the study no longer at risk at 1 year (three in the NDD group and seven in the DCD group). The study reported only four deaths, so it is unclear from the study's reporting what happened to the other six individuals no longer at risk (e.g., they may have been lost to follow-up or other events).

Within the DCD group, there was no significant difference in age, sex, blood group, height, or cause of death between the NRP and DPP procurement technique subgroups. There was no difference between recipients of DCD hearts procured via DPP or NRP in survival at 30 or 90 days ($P > .05$ for both; Table 3).³⁶ The causes of the two deaths in the NRP subgroup at POD 31 and POD 88 are described in Table 2. No information was provided on the survival of these subgroups of DCD heart recipients beyond 90 days.

Table 3: Survival of Donation After Cardiocirculatory Death Heart Transplant Recipients by Procurement Technique Subgroup

Outcome	DCD Procurement		P
	Direct Procurement and Perfusion, n (%)	Normothermic Regional Reperfusion, n (%)	
Survival at 30 days	12 (100)	14 (100)	1.00
Survival at 90 days	12 (100)	12 (100)	0.48

Abbreviations: DCD, donation after cardiocirculatory death.

Source: Messer et al, 2017.³⁶

Early Post-operative Outcomes and Graft Function

During the early post-operative period in the ICU, DCD hearts had statistically significantly better cardiac output (median 4.9 vs. 3.9 L/min/m²; unadjusted $P = .006$; adjusted $P = .03$) compared with NDD hearts while on similar mechanical or inotropic support (Table 4).³⁶ After statistical adjustment for multiple comparisons, there was no difference between groups in cardiac index. There was no difference between the DCD and NDD groups in other early hemodynamic measures, including mean arterial pressure, mean central venous pressure, or mean pulmonary artery pressure.³⁶

The number of people requiring various types of mechanical support (i.e., extracorporeal membrane oxygenation [ECMO], intra-aortic balloon pump, or VAD) did not statistically significantly differ between the DCD and NDD groups ($P > .50$ for all), nor did the mean number of days requiring mechanical ventilation ($P = .84$).³⁶ There were no significant differences in any early post-operative outcomes between the DCD procurement techniques (Table 4).

Table 4: Post-operative Outcomes and Graft Function After Heart Transplant With Either Donation After Cardiocirculatory Death Hearts Using a Portable Normothermic Cardiac Perfusion System or Donation After Neurological Determination of Death Hearts

Donor Heart, n	Cardiac Index, MD L/min/m ² (IQR)	Cardiac Output, MD L/min/m ² (IQR)	Support, n (%)	Ventilation MD days (IQR)
NDD, 26	2.0 ^a (1.4–2.4)	3.9 ^b (3.2–4.4)	Mechanical: 5 (19) ECMO: 1 (4) IABP: 4 (15) Pharmacologic (MD mcg/kg/min) Dopamine: 5.0 ^a Adrenaline: 0.04 Norepinephrine: 0.03	1.8 (0.7–2.5)
DCD, 26	2.5 ^a (2.1–2.7)	4.9 ^b (4.0–5.2)	Mechanical: 11 (43) ECMO: 3 (12) IABP: 7 (27) VAD: 1 (4) Pharmacologic (MD mcg/kg/min) Dopamine: 4.8 ^a Adrenaline: 0.04 Norepinephrine: 0.01	0.9 (0.5–3.3)
DPP, 14	2.5 (1.7–2.8)	4.6 (3.4–5.5)	8 (57) ECMO: 2 (14) IABP: 5 (36) VAD: 1 (7)	2.5 (0.5–3.6)
NRP, 12	2.5 (2.4–2.7)	5.0 (4.3–5.1)	3 (25) ECMO: 1 (8) IABP: 2 (17)	0.6 (0.4–1.1)

Abbreviations: DCD, donation after cardiocirculatory death; DPP, direct procurement and perfusion; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IQR, interquartile range; MD, median; n, number; NDD, donation after neurological determination of death; NRP, normothermic regional reperfusion; VAD, ventricular assist device.

^aStatistically significant difference between groups in unadjusted analysis ($P = .04$).

^bStatistically significant difference between groups in analysis adjusted for multiple comparisons with Benjamini–Hochberg correction ($P = .03$).

Source: Messer et al 2017.³⁶

Length of Stay

There was no statistically significant difference in the length of stay between the two groups of heart transplant recipients. Recipients of DCD hearts remained in the ICU for a median of 5 days after transplant (interquartile range [IQR]: 3–8), whereas recipients of NDD hearts remained in the ICU for a median of 7 days (IQR: 4–9, $P = .49$).³⁶ Hospital length of stay for DCD heart recipients was numerically but not statistically significantly shorter for DCD heart recipients with a median of 20 days (IQR: 17–28), compared with 27 days for NDD recipients (IQR: 21–34, $P = .09$).³⁶

There was no significant difference between DCD procurement techniques in terms of recipient length of stay in the ICU (DCD-DPP median of 6 days, IQR: 3–10 vs. DCD-NRP median of

5 days, IQR: 4 to 5, $P = .67$), nor in hospital (median of 20 days, IQR: 19–27 vs. median of 19 days, IQR: 17–27, respectively, $P = .58$).³⁶

Results of Donation After Cardiocirculatory Death Subgroup Analysis: Direct Procurement and Perfusion Versus Normothermic Regional Reperfusion

Ischemic time

Ischemic time of DCD hearts was compared between the two different procurement techniques. Hearts procured via DPP had significantly longer functional warm ischemic time (i.e., from systolic blood pressure < 50 mmHg) and donation withdrawal ischemic time (i.e., from WLST) than those procured via NRP ($P < .01$ for both).³⁶ These results are summarized in Table 5.

Table 5: Ischemic Time for Donation After Cardiocirculatory Death Hearts, by Procurement Technique

Outcome	DCD Procurement Technique, MD (IQR)		P
	DPP (min)	NRP (min)	
Functional warm ischemic time ^a	26 (23–31)	17 (15–17)	< .001
Donation withdrawal ischemic time ^b	37 (33–42)	24 (21–28)	< .003
Perfusion time on portable normothermic cardiac perfusion system	241 (210–280)	170 (140–179)	< .003

Abbreviations: DCD, donation after cardiocirculatory death; DPP, direct procurement and perfusion; IQR, interquartile range; MD, median; NRP, normothermic regional reperfusion.

^aMeasured from when systolic blood pressure is < 50 mmHg, thus organs are presumed to be poorly perfused. Functional warm ischemic time is considered to be ended upon reperfusion on a portable normothermic cardiac perfusion system.

^bMeasured from withdrawal of life-sustaining therapy. Donation withdrawal ischemic time is considered to be ended upon reperfusion on a portable normothermic cardiac perfusion system.

Source: Messer et al, 2017.³⁶

The duration of mechanical perfusion of the donor hearts on a portable normothermic cardiac perfusion system was significantly longer for DPP hearts than for NRP hearts (MD 241 vs. 170 min, $P = .003$).³⁶ The authors account for the significant difference in ischemic and perfusion time as arising from the closer geographical proximity of the centres participating in the NRP protocol to the study hospital. Ischemic time is associated with mortality¹⁷; however, there were no significant differences in survival outcomes between the groups. All DCD hearts met the required functional warm ischemic time limit of less than 30 minutes as per the study protocol.

Donor Heart Assessment and Detection of Hidden Pathology

Three DCD hearts procured using the DPP technique were declined after instrumentation on the perfusion system. Compromised cardiac function was detected in one heart (left ventricular hypertrophy). In another, it was reported that lactate levels in the perfusate were rising rapidly (data not specified).³⁶ The third heart was declined due to subsequent identification of pancreatic malignancy in the donor.³⁶

There were no reported occurrences of hearts declined due to technical issues or device-related complications of using a perfusion system. No information on symptoms, quality of life, or long-term graft survival was reported in the study.

Adverse Effects

Infection

One case of opportunistic fungal infection in the DCD-NRP group required hospital readmission and resulted in death (Table 2).³⁶

Acute Rejection

There was no significant difference in the number episodes of treated rejection. There were nine cases (35%) in the DCD group and 15 (58%) in the NDD group ($P = .15$).³⁶ There were five cases (36%) of treated rejection in the DCD-DPP group and four cases (33%) in the DCD-NRP group. This difference was also not significant ($P = 1.00$).³⁶ One DCD heart recipient died from antibody-mediated rejection on post-operative day 291 despite having been discharged from hospital 23 days after transplant (see Table 2, footnote a).³⁶

Primary Graft Dysfunction

There was one death in each of the NDD and DCD groups caused by primary graft dysfunction and sequelae (Table 2).³⁶

No information on chronic rejection, cardiac allograft vasculopathy, or volume of deaths on the waitlist or transplants before and after DCD was reported in the study.

Case Reports and Case Series

Two published case series explored the feasibility of DCD heart transplant using the Organ Care System Heart portable normothermic cardiac perfusion system to preserve and transport the donor heart.^{39,40} Table 1 provides an overview of the characteristics of the case series.

One case series reported the clinical course of two high-risk recipients of DCD heart transplant—they were people with implanted LVADs as bridge to transplant.⁴⁰ The individuals were listed for transplant in the United Kingdom and had provided informed consent for both NDD and DCD hearts. The other case series reported three successful transplants after distant procurement.³⁹ The transplants were performed as part of a broader Australian study of extended criteria transplants, which included DCD donation. The three recipients were at low-risk and had been on the waitlist for 4 days, 6 weeks, and 321 days.

The clinical course of the people in both case series is described in Table 6. There was no defined study design, a priori outcome definition, or analysis in either case series.

Table 6: Case Series of Donation After Cardiocirculatory Death Heart Transplant Using a Portable Normothermic Cardiac Perfusion System

Author, Year	Recipient	Donor	Procurement	Clinical Course
García-Sáez et al, 2016 ⁴⁰	52-yr-old male Diagnosis: idiopathic dilated cardiomyopathy Implanted HeartWare HVAD as bridge to transplant (289 d) No surgery prior to LVAD Stage 3 CKD	39-yr-old male Cause of death: intracranial hemorrhage, trauma Cardiac arrest 5 d before WLST (> 20 min) Cocaine abuse	Location of WLST: Anaesthetic Room Procurement: DPP Total ischemic time: 77 min WIT: 13 min Total OCS perfusion time: 360 min A/V baseline lactate: 5.25/4.92 A/V final lactate: 2.47/2.48	<ul style="list-style-type: none"> • Weaned off CPB after 18 h • 1 d on mechanical ventilation • Good biventricular function on initial TEE • Mild hypokinesia of inferolateral wall • Complications: acute kidney injury • Treated with hemofiltration • Discharged to ward: POD 8 • Discharged from hospital: POD 62 • Well at POD 291
	26-yr-old male Diagnosis: anthracycline-induced dilated cardiomyopathy secondary to childhood leukemia Implanted Thoratec HeartMate II LVAD as bridge to transplant (1,958 d) Acute LVAD driveline infection and thrombosis Prior bicuspid aortic valve replacement	21-yr-old female Cause of death: intracranial hemorrhage, trauma	Location of WLST: OR Procurement: DPP Total ischemic time: 86 min WIT: 21 min Total OCS perfusion time: 307 min A/V baseline lactate: 6.16/5.99 A/V final lactate: 4.02/4.01	<ul style="list-style-type: none"> • Weaned off CPB on POD 5 • 18 d on mechanical ventilation • Good biventricular function on initial TEE • Deterioration of right ventricle function • Complications: coagulopathy, vasodilatation, thick purulent secretions, tracheostomy • Discharged to ward: POD 32 • Discharged from hospital: POD 46 • Well at POD 290
Dhital et al, 2015 ³⁹	57-yr-old male Diagnosis: familial dilated cardiomyopathy	26-yr-old male Cause of death: hypoxia	Location of WLST: OR Procurement: DPP Total ischemic time: 90 min WIT: 28 min Total OCS perfusion time: 257 min A/V baseline lactate: 8.30/8.10 A/V final lactate: 3.60/3.60 Transport by road	<ul style="list-style-type: none"> • Severe left ventricle impairment upon weaning from CPB <ul style="list-style-type: none"> ○ Venoarterial femoro-femoral ECMO for 4 d ○ IABP placed percutaneously, removed after 24 h • Moderate cellular rejection (no impairment in left ventricle): POD 20 • Discharged from hospital well: POD 28 • Well at POD 91

Author, Year	Recipient	Donor	Procurement	Clinical Course
	43-yr-old female Diagnosis: viral dilated cardiomyopathy	26-yr-old male Cause of death: trauma	Location of WLST: ICU Procurement: DPP Total ischemic time: 96 min WIT: 25 min Total OCS perfusion time: 260 min A/V baseline lactate: 6.79/6.48 A/V final lactate: 2.80/2.30 Transport by air	<ul style="list-style-type: none"> • Weaned off CPB with small doses of inotropic support • Discharged from hospital well: POD 26 • Mild left ventricle impairment secondary to moderate cellular rejection <ul style="list-style-type: none"> ◦ Admitted for steroid pulse treatment • Well at POD 176
	57-yr-old male Diagnosis: arrhythmogenic right ventricular dysplasia	27-yr-old male Cause of death: trauma	Location of WLST: Anaesthetic Bay Procurement: DPP Total ischemic time: 107 min WIT: 22 min Total OCS perfusion time: 245 min A/V baseline lactate: 7.60/7.40 A/V final lactate: 2.69/2.54 Transport by air	<ul style="list-style-type: none"> • Left ventricle impairment upon weaning from CPB <ul style="list-style-type: none"> ◦ IABP placed percutaneously, removed POD 2 • Hyperdynamic biventricular function since POD 2 • Planned discharged postponed due to moderate pericardial effusion <ul style="list-style-type: none"> ◦ Drained without complication • Discharged from hospital well: POD 21 • Well at POD 77

Abbreviations: A/V, arterial/venous; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; DPP, direct procurement and perfusion; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICU, intensive care unit; LVAD, left ventricular assist device; OCS, Organ Care System Heart portable normothermic cardiac perfusion system; OR, operating room; POD, post-operative day; TEE, transesophageal echocardiogram; WIT, warm ischemic time; WLST, withdrawal of life-sustaining therapy.

Sources: Dhital et al, 2015³⁹; Garcia-Saez et al, 2016.⁴⁰

All individuals in both case series were alive and well at last follow-up (range: 77–291 days after transplant; Table 6).^{39,40} All arising complications were treated and successfully resolved.

The case series by Dhital et al³⁹ was the first to report outcomes in low-risk recipients of DCD heart transplant using a portable normothermic cardiac perfusion system. The clinical sequelae suggest that the system can adequately preserve donor hearts, enabling safe transplantation of DCD hearts procured at a considerable distance from the recipient. A larger cohort of consecutive patients with appropriate statistical analysis would enable drawing conclusions.

The short-term outcomes of two DCD heart transplants using a perfusion system for recipients who had an LVAD as bridge therapy, were successful.⁴⁰ This research suggests a potential role for a perfusion system even in cases of heart transplant with high-risk recipients.

Discussion

The available evidence shows that DCD heart transplantation is feasible and that short- and medium-term recipient outcomes did not differ significantly from those after NDD heart transplant. The studies carefully selected recipients and donors based on key clinical characteristics and employed a portable normothermic cardiac perfusion system to enable DCD heart transplantation, largely via the DPP technique. This evidence is relevant to the intended practice in Ontario and the goal to expand the donor pool to include DCD heart transplantation.

We have very low confidence in these effect estimates owing to limitations in the quality of the body of evidence (Table A2). However, heart transplantation is a very high-risk intervention reserved for end-stage heart failure patients who have no other treatment options for a condition that invariably results in mortality.⁴² The GRADE Working Group holds the position that in a life-threatening clinical situation, low quality evidence may warrant a strong recommendation despite very low confidence in the effect estimates.³⁸

A few international groups have previously summarized the emerging evidence for promising solid organ perfusion technologies on the horizon, including technologies for heart transplantation.^{1,43} In early 2017, the New South Wales Ministry of Health conducted a health technology assessment of literature published up to June 2016 that included the use of a portable normothermic cardiac perfusion system for overall heart transplantation in NDD (standard and extended criteria hearts) and DCD.⁴ In contrast, we focused our scope on a perfusion system as applied to a single potential new donor pool and captured new evidence—an additional case series in high-risk recipients and the only comparative study in DCD published after the search date of the Australian assessment. We did not address a wider application of a perfusion system for global donor pool expansion. To our knowledge, ours is the first systematic review examining a perfusion system exclusively in the context of DCD.

The findings of our review are consistent with previously published clinical trials in heart transplantation with NDD hearts, though we are considerably more uncertain.^{12,29} The post-operative course of DCD heart transplantation had similarities to that of DCD lungs and kidneys. There may be a higher rate of mechanical support in the early post-operative period and some delayed graft function, however the organs need some supported time to recover and subsequently function comparably to NDD organs.⁴⁴ This was seen in the study by Messer et al,³⁶ with a greater number of DCD recipients requiring substantive mechanical support (i.e., VAD or ECMO) in the early post-operative period than did NDD heart recipients (four versus one).

The primary outcome of the comparative study by Messer et al³⁶ was survival, a clinically and patient-important outcome when compared with graft function and surrogate clinical endpoints. However, the duration of follow up was limited. This is significant because adverse events such as cardiac allograft vasculopathy and other longer-term safety and effectiveness outcomes are unlikely to occur during the study period, and require multi-year follow-up (i.e., at least 5 years). Although not analysed statistically, patients in the case series, including those at high-risk due to having an implanted LVAD as a bridge to transplant, were reported as alive and well beyond 90 days post-DCD heart transplant (range: 71–291 days). Three hearts were determined unsuitable for transplant after they were connected to a perfusion system, which has implications for human resources and costs associated with using it.³⁶ Messer et al³⁶ employed a matched-cohort design to account for important confounders, strengthening the analysis. A further strength of the evidence is that the immunosuppressive regimen and clinical standard of care remained consistent over the course of the study so as to not introduce further potential confounding in the form of optimizations in clinical care.

The comparative evidence is limited in that it does not strictly confirm noninferiority or equivalence of DCD and NDD cardiac transplant outcomes. Additionally, the available evidence is not from randomized controlled trial study design. Only secondary outcome analyses were adjusted for multiple comparisons and adjusted *P* values were rarely reported. It is possible that some of the associations might be spurious (i.e., type I error).⁴⁵ Comparisons are also plagued by low power due to small sample sizes and low event rates, which is a pervasive challenge in generating evidence for rare interventions such as solid organ transplantation.⁴⁶ A further challenge to adequate power is that heart transplant is a highly effective treatment and thus it is difficult to demonstrate an incremental benefit. The most powerful study design to measure outcomes would be a randomized controlled trial (RCT). However, it is unlikely to ever be possible to conduct an RCT comparing outcomes of DCD versus NDD heart transplants because organ allocation is complex and beyond researchers' control and patient preference plays a role.⁴⁶

The Organ Care System Heart portable normothermic cardiac perfusion system is not yet approved by a North American regulatory body (i.e., the FDA or Health Canada). We designed our systematic review deliberately to be inclusive of all study designs after an a priori observation of sparse published clinical studies. Although our ability to draw firm conclusions from case series is limited, these early studies may catalyze further investigation into practices (e.g., DCD heart transplant for patients bridged with LVAD) via methods that are more systematic. Machine perfusion is an active area of research and more perfusion systems are likely to come to the market over time.

Ongoing Studies

We became aware of one relevant study that was expected to be published in the second half of 2018. Our understanding is that the study will report on 23 recipients of DCD heart transplant using the Organ Care System Heart portable normothermic cardiac perfusion system at St. Vincent's Hospital, Sydney, Australia. We contacted the authors and this study is anticipated to update the case series of three patients by Dhital et al,³⁹ which is included in this health technology assessment. At the time of writing of this HTA, the study is yet to be published.

Conclusions

DCD heart transplantation using a portable normothermic cardiac perfusion system to preserve and transport the donor heart:

- Resulted in similar recipient survival at 30 days, 90 days, and 1 year after transplant as NDD heart transplant (GRADE: Very Low)
- Required similar levels of mechanical or inotropic support in the early post-operative period, as well as similar ICU and hospital length of stay as NDD heart transplant (GRADE: Very Low)
- Resulted in better cardiac output than NDD hearts in the early post-operative period (GRADE: Very Low)

ECONOMIC EVIDENCE

Research Question

What is the cost-effectiveness of using a portable normothermic cardiac perfusion system for preservation of adult donor hearts after cardiocirculatory death compared with cold storage of hearts donated after neurological determination of death?

Methods

Economic Literature Search

We performed an economic literature search on April 4, 2018, to retrieve studies published from January 1, 1998, until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for literature search strategies, including all search terms.

Inclusion Criteria

- English-language full-text studies published between January 1, 1998, and April 4, 2018
- Individual-level economic evaluations conducted alongside randomized controlled trials (i.e., trial-based) or economic analyses based on decision analytic models (i.e., model-based) that:
 - Included adults indicated for heart transplant
 - Compared a portable normothermic cardiac perfusion system to cold static storage of hearts donated after neurological determination of death (NDD)

Exclusion Criteria

- Editorials, case reports, conference abstracts, and commentaries
- Cost of illness studies

Outcomes of Interest

- Incremental costs
- Incremental effectiveness outcomes (e.g., incremental quality-adjusted life-years)
- Incremental net benefit
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. The

reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.⁴⁷ We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly or partially applicable.

Results

Literature Search

The economic literature search yielded 62 citations published between January 1, 1998, and April 4, 2018, after removing duplicates. We excluded a total of 61 articles based on information in the title and abstract. We obtained the full text of one potentially relevant article for further assessment; this study met the inclusion criteria. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

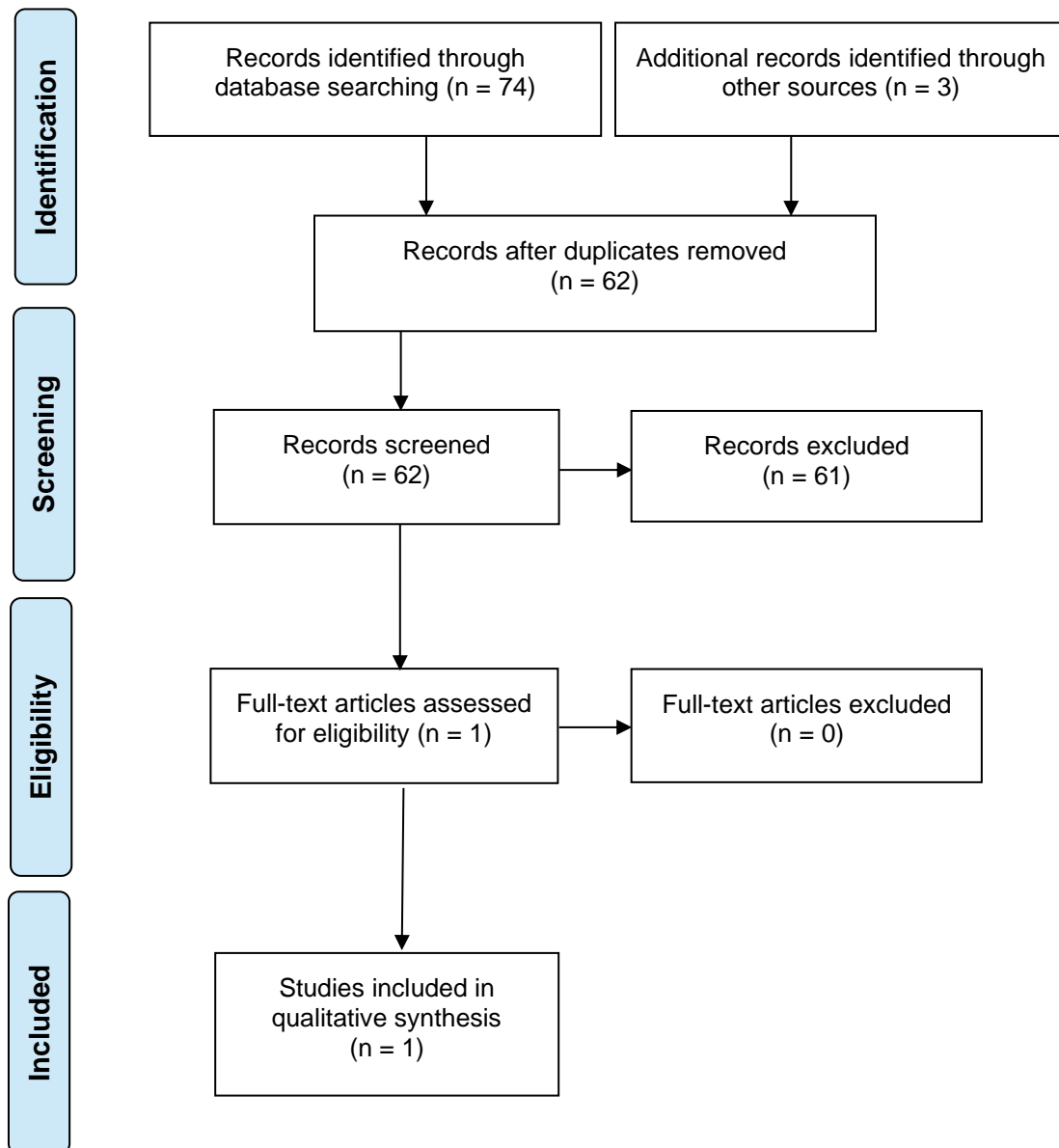


Figure 2: PRISMA Flow Diagram—Economic Search Strategy

Source: Adapted from Moher et al, 2009⁴¹

Overview of Included Economic Study

Table 7 summarizes the included study. The New South Wales Ministry of Health⁴ (Australia) conducted a cost–utility analysis using a semi-Markov model.⁴ The standard of care was cold storage for hearts from NDD and the comparator was a normothermic cardiac perfusion system for either donation after cardiocirculatory death (DCD) hearts or donor hearts from NDD in addition to standard care. The costing perspective was from the Australian government health care payer, and all costs and outcomes were discounted at 5%. The time cycle was 1 month, and the model had a lifetime time horizon. The model assumed that the wait time for heart transplant would decrease due to the availability of DCD hearts. Patients could receive medical management or have a ventricular assist device (VAD) implanted while on the wait list. The mean costs per person were \$312,328 AUD for the standard of care and \$349,990 AUD for the comparator, yielding an incremental cost of \$37,662 AUD. The mean quality-adjusted life-year (QALY) per person was 6.11 for standard of care and 6.50 for the comparator, yielding an incremental gain of 0.38. In turn, the incremental cost-effectiveness ratio (ICER) was \$97,845 per QALY gained. This was higher than a willingness to pay threshold of \$50,000 AUD per QALY gained.

Table 7: Results of Economic Literature Review—Summary

Author, Year, Country of Publication	Study Design and Perspective	Population	Intervention and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
New South Wales Ministry of Health, 2017, Australia ⁴	Type of economic analysis: cost-utility analysis Study design: semi-Markov model Perspective: Australian government health care payer Discount rate: 5%	People on a waiting list for heart transplant	Interventions: (1) portable normothermic cardiac perfusion system for hearts from NDD, and (2) DCD hearts Comparator: cold storage of hearts from NDD	Total QALYs (mean per person), intervention vs. comparator: 6.50 vs. 6.11	Currency: Australian dollars (AUD) Cost year: NR Total costs (mean per person), intervention vs. control: \$349,990 vs. \$312,328	ICER: \$97,845 AUD per QALY gained

Abbreviations: DCD, donor after cardiocirculatory death; ICER, incremental cost-effectiveness ratio; NDD, neurological determination of death; NR, not reported; QALY, quality-adjusted life year.

Applicability of the Included Study

Appendix 3 lists the results of the applicability checklist for economic evaluations. The single included study was deemed not applicable to the research question and not relevant to the Ontario setting (i.e., it used a perfusion system for NDD hearts).

Discussion

We identified one economic evaluation comparing a portable normothermic cardiac perfusion system to static cold storage for hearts from NDD. The intervention included the use of hearts from NDD, and patients on the transplant waitlist could receive a VAD implantation while waiting. This study was not applicable to the Ontario setting because a perfusion system is not planned for use on hearts from NDD donors. Additionally, the study represented procedures and costs associated with the health care system in Australia.

Conclusions

We identified one economic study comparing the cost-utility of a portable normothermic cardiac perfusion system with NDD or DCD hearts to cold storage in adults awaiting heart transplants. However, it was not applicable to the Ontario context.

PRIMARY ECONOMIC EVALUATION

A portable normothermic cardiac perfusion system for DCD hearts would most likely be used in addition to the current practice (i.e., static cold storage preservation of hearts from NDD donors). Our clinical and economic evidence reviews did not identify moderate or high-quality evidence on the outcomes of using a perfusion system for DCD hearts. Given the lack of clinical and economic evidence on long-term outcomes to inform a formal cost-effectiveness analysis, we did not pursue a full primary economic evaluation but performed only a budget impact analysis.

BUDGET IMPACT ANALYSIS

Research Question

From the perspective of the Ontario Ministry of Health, what is the 5-year net budget impact of publicly funding a portable normothermic cardiac perfusion system for DCD heart transplantation in Ontario's waitlist recipients?

Methods

Analytic Framework

The net budget impact of a portable normothermic cardiac perfusion system for DCD hearts was estimated based on the cost difference between two scenarios: the current scenario, which is current clinical practice without DCD heart transplant (donation after NDD), and the new scenario, which is the anticipated clinical practice of transplantation of DCD hearts preserved with a perfusion system. The model schematic is shown in Figure 3.

We conducted a reference case analysis and scenario analyses. Our reference case analysis represented the analysis with the most likely set of input parameters and model assumptions. In the scenario analyses, we explored how the results are affected by varying input parameters and model assumptions.

Interventions

We compared the net budget impact of heart transplantation using DCD hearts preserved with a portable normothermic cardiac perfusion system to current practice. As mentioned previously (see Background, above), organ donation can occur after death as defined by neurological criteria (sometimes referred to as NDD) or after cardiocirculatory death (i.e., DCD).¹¹ In Ontario, NDD is the major source of organ donation (69% in 2017, DCD 30%) and the only source of donor hearts for transplantation¹³ (Trillium Gift of Life Network, written communication, March 2018). The current practice is to preserve explanted donor hearts using static cold storage, where the organ is flushed with a solution and then placed on ice and transferred to the organ recipient. The volume of solid organ transplantation in Ontario other than the heart has increased since implantation of DCD organs (such as liver, lungs, and kidneys) was introduced in 2006.¹³ However, hearts procured after DCD and stored using cold static storage are not used in Ontario due to various clinical challenges (e.g., physiological damage to the heart and lack of direct functional assessment).⁴⁸

The intervention of interest is a portable normothermic cardiac perfusion system to preserve DCD hearts. TransMedics, Inc. is currently the sole manufacturer of the system, marketed under the brand name Organ Care System Heart. See Background, above, for a description of the intervention. A perfusion system may create a new donor pool and increase the number of heart transplants in Ontario.

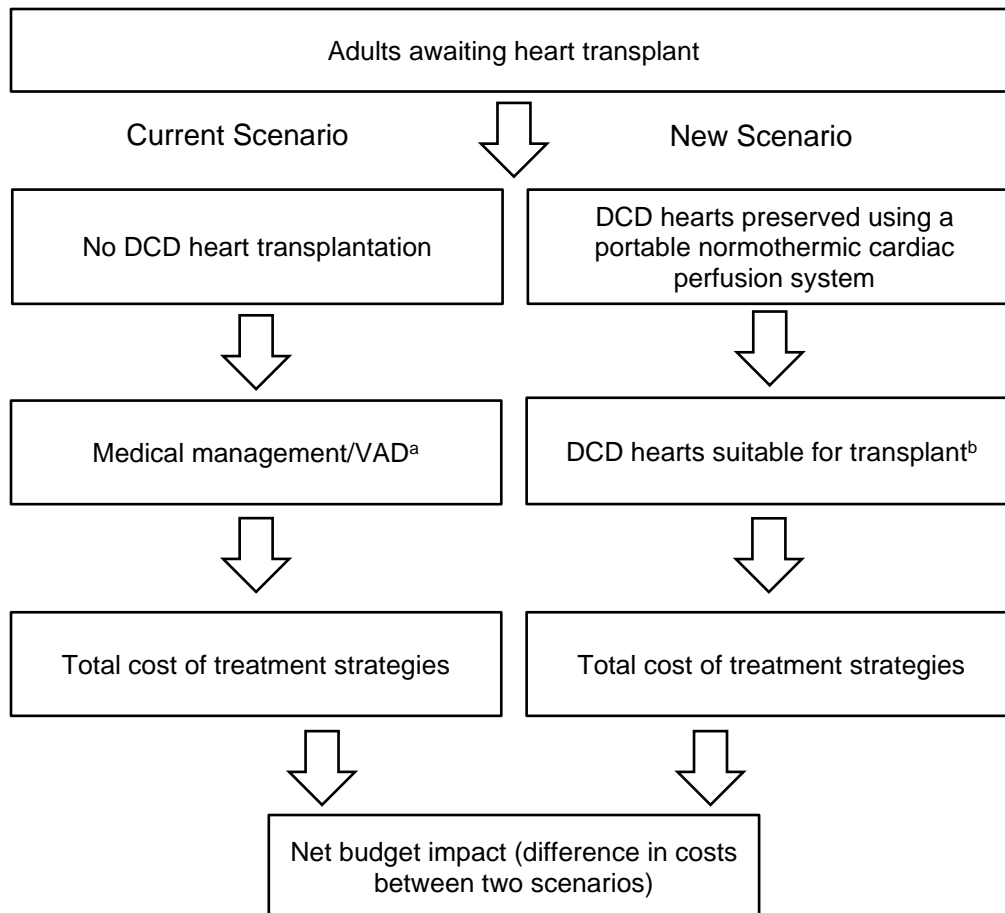


Figure 3: Budget Impact Model Schematic

^aCurrent scenario assumes that recipients waited one additional year for heart transplant (NDD) than recipients in the new scenario. They were managed with medications and a ventricular assist device while waitlisted.

^bAssumes 30% of DCD hearts in year 1 and 40% of DCD hearts in years 2–5 will be determined suitable for transplant. The proportion of DCD hearts instrumented on a normothermic cardiac perfusion system and subsequently declined was 17%.

Key Assumptions

- The proportion of DCD hearts eligible to be assessed for heart transplant (i.e., from donors < 40 years old) was projected from estimates from the past 5 years (Trillium Gift of Life Network, written communication, March 2018)
- The proportion of assessed DCD hearts determined to be suitable for heart transplant was 30% in year 1 and increased to 40% in years 2 to 5. This increase is due to the increased familiarity of health teams with the surgical procedure and process of determining potentially suitable hearts without direct functional assessment
- DCD heart transplantation assumed direct procurement of the donor heart. In this approach, the donor heart is explanted and directly connected to a perfusion system. Since direct procurement does not allow for a functional assessment of the heart, surgeons typically rely on an assessment carried out either before death (e.g., while the potential donor is in the intensive care unit) or by surrogate markers (i.e. lactate level measurements from a perfusion system). The implantation team may decline the heart after it is connected to a perfusion system (i.e., instrumentation) for clinical reasons or due to structural damage incurred during preservation on the system

- The proportion of DCD hearts connected to (or instrumented on) a portable normothermic cardiac perfusion system and subsequently declined was 17% (i.e., use rate was 83%)³⁶
- Clinical follow-up for DCD heart transplant recipients was assumed to follow current guidelines for NDD heart transplants
- Transplant recipients are assumed to be compliant with all follow-up medical care
- The recipient in the future scenario received a DCD heart transplant in year 1. The same person in the current scenario was assumed to be on the waiting list for 1 additional year. During this time (i.e., year 1), the person would be managed with medications and VAD (as the bridge to transplant). After that waiting period, the person would receive an NDD heart transplant (year 2)
- The outcomes of DCD and NDD heart transplant were assumed to be equivalent 1 year after transplant

Target Population

The target population included adults awaiting heart transplants who are willing to receive a DCD heart in Ontario. We forecasted the volume in the next 5 years using information provided by the Trillium Gift of Life Network. Table 8 lists the expected volume of intervention from years 1 to 5. The change in the number of DCD hearts eligible to be assessed for heart transplant (i.e., from eligible DCD donors < 40 years) was based on estimates from the past 5 years. We arrived at our estimate after consultation with clinical experts (i.e., cardiologists, cardiac surgeons) due to a lack of published evidence. We assumed 30% of DCD hearts in year 1 and 40% for years 2 to 5 would be eligible for transplant to reflect increased clinical experience in identifying hearts potentially suitable for transplant. All model assumptions were validated by clinical experts and TransMedics Inc.

Current Intervention Mix

There is no published clinical evidence or consensus from clinical experts on how the availability of DCD hearts would change the wait time for heart transplants in Ontario. To address this shortcoming, we made a simplified assumption in the current scenario that patients would wait approximately 1 year and then would receive an NDD heart transplant. This assumption could be explained by historic wait times in Ontario and Canada, which have averaged about 6 to 12 months (S. Smith, MD, written communication, August 18, 2018).⁴⁹ In accordance with current guidelines,^{8,50} we assumed that people on the waitlist receive treatment as usual, including medication and a VAD implant (as a bridge to transplant). Based on data provided by the Trillium Gift of Life Network with respect to the annual number and proportion of VAD implants used as a bridge to transplant between 2013 and 2017 in Ontario (Trillium Gift of Life Network, personal communication, March 2018), we projected that about 14% of all people waiting for a heart transplant received VADs while waiting for heart transplants. This estimate was tested in sensitivity analyses.

Uptake of the New Intervention

In the future scenario, a portable normothermic cardiac perfusion system was assumed to be used to preserve DCD hearts. This intervention was assumed to be used in addition to the current heart transplant practice (i.e., NDD hearts preserved using cold static storage) and would not influence the number of NDD heart transplants being carried out.¹³ The addition of a perfusion system for DCD hearts could create a new donor pool that reduces the wait time while

increasing the number of heart transplants performed each year. As mentioned above (see Target Population), we assumed the proportion of potential DCD hearts to be 30% in year 1 and 40% in subsequent years. This uptake rate was tested in a sensitivity analysis (see data in scenario analysis 1 and Table 13). We also assumed that all potential DCD hearts would be connected to a perfusion system and that 17% would subsequently be declined due to either clinical concerns identified by the transplant surgical team or to structural damage incurred during preservation.³⁶ The estimated number of DCD heart transplants was 7 in year 1, increasing to 12 in year 5 (Table 8).

Table 8: Volume of Intervention

	Year 1	Year 2	Year 3	Year 4	Year 5
DCD (all organs)	113	122	132	141	150
DCD donor < 40 years ^a	26	29	31	33	35
Potential DCD donor hearts	8	11	12	13	14
DCD hearts considered not suitable after normothermic preservation	1	1	2	2	2
Number of DCD heart transplants	7	10	10	11	12

Abbreviation: DCD, donation after cardiocirculatory death.

^aProjections estimated from data related to the number of DCD donors < 40 years, fiscal years 2013/14 to 2016/17, as provided by Trillium Gift of Life Network in March 2018.

Resources and Costs

Our budget impact analysis includes cost items incurred by the Ontario Ministry of Health. Tables 9 and 10 list the cost items, resource use, and sources of information.

TransMedics, Inc. provided the costs of the system, a perfusion liquid, and maintenance. Based on this information, we assumed a perfusion system had a service life of 3,000 hours of active use, or approximately 10 years.¹ Procurement of DCD donor hearts was assumed to be performed in accordance with the Papworth protocol using direct procurement.⁵¹ The procurement team consisted of a cardiothoracic surgical fellow (\$80,000/yr), two nurses (who do not require additional salary funding or training), a surgical recovery coordinator (\$55,000/yr), and a perfusionist (\$125,000/yr). The manufacturer provided the training. This cost was included in the cost of a perfusion system. The 30% full-time equivalent for DCD heart procurement included transportation time (from the transplant centre to the donor site, to the recipient hospital, and back to the transplant centres in Ontario), and time to carry out donor cardiectomy (removal of the donor heart). The procurement team was assumed to be the same for the future and the current scenarios. Salary information for each member of the procurement team was estimated based on information provided during expert consultation and was tested in sensitivity analysis.

Table 9: Costs of Donor Heart Preservation and Procurement Used in Budget Impact Analysis

Intervention	Cost ^a	Reference
Perfusion system ^b	357,117.75	TransMedics Inc., written communication, June 27, 2018
Disposable (per transplant) ^b	71,423.55	TransMedics Inc., written communication, June 27, 2018
Maintenance cost ^c	24,424.82	New South Wales Ministry of Health, 2017 ⁴
Cold storage	1,467.42	Trillium Gift of Life Network, 2017 ⁵²
Donor heart procurement team ^d	78,000.00	University Health Network, written communication, June 13, 2018; and Trillium Gift of Life Network, written communication, August 20, 2018

^aAll costs are reported in 2018 Canadian dollars.

^bPortable Normothermic Cardiac Perfusion System. Total amount is assumed to be incurred in year 1. The cost of a perfusion system and disposables was \$275,000 and \$55,000 USD, respectively. The calculations assumed the conversion rate of 1.298:1 for Canadian dollars⁵³

^cMaintenance costs estimated from the literature data (\$20,000 AUD, 2016, over 10 years) after adjusting for purchasing power parity and inflation ($\$20,000 \cdot 1.19 \cdot (129/125.7) = \$24,424.82$).^{54,55}

^dTotal labor cost of the procurement team was calculated as 30% of a full time equivalent ($\$80,000 \cdot 0.30$) + ($\$55,000 \cdot 0.30$) + ($\$125,000 \cdot 0.30$) = \$78,000.00.

The costs of heart implantation and postsurgical care are based on data from the Ontario Case Costing Initiative (OCCI) and the Ontario Health Insurance Plan (OHIP) Schedule of Benefits.^{56,57} Heart transplant recipients may require mechanical support via extracorporeal membrane oxygenation (ECMO) immediately after surgery. Our probability calculation was based on Messer et al³⁶ and clinical opinion. The cost of each item was based on published literature or the OCCI (Table 10).^{56,58} The influence of the cost of ECMO and probability of having ECMO in the future scenario was further tested in sensitivity analyses.

Table 10: Costs of Heart Transplant Used in Budget Impact Analysis

	Cost ^a	Reference
Primary surgeon	1,443.05	Ministry of Health and Long-Term Care, 2016 ⁵⁷
Anesthesiologist	420.28	Ministry of Health and Long-Term Care, 2016 ⁵⁷
Surgical assistant	216.72	Ministry of Health and Long-Term Care, 2016 ⁵⁷
Mechanical support using ECMO	9,712.63	St-Onge et al, 2015 ⁵⁸
Post-surgical in-patient care	136,312.77	Ministry of Health and Long-Term Care, 2017 ⁵⁶

Abbreviation: ECMO, extracorporeal membrane oxygenation.

^aAll costs are reported in 2018 Canadian dollars.

Individuals waiting for heart transplant were managed using the recommended pharmacological regimen^{49,50} for end-stage heart failure. Cost was based on the Ontario Drug Benefit Formulary.⁵⁹ We used the average cost of drugs within the same class (e.g., beta blocker; detailed in Appendix 4). We based the cost and probability of hospitalization or death due to delayed heart transplant in those on medication management on the OCCI (cost) and published literature (probability) (Tables 11 and 12).^{56,60,61} The cost of a VAD implantation as the bridge to transplant per case funding was based on data available in our 2016 health technology

assessment.⁵ The cost of perfusion system and surgery per case funding was estimated to be about \$182,600 and the professional service cost per person was estimated to be about \$2,800, yielding a total cost for a VAD procedure of about \$185,400 (Table 11). Annual per-person outpatient costs (for those who survive the procedure) was about \$18,923.

Follow-up medical care after discharge was assumed to be the same for DCD heart transplants as for NDD and followed the current practice for transplants using NDD hearts.⁴⁹ Appendix 4 lists the types and frequencies of clinical consultation and investigation after discharge based on the recommended schedule.⁴⁹ The cost of each item was based on the OHIP Schedule of Benefits⁵⁷ and the annual cost was estimated by summing all components in a specific year after transplant. The type of medication included in the immunosuppression regimen was based on clinical opinion (L. Mielniczuk, written communication, June 21, 2018) and its cost was based on the Ontario Drug Benefit Formulary.⁵⁹ For values that vary depending on patient characteristics or transplant outcome (e.g., dosage, duration of immunosuppression therapy, etc.), we used the median value of a clinically feasible range. For example, the loading phase of the immunosuppression regimen typically lasts 3 months to 1 year, so we assumed that all transplant recipients took the regimen at the loading phase dosage for 7 months and at the maintenance phase dosage for the duration of the transplant. We assumed that all transplant recipients were compliant with all recommended follow-up care. The costs of in-patient care associated with each type of adverse event (e.g., hemofiltration, implant rejection, etc.) were based on the Ontario Case Costing Initiative (Table 11).⁵⁶ All costs are expressed in 2018 Canadian dollars, converted using Purchasing Power Parity and Consumer Price Index from Statistics Canada (and annual exchange rate from the Bank of Canada where necessary).⁵³⁻⁵⁵

Table 11: Annual Costs Used in Budget Impact Analysis: Routine Clinical Care Before and After Heart Transplant

	Annual Cost ^a	Reference
While on waitlist		
Medication	4,343.80	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
VAD (BTT): implantation and professional fees per case funding	185,400.00	Health Quality Ontario, 2016 ⁵
VAD (BTT), outpatient costs post-implant	18,923.00	Health Quality Ontario, 2016 ⁵
Cardiologist consultation	314.00	Ministry of Health and Long-Term Care, 2016 ⁵⁷
Routine clinical tests	656.41	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; 2017 ⁶²
Hospitalization due to heart failure	8,914.49	Ministry of Health and Long-Term Care, 2017 ⁵⁶
Year 1 after discharge		
Immunosuppression medication	12,964.09	Ministry of Health and Long-Term Care, 2016; ⁵⁹ L. Mielniczuk, written communication, June 21, 2018
Routine clinical tests	4,012.26	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Physician visits	2,632.20	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹

	Annual Cost ^a	Reference, Year
Year 2 after discharge		
Immunosuppression medication	9,939.79	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; L. Mielniczuk, written communication, June 21, 2018
Routine clinical tests	270.98	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Physician visits	259.65	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Year 3 after discharge		
Immunosuppression medication	9,939.79	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; L. Mielniczuk, written communication, June 21, 2018
Routine clinical tests	282.04	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Physician visits	259.65	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Year 4 after discharge		
Immunosuppression medication	9,939.79	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; L. Mielniczuk, written communication, June 21, 2018
Routine clinical tests	260.74	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Physician visits	259.65	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Adverse events (per event)		
Hemofiltration	24,420.72	Ministry of Health and Long-Term Care, 2017 ⁵⁶
Acute/treated rejection	12,564.42	Ministry of Health and Long-Term Care, 2017 ⁵⁶
Renal transplant	36,349.88	Ministry of Health and Long-Term Care, 2017 ⁵⁶

Abbreviation: VAD (BTT), ventricular assist device as a bridge to transplant.

^aAll costs are reported in 2018 Canadian dollars.

Inputs: Probabilities of Adverse Events

Table 12 presents input values associated with the probabilities of potential complications or adverse events of the medical management and VAD during the waitlist period, after heart transplant surgery, and after discharge. Most of these estimates were reported in the clinical review (see Adverse Effects, page 25, above). We accounted for these parameters because they could affect the total costs of each scenario.

Based on the published literature, we accounted for the probability of hospitalization and/or death waitlisted people, who are being treated with medication or VAD.^{5,60,61}

Immediately after surgery, the recipient may require mechanical support via ECMO. We assumed a probability based on Messer et al³⁶ and clinical opinion (see Table 12). This was further tested in our sensitivity analysis. The probabilities of death, acute rejection, and hemofiltration were mostly based on the findings of Messer et al,³⁶ discussed in detail in our clinical review (Tables 2–4, pages 21–23). Both scenarios were assumed to have same survival

for 1 year after surgery.³⁶ For this input value, we assumed and used currently available estimates of death post-heart transplant in Ontario of 9.4%.⁴⁹

Due to the lack of published evidence on long-term outcomes post-discharge for DCD heart transplants, we assumed that the type and frequency of adverse events beyond 1 year post-discharge were the same between DCD and NDD heart transplants (L. Mielniczuk, written communication, May 7, 2018; C. Payne, written communication, May 17, 2018). Thus, based on data from NDD hearts, we assumed probabilities for acute rejection and renal transplant after discharge of 9% and 0.2%, respectively.⁶³ Mortality in the subsequent years after discharge is small (less than 4%).⁴⁹ Given the small number of anticipated DCD heart recipients, and for simplicity, we assumed no impact of mortality on post-transplant costs.

Table 12: Probability of Adverse Events Used in Budget Impact Analysis

	Current Scenario	Future Scenario	Reference, Year
While on Waitlist			
Death, medical management	0.053	NA	Burnett et al, 2017 ⁶⁰
Death, VAD	0.19	NA	Health Quality Ontario, 2016 ⁵
Hospitalization due to heart failure	0.039	NA	McMurray et al, 2014 ⁶¹
Post-surgery			
Mechanical support using ECMO	0.04	0.30	Messer et al, 2017 ³⁶ and assumption
Death	0.094 ^a	0.094 ^a	Messer et al, 2017 ³⁶ ; Trillium Gift of Life Network, 2018 ⁴⁹
Acute/treated rejection	0.58	0.36	Messer et al, 2017 ³⁶
Hemofiltration	0.27	0.36	Messer et al, 2017 ³⁶
Years 1 and 2 after discharge^a			
Acute/treated rejection	0.09	0.09	Lund et al, 2014 ⁶³
Renal transplant	0.002	0.002	Lund et al, 2014 ⁶³
Years 3 and 4 after discharge^a			
Acute/treated rejection	0.09	0.09	Lund et al, 2014 ⁶³
Renal transplant	0.002	0.002	Lund et al, 2014 ⁶³

Abbreviations: ECMO, extracorporeal membrane oxygenation; VAD, ventricular assistive device.

^aOur assumption that survival outcomes would be the same in both scenarios was based on the results of the clinical evidence review and on the available data from Trillium Gift of Life Network.⁴⁹

Analysis

Reference Case

The net budget impact was estimated as the difference in cost between the current and future scenarios. The cost of the future scenario was estimated by combining the cost of new heart transplantation operations each year and the costs of follow-up medical care for heart recipients who survived up to that year based on parameter inputs from Tables 11 and 12. For example, the year 2 budget impact included the costs of DCD heart transplantation and post-transplant

care that occurred in year 2, plus the costs of follow-up care for individuals who received a heart transplant in year 1 and survived to year 2.

We assumed that the same individuals who received DCD heart transplants in a specific year in the future scenario waited for 1 year to receive NDD heart transplants in the current scenario. While the individuals were on the transplant wait list, they received pharmacological management and VAD. In the current scenario, the budget impact in year 2 would include both the cost of an NDD heart transplant and post-surgical care for those who were on the wait list in year 1, as well as the cost of hospitalization due to heart failure and costs of medication and VAD for those new to (i.e., in their first year on) the waitlist. All analyses were carried out using Microsoft Excel 2016.

Sensitivity Analyses

Our analyses employed assumptions due to uncertainties in the evidence and lack of implementation of DCD in Ontario. We explored changes to the estimated reference case net budget impact by testing our assumptions in three scenarios and additional sensitivity analyses. Our three scenario analyses quantified the net budget impact for:

- Greater availability of DCD hearts
- Target population with advanced heart failure where heart transplantation is clinically indicated, but patients are not eligible for or do not wish to receive a VAD
- A negotiated financial agreement with the manufacturer

We also conducted seven additional deterministic sensitivity analyses to address uncertainty around input value. We assumed the following:

- Greater probability of receiving a VAD as a bridge to transplant
- Optimistic post-transplant outcomes
- Inclusion of all labour costs
- Higher costs of the ECMO procedure
- Changes in the cost of the DCD procedure with respect to redistribution of the cost of disposables and of perfusion system maintenance
- Possibility of medication cost sharing
- Gradual annual increase in the procedure uptake

Scenario Analyses

Scenario Analysis 1: Greater Availability of DCD Hearts. The addition of DCD hearts was assumed to increase overall heart transplantation by 20%.⁴⁸ The number of heart transplant operations using DCD hearts were estimated using the assumptions described in Target Population, above. We based our forecasted number of NDD hearts on trends from the past 10 years, provided by the Trillium Gift of Life. Table 13 describes the expected volume of heart transplants.

Table 13: Expected Number of Heart Transplants by Donor Type

	Year 1	Year 2	Year 3	Year 4	Year 5
NDD heart transplants	91	94	97	101	104
Potential DCD donor hearts	18	19	20	20	21
DCD hearts considered not suitable after normothermic preservation	3	3	3	3	4
Number of DCD heart transplants	15	16	17	17	17

Abbreviations: DCD, donation after circulatory death; NDD, neurological determination of death.

Scenario Analysis 2: Target Population With Advanced Heart Failure Where Heart Transplantation Is Clinically Indicated, But Patients Are Not Eligible for or Do Not Wish to Receive a VAD. Given the novelty of the DCD heart transplant procedure in Ontario, it is possible that in the first few years after adoption, the target population will be Ontario recipients with advanced heart failure where heart transplantation is clinically indicated, but who do not qualify for or do not wish to receive a VAD. Scenario 2 describes the net budget impact for this selected target population, accounting for the costs of medical management solely for those on a waitlist.

Scenario Analysis 3: A Negotiated Financial Arrangement With the Manufacturer. The hospital is assumed to lease a perfusion system from the manufacturer contingent on continuous purchase of disposables (i.e., cartridges and perfusion liquid) from the manufacturer.

Additional Sensitivity Analyses

We conducted the following sensitivity analyses to estimate the impact of uncertainty around the following input parameter values:

Analysis 1: Greater Probability of Receiving a VAD as a Bridge to Transplant. Assumes a 1.5-times (analysis 1a) and 3-times (analysis 1b) higher probability of receiving a VAD while waiting for a heart transplant than the value used in the reference case analysis (14%); namely, 21% and 42%, respectively.

Analysis 2: Optimistic Post-transplant Outcomes. Assumes the same probability of transplant rejection, hemofiltration, and use of ECMO post-surgery between the current and future scenarios, with optimistic values of 36% for transplant rejection and hemofiltration and 4% for ECMO.³⁶

Analysis 3: Inclusion of All Labour Costs. Labour costs include an additional \$69,000 for two nurses (30% FTE, at a labour cost of \$115,000 per year), who are part of the procurement and surgical teams.

Analyses 4a and 4b: Higher Costs of ECMO. Assumes a 1.5- (analysis 4a) and 5-times (analysis 4b) higher costs for using ECMO, compared with the approximate \$10,000 cost in the reference case analysis.

Analysis 5: Changes in the Cost of the DCD Procedure With Respect to the Redistribution of the Cost of Disposables and of Perfusion System Maintenance. Assumes an increase in the cost of disposables from \$55,000 to \$65,000 USD and about a 3-times decrease in the maintenance perfusion system costs from the reference case of about \$24,000 CAD). This analysis could potentially account for future changes in the financial agreement with the manufacturer.

Analysis 6: Possibility of Medication Cost Sharing. Our reference case analysis assumed that the medication cost was fully covered by the Ontario Ministry of Health through the Trillium Drug Program.⁶⁴ This approach ensures that all people on a transplant list are guaranteed to receive the medications needed to enable successful post-transplant outcomes.⁶⁵ This approach is also in accord with the current guidelines for people waiting for solid organ transplant.⁶⁶

In our sensitivity analyses, we explore changes in the net budget impact in the event of a cost-sharing arrangement between public and private insurers. The possible percentage of cost-sharing between a third-party public payer and private insurers in Ontario is unclear.^{65,67} Some recent research suggests that Ontario does not have an established cost-sharing policy between public and private coverage for high cost medications.⁶⁷ Therefore, we explored changes in the net budget impact and potential amount of cost-savings possible if the public coverage of medication costs was 10% (analysis 6a), 25% (analysis 6b), 50% (analysis 6c), or 75% (analysis 6d), compared with full (100%) medication cost coverage assumed in the reference case analysis.

Analysis 7: Gradual Annual Increase in the Procedure Uptake. Our reference case analysis assumed an uptake of 30% in year 1 (n = 7) and an uptake in subsequent years of 40% (n = 12 in years 2–5). This increase represents an additional 49 DCD heart transplants over 5 years. In this analysis, we assumed an increase of 10% per year in procedure uptake for next 5 years (from 10% in year 1 [n = 2] to 50% in year 5 [n = 15]), resulting in 40 additional DCD heart transplants.

Results

Reference Case

Table 14 describes the results of the budget impact analysis of publicly funding a portable normothermic cardiac perfusion system for DCD heart transplants. Based on the number of DCD donors < 40 years old in the past 5 years and the estimated number of potential DCD heart transplants in the next 5 years (ranging from 7 in year 1 to 12 in year 5), we estimated that the budget impact in the future scenario would be about \$2.26 million in year 1, increasing to \$3.55 million by year 5. The cost of the current scenario in year 1 was lower (compared to the total costs estimated for year 1 in the future scenario), at about \$228,000, which represents the costs associated with LVAD and medication incurred while people were on the wait list. In the current scenario, the total cost increased from about \$1.57 million in year 2 to about \$2.49 million in year 5. The net budget impact was \$2.03 million in year 1, and averaging \$0.89 million in years 2–5 (people in both scenarios, received heart transplants during this period). Consequently, a total net budget impact over the next 5 years amounted to about \$5.61 million.

Table 14: Results of Reference Case Budget Impact Analysis

	Total Budget Impact ^a					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current scenario	228,049	1,572,654	2,192,746	2,353,060	2,492,472	8,838,980
Future scenario	2,261,825	2,577,750	2,852,252	3,205,888	3,548,771	14,446,486
Net budget impact	2,033,776	1,005,097	659,506	852,828	1,056,299	5,607,506

^aAll costs are reported in 2018 Canadian dollars.

Figure 4 shows the annual net budget impact broken down by type of cost. As expected, the annual net budget impact is mostly explained by costs incurred from the heart transplant, procedure, and perfusion system. Compared with current practice, a perfusion system for DCD heart transplants may result in some cost offsets over time (on average, about \$195,000 yearly). These cost savings result from possible reductions in other types of costs such as those associated with VAD implants and post-transplant complications (e.g., acute rejection). Given the limited evidence on additional clinical benefits of DCD heart transplant over current practice, the amount of cost savings needs to be interpreted with caution.

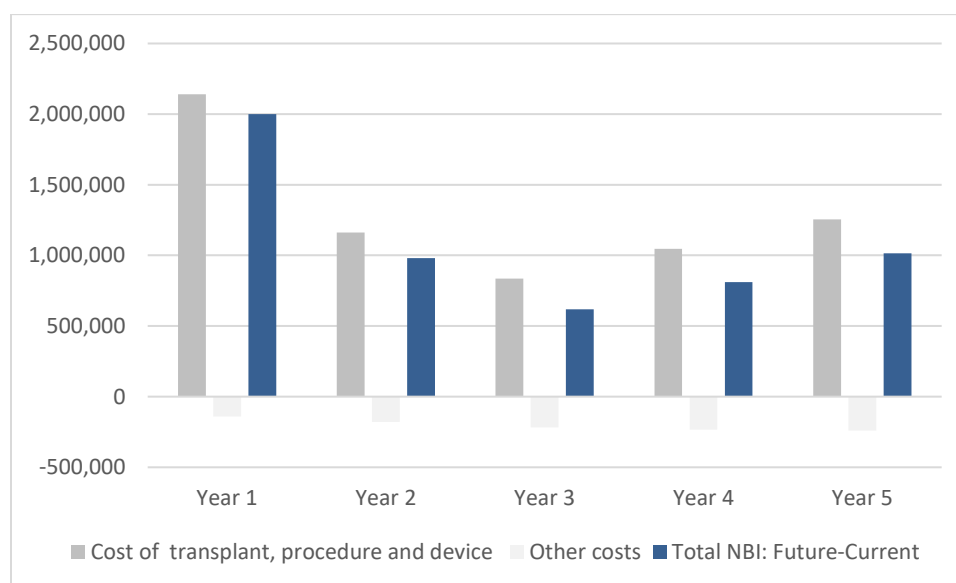


Figure 4: Net Budget Impact—Major Cost Components

Abbreviation: NBI, net budget impact.

Sensitivity Analyses

Scenario Analysis 1: Greater Availability of DCD Hearts

We estimated the net budget impact if the availability of DCD heart transplants increased the overall volume of heart transplants by 20%, which is approximately 1.5 to 2.0 times the number of DCD heart transplants in the reference scenario. Table 15 summarizes the budget impact of the current and future scenarios. The net budget impact was \$4.19 million in year 1 and averaged about \$1.53 million in years 2 to 5, yielding a total 5-year net budget impact of about \$10.30 million.

Scenario Analysis 2: Heart Transplantation Is Indicated, but Target Population Not Eligible for a VAD

If a portable normothermic cardiac perfusion system for DCD heart transplants is done solely in people with advanced heart failure where heart transplantation is clinically indicated but who do not qualify for or do not wish to receive a VAD, the net budget impact would increase as compared to the reference case. The budget impact would be about \$2.23 million in year 1 and, on average, about \$1.42 million in years 2 to 5, yielding a total 5-year net budget impact of about \$7.91 million (Table 15).

Scenario Analysis 3: A Negotiated Financial Arrangement With the Manufacturer

If the manufacturer and the hospital reach a financial arrangement regarding a lease of a perfusion system, this would only affect the year 1 budget impact of the future scenario (Table 15), reducing it to \$1.68 million. The budget impact of the future scenario is the same as for the reference case estimate in subsequent years. Therefore, the total 5-year net budget impact for the future scenario was slightly smaller than that estimated for the reference case, about \$5.25 million.

Table 15: Results of the Budget Impact Scenario Analyses

	Total Budget Impact ^a					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Reference case analysis						
Net budget impact	2,033,776	1,005,097	659,506	852,828	1,056,299	5,607,506
Scenario 1^b						
Current	297,678	2,616,697	3,025,261	2,835,587	2,881,126	11,656,349
Future	4,483,009	4,344,981	4,394,996	4,161,015	4,569,549	21,953,550
Net budget impact	4,185,331	1,728,284	1,369,735	1,325,428	1,688,423	10,297,201
Scenario 2^c						
Current	37,200	1,302,669	1,732,952	1,846,760	2,138,257	7,057,837
Future	2,267,528	2,715,947	2,990,449	3,320,063	3,678,762	14,972,749
Net budget impact	2,234,992	1,413,278	1,257,497	1,473,303	1,540,505	7,914,912
Scenario 3^d						
Current	228,049	1,572,654	2,192,746	2,353,060	2,492,472	8,838,980
Future	1,904,707	2,577,750	2,852,252	3,205,888	3,548,771	14,089,368
Net budget impact	1,676,658	1,005,097	659,506	852,828	1,056,299	5,250,388

Abbreviations: DCD, donation after circulatory deaths; VAD, a ventricular assist device as bridge to transplant.

^aAll costs are reported in 2018 Canadian dollars.

^bGreater availability of DCD hearts

^cTarget population with advanced heart failure where heart transplantation is clinically indicated, but patients are not eligible for or do not wish to receive a VAD. This model may not take into account current organ sharing agreements across Canada (S. Smith, written communication, October 8, 2018).

^dA negotiated financial arrangement from the manufacturer.

Additional Sensitivity Analyses

Appendix 5 and Figure 5 present the results of seven sensitivity analyses that addressed uncertainty around some input parameter values used for the calculation of the net budget impact. Below, we briefly summarize our findings:

- Analysis 1: assuming a probability of receiving VAD that is 1.5 times and 3 times higher (21% and 42%), than in the reference case (14%), we found a decrease in the total 5-year net cost of \$4.73 and \$3.44 million, respectively, compared with the estimated \$5.61 million in the reference case analysis
- Analysis 2: assuming a similar probability of rejection, of hemofiltration, and of the use of ECMO after surgery between the current and future scenarios, the total 5-year net cost slightly decreased to about \$5.60 million
- Analysis 3: considering higher labor costs (including additional costs incurred for the nurse salaries), we estimated a 5-year net cost of \$6.30 million, an increase over the reference case cost of \$5.61 million
- Analysis 4: assuming 1.5 times and 5 times greater costs of using ECMO compared with the reference case (approximately \$10,000), the 5-year net cost increased to \$5.68 million and \$6.19 million, respectively, over the reference case cost of \$5.61 million
- Analysis 5: if the cost of disposables were higher and the cost of maintenance associated with a portable normothermic cardiac perfusion system for DCD heart transplant were lower (about \$84,410 and about \$8,000, respectively), then the total 5-year net cost would increase to about \$6.34 million compared with the reference case of \$5.61 million
- Analysis 6: a limited public coverage of medication costs of 10%, 25%, 50%, or 75% (Appendix A5, Table A5, analyses 6a to 6d, respectively), the total costs for both scenarios would decrease compared with the reference case assumption of 100% public coverage. The average annual cost-saving was about \$221,200, \$216,800, \$209,500, and 202,200 for 10%, 25%, 50%, and 75% coverage, respectively. Each represents a greater savings than the reference case (savings of about \$195,000). Although the total costs for all scenarios showed a larger decreased than the reference case, the medication cost-sharing approach did not strongly affect changes in the total 5-year net budget impact that ranged from \$5.83 million with 10% cost sharing to \$5.67 million with 75%
- Analysis 7: assuming a gradual 10% annual increase in DCD heart transplants over next 5 years (from 10% to 50%), the 5-year net cost did not decrease substantially. We estimated it at \$5.78 million, slightly larger than the reference case cost of \$5.61 million

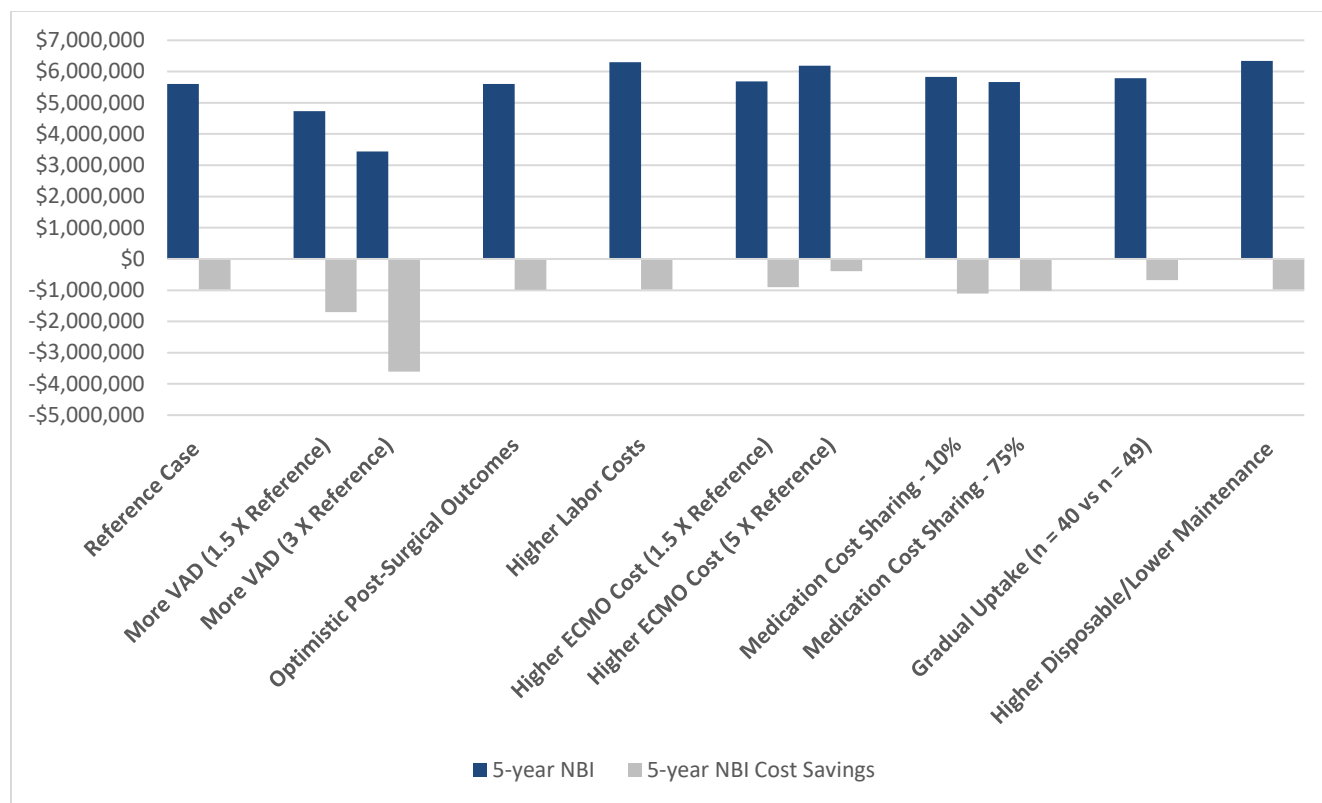


Figure 5: Net Budget Impact—Results of Additional Sensitivity Analyses

Abbreviation: ECMO, extracorporeal membrane oxygenation; NBI, net budget impact; VAD, ventricular assist device.

Discussion

Based on the number of DCD donors in the past 5 years who were less than 40 years old, we estimated that making DCD hearts available for transplantation would result in seven DCD heart transplants in year 1, increasing to 12 heart transplants in year 5. The net budget impact from the addition of DCD heart transplants was about \$2.0 million in the first year and averaged \$0.9 million per year for years 2–5, yielding a total 5-year net budget impact of about \$5.6 million.

The total 5-year net budget impact increased by about 54% if the volume of transplants approximately doubled over our time horizon. Also, if DCD heart transplantation was offered only to people with end-stage heart failure who are waiting for heart transplants but do not qualify for a VAD, the total 5-year net budget impact would increase by about 42% compared to the reference case estimate. A financial agreement with the manufacturer regarding lease of a perfusion system contingent on purchase of disposables achieves only a slight decrease in total costs.

We accounted for the differences in downstream costs (i.e., follow-up care, hospitalization) between the future and current scenarios. Also, for the reference case analysis, our target population considered all waitlist recipients in Ontario eligible for DCD heart transplants. One key limitation was the lack of published clinical evidence, particularly on the long-term outcomes of DCD heart transplants. Therefore, the impact of input parameters on heart transplant volume

and outcomes was primarily based on low-quality evidence or extrapolations from the current practice with NDD transplants. In various analyses, we explored the impact of the clinical and input parameter assumptions. A majority of these analyses, which reflected changes in costs or probabilities of procedure-related complications, did not substantially affect the overall net budget impact. The exception was the probability of receiving a VAD as a bridge to transplant and the costs and outcomes associated with this procedure during the waitlist period and in the first year after a heart transplant. Our results suggest that cost savings may be achieved if the waitlist period is reduced, thus reducing the proportion of people receiving a VAD. However, given very limited evidence on post-transplant outcomes in people receiving DCD heart transplants, the results of our reference case and sensitivity analyses should be interpreted with caution. Further, province-wide implementation may be impacted by resource capacity, including the availability of trained perfusionists.

Conclusions

Based on the findings of our analyses, we estimate that the net budget impact of a portable normothermic cardiac perfusion system for DCD heart transplantation is about \$2.0 million in the first year, and about \$0.9 million in each of years 2–5, yielding a total net budget impact of about \$5.6 million over the next 5 years.

PATIENT PREFERENCES AND VALUES

Objective

The objective of this analysis was to explore the underlying values, needs, and preferences of patients and families who have lived experience with heart transplantation and the potential impact of a portable normothermic cardiac perfusion system.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).⁶⁸⁻⁷⁰ Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are not often adequately explored in published literature, we speak directly with people who live with a given health condition, including those who may have experience with the intervention we are exploring.

A portable normothermic cardiac perfusion system is not currently used in Ontario. However, it has the potential to impact heart donation and transplantation in Ontario. Therefore, although we were unable to speak with anyone who had received a heart transplant using this system, we did speak to patients and families who may be impacted by this perfusion system, as well as people who have received heart transplants or are currently waiting for a heart transplant, and family members of willing donors who may or may not have been able to donate their heart upon death. In all, we interviewed seven patients and three family members. Gaining an understanding of the day-to-day experience of people living with heart failure, including where possible people's experiences with heart transplant, helps us assess the potential value of this intervention from the perspective of patients and caregivers.

Methods

Engagement Plan

The engagement plan for this health technology assessment focused on consultation to examine the experiences of people with heart failure who are waiting for a heart transplant, those who have received a heart donation, and donor families. Participants were also asked for their thoughts on the potential impact of a perfusion system.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of participants, as well as those of their family and

caregivers.⁷¹ The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our primary choice of an interview methodology.

Participant Outreach

We used an approach called purposive sampling,⁷²⁻⁷⁵ which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including heart failure clinics, transplant support associations, and clinicians to help spread word of this engagement activity and to contact people with experience of the intervention in question.

Inclusion Criteria

People with heart failure who are waiting for or have received a heart transplant, and family members of organ donors (including those who were unable to donate their heart upon death).

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with 10 individuals: three who were currently waiting for a heart transplant, four who had received a heart transplant, and three family members of organ donors.

All participants were able to speak to heart transplantation and the decision-making process behind seeking a transplant or donating organs. Because a perfusion system is not used in Ontario, participants were not able to comment on a perfusion system directly. However, participants were asked for their thoughts and perspectives on the potential impact of a perfusion system on heart transplantation in Ontario.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and, upon request, in a letter of information (Appendix 6). We then obtained each participant's verbal consent before starting the interview. With participants' consent, we audio-recorded the interviews and then transcribed the recordings.

Interviews were conducted by phone or in person and lasted 20 to 90 minutes. The interviews were loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.⁷⁶ Questions focused on heart failure, heart transplantation, and the considerations behind the decisions they made. We also asked participants for their perspectives on the potential impact of a perfusion system. See Appendix 7 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allows us to organize and compare information on experiences

across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.^{77,78} We used the qualitative data analysis software program NVivo⁷⁹ to identify and interpret patterns in interview data. The patterns we identified allowed us to highlight the themes and perspectives of participants surrounding heart transplantation.

Results

Lived Experience of Heart Failure

Participants who had either received or were waiting for a heart transplant spoke extensively of their experience with heart failure and its impact on their lives. They also spoke of the challenges heart failure presented on activities of daily living. The nature of their individual conditions varied widely. Some suffered from long-standing congenital heart defects, while others experienced an unexpected heart failure with an unknown cause.

Despite these differences, participants reported many commonalities when describing the impact of heart failure. Common symptoms included shortness of breath and fatigue. Their symptoms limited their ability to perform many regular activities and tasks. Often, participants reported needing to adjust or restrict work responsibilities and make accommodations for their lessened ability to perform physical tasks, noting:

I think it was about 10 years ago really was my first episode of heart failure. I was washing the car and I felt really short of breath and my lungs started to fill with fluid.

[The doctor] said all along I could have not worked anytime, but that was important to me.

You just adjusted, slowly over time you did less and less and less....I did everything upstairs before coming downstairs; [I] didn't go back upstairs until the end of the day.

You sort of change your way of life so gradually that it becomes your normal.

Participants reported that this change in ability to perform daily tasks had an emotional impact on themselves and their families. Participants reported feeling distressed, frustrated, and scared at their physical condition and the potential worsening of the condition. These emotions could become more severe as their medical condition worsened:

I started noticing that I was feeling worse and worse, like I couldn't take the stairs anymore, I had to take the elevator. So that bothered me.

I really realized how sick I was probably a year and half before my transplant. I was swimming and I got short of breath. I couldn't swim the whole length and that's when I started crying. It was like, "Holy smoke, I really am sick."

Several participants spoke of their fear for the future, given that all other treatment options were exhausted. Knowing that they required a heart transplant, but not knowing if or when one would become available; this uncertainty and fear was an added burden:

Yes, scary, because it's something we don't know what's going to happen tomorrow, what's going to be after tomorrow.

I just say in the meantime we have the faith to believe that if we left ourselves in that "atmosphere of scaring," it cannot help...so we must have encouragement that the solution is going to come as soon as possible.

Every day you're waiting...Every day you're thinking about it, and you don't know when it's going to come.

Deciding to Get On the Transplant List

We spoke with seven people who were either waiting for or had recently received a heart transplant. In each case, their heart failure was severe. Their conditions were not manageable through other medical interventions or treatments. Each spoke of the challenges of their worsening condition and the ultimate decision that a heart transplant was necessary. Participants were asked if the use of a perfusion system to transport hearts donated after cardiac death would have potentially influenced their choice.

The decision to be placed on the transplant list was significant and personal. Some people spoke of the difficulties and challenges behind that decision. They reported that it could be difficult to accept that a heart transplant, which requires major surgery with significant risk, was the only remaining option for treatment:

When you have good days, you can delude yourself to think you're going to be okay and maybe this really isn't happening and maybe I'm not as bad as they say I am. And then there are other days where I wasn't getting out of bed, and I was like, "I can't do anything. When do I go to the hospital?" So, it plays with your head.

Things just didn't get better. I did everything I was supposed to do. I tried getting on the treadmill as often as I could to try to just keep exercising what little I was allowed...if anything, my health was declining. So we decided we had to go ahead with the transplant.

It took me about a month or so to come to terms that transplant was the only way...I refused to believe it.

Participants often spoke of the trust they felt towards their medical teams, who provided guidance in making their decision to be placed on the transplant list. Often, they had suffered from heart failure for a number of years, so were familiar and comfortable with their health care providers:

I trust [the medical team] with my life. To be fair, I knew them for six years before I had to be listed...It's the team who knows that you need this if you want to still be alive and see your family grow up.

I have to rely on all these other things. I can't sweat those things I can't control. [I've] got to expect that the surgeon knows what he's doing, that my cardiologist is telling me the right things. What I can control is doing all the things they say and control my attitude and keep it positive.

Several participants were especially pragmatic in their decision-making. They spoke of wanting to extend their life, of wanting to see their families and their watch children grow older. Since heart transplant was the only remaining option, the decision was practical and relatively easy:

That was the toughest day. But, honestly, within minutes of making that decision and saying the words out loud, now it was, "Okay, everything now has to be focused on success, and what are we going to do to make sure this works?"

I mean, everybody wants to stay alive. It took a while obviously to come to grips with it, but I've got a daughter and that's basically been my driving force.

When you're told that you need to be on the transplant list, there is no other choice. And if you want to see your kids grow up, you need to be on the list. Otherwise, you'll be dead.

Deciding to Make an Organ Donation

We were able to speak to three family members of organ donors. When discussing organ donation, these participants spoke strongly of the desire to honour the wishes of their loved ones to donate their organs upon their death. The practical benefits of organ donation—how other patients could be saved through the act of donating organs—was a factor mentioned by all family members. They reported that the combination of the desire of their loved one to donate, together with the knowledge that the donation might save other lives, helped make the decision an easier one:

We made the decision quickly to fulfill [our family member's] wishes...it's tremendous to have others live a full life... A lot of people just don't have the opportunity to give.

That's the kind of person that [our family member] was; that's what they would have wanted.

Four different people were helped because of [our family member].

Some family members of donors we spoke to mentioned not knowing a great deal about organ donation and relied upon the expertise and guidance of the medical teams. The trust and comfort established with the medical team also made the decision easier to agree to organ donation:

We knew so little about organ donation...We turned it over to the medical team.

We had pretty good support from the medical team. People [went] way above and beyond what we expected.

Confusion and Distress When a Donated Heart Is Ineligible for Transplant

While family members of organ donors all spoke of the value that the organs had for potential recipients, some expressed a feeling that some organs were more important than others. Two

family members reported they felt that heart donations were of greater significance. This was due not just to its symbolic value, but also to the practical value. When it was not possible to donate the heart, family members expressed confusion and distress at this outcome. When the potential impact of a perfusion system was discussed, participants expressed the feeling that any perfusion system that could increase the potential for successful donation—to not have the organs ‘wasted’—would be of comfort and value:

I didn't understand at all [why our family member's heart could not be donated]. I thought it was a moral kind of thing. I didn't understand until later. It was upsetting for me. I know people need hearts...this was a [young,] strong heart. So it did bother me.

We're talking about a heart that was really really strong... You feel the pain for the other people who lose the organs.

Heart Transplantation and a Portable Normothermic Cardiac Perfusion System

Those people who received a heart transplant expressed appreciation for the organ donation. While the circumstances surrounding individual surgeries were different, each person interviewed related positive stories and experiences concerning the medical care and the transplantation.

An important implication of a perfusion system is that it could provide opportunities for donor hearts to be made available from patients who die of cardiac death. When this possibility was raised with those who had received a heart transplant, participants were also fairly consistent in trusting the medical team to assess the viability of the donor heart. One participant wondered, as a recipient, whether they would want to know if the heart came from a cardiac or neurological death.

The hardest part is knowing that somebody has to die in order for me to continue living, but, other than that, no, I don't really care where it comes from. They're the doctors; they wouldn't present me with an organ that wouldn't pass.

And [the viability of the heart] is one of those things for me where I had to put my—for lack of better term—faith in the medical system.

I wouldn't have thought that all through. I would have thought it would be difficult for the donor family. Then, on the other [hand], do I really want to know as a patient if it was a cardiac death or a brain death?

For those people still waiting for a heart transplant, the perceived benefit from a perfusion system was its potential to increase the number of donor hearts available. Participants expressed hope that it would increase the range of people qualified for donation, and therefore the overall number of donors, which in turn would increase the likelihood of a positive match. These participants made clear their willingness and strong need for a heart transplant. The type of heart was a decision left to the health care team:

Yeah, for sure we [would accept a heart via a perfusion system]; we are fighting for life. And my wife, she is young, so to give her a chance to survive

and see her children and her grandchildren will be the best, the best. And the best thing we can take. So, we are ready any time, and we are so prepared any time. If the donor is there, we are ready.

If you want me to still be alive, I need to have a heart transplant.

One participant said that learning of a donor condition related to heart failure may prompt them to become more educated and aware of the origin of the heart.

Discussion

Participants included people currently waiting for heart transplant or who had received a heart transplant, and family members of organ donors who may or may not have been able to donate their heart after death. We were not able to ask patients or families of their experiences or perspectives on a perfusion system because it is not currently in use in Ontario. Instead, we engaged with participants on those topics surrounding heart transplantation that may be impacted by the use of a perfusion system.

One limitation of our participant cohort is that there is a natural bias to be amenable to heart transplants. We were not able to reach anyone who was no longer on the heart transplant list, or who was not willing to accept a transplant. Those with whom we spoke did not express any ethical concerns or hesitation with organ transplantation.

Those interviewed had extensive experience with heart failure and were able to report on the impact heart failure can have on activities of daily living, as well as the emotional well-being of the patient. When considering potential heart transplant as a final treatment option for heart failure, participants spoke of the momentous and complicated nature of this decision-making process. As a group, their trust in their health care teams helped guide their decision.

Participants who had received a heart transplant generally felt that receiving a heart secured after cardiac arrest would not have caused them to reconsider accepting their donated heart. They trusted their health care teams to determine viability of the heart for donation. Several family members of donors reported placing a high value on the ability to donate the heart, even over other organs, and all expressed a desire to honour the wishes of their loved-ones. A device such as a perfusion system, which could increase the potential for successful donation, was seen to be of value.

Conclusions

Heart failure has a significant impact on the lives of patients and families. People we spoke to who have received a heart transplant or are currently on the waitlist are willing to accept a heart donated after cardiac arrest; they trust their health care team to assess the viability and appropriateness of a heart for transplant regardless of its source. Those waiting for a heart donation are hopeful that a perfusion system, if approved, will increase the range and number of heart donations. For families of organ donors, a technology that increases the chances that a heart will be suitable for transplantation provides comfort and value.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

The clinical evidence showed that outcomes for recipients of DCD hearts preserved with use of a portable normothermic cardiac perfusion system were similar to that for recipients of NDD heart transplantation, but there is uncertainty due to the limited evidence.

If public funding of adult transplantation of DCD hearts preserved with a portable normothermic cardiac perfusion system is implemented in Ontario, the province can expect an increase in the total net budget of about \$5.6 million over the next 5 years.

People who underwent a heart transplant operation did not express reservations concerning receiving hearts from DCD donors. They reported trusting their health care teams to properly identify healthy hearts suitable for transplant and were hopeful that increasing the donor pool would result in shorter wait times and greater chance of survival. Family members of people who donated hearts reported a feeling that, because they were lifesaving, heart donations give a greater sense of comfort than donations of other organs. They place value on medical technology that has the potential to increase the pool of eligible donors.

ABBREVIATIONS

DCD	Donation after cardiocirculatory death
DPP	Direct procurement and perfusion
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
NDD	Donation after neurological determination of death (also called donation after brain death)
NRP	Normothermic regional reperfusion
VAD	Ventricular assist device
WLST	Withdrawal of life-sustaining therapy

GLOSSARY

Adverse event	An adverse event is any unexpected problem that happens during or as a result of treatment, regardless of the cause or severity.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., its affordability). It is based on predictions of how changes in the intervention mix impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness analysis	Used broadly, “cost-effectiveness analysis” may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, “cost-effectiveness analysis” may refer to a specific type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years (QALYs), which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.
Direct procurement and perfusion (DPP)	A method of organ recovery after cardiocirculatory death in which the organ is explanted rapidly and then placed on a machine that continuously perfuses it with substances such as preservation solution, oxygen, and donor blood until it is implanted into the recipient.

Donation after cardiocirculatory death (DCD)	An organ donation from a person with an irreversible injury or illness but who does not meet criteria for brain death. In such cases, a diagnosis of death is determined when the heart has stopped beating (asystole), and there is no longer blood flow or a pulse for a defined period of time.
Donation after neurological determination of death (NDD)	An organ donation from a person who has experienced brain death. In such cases, a diagnosis of death is determined according to specific nationally-defined criteria, when there is an absence of neurological function after a known, irreversible cause.
Incremental cost	An incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.
Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.
Normothermic regional reperfusion (NRP)	A perfusion technique used in organ donation following cardiocirculatory death in which, after determination of cardiocirculatory death, the donor is connected to mechanical cardiorespiratory support to perfuse the organs in the thoracic cavity with substances such as preservation solution and donor blood so their function can be assessed before they are recovered.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Sensitivity analysis	<p>Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.</p>
Utility	<p>Utilities are values that represent people's preferences for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.</p>
Willingness-to-pay value	<p>A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.</p>

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: April 3, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 28, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 14>, Ovid MEDLINE(R) ALL <1946 to April 02, 2018>

Search Strategy:

- 1 Heart Transplantation/ (80560)
- 2 ((heart* or cardiac) adj1 (transplant* or graft* or allograft* or allotransplant*)).ti,ab,kf. (80855)
- 3 ((donor or donors) adj2 (cardiectomy* or heart*)).ti,ab,kf. (10074)
- 4 (((donation* or donor*) adj3 (cardiac death* or cardiocirculatory death* or circulatory death*)) or DCD or DCDD).ti,ab,kf. (8986)
- 5 Brain Death/ (21020)
- 6 (((brain* or cerebral*) adj1 (death or dead*)) or brain arrest or cerebral circulatory arrest* or irreversible coma* or DND or ((donation* or donor*) adj2 neurological death)).ti,ab,kf. (20067)
- 7 (neurological determin* adj2 death).ti,ab,kf. (73)
- 8 "Tissue and Organ Procurement"/ (124796)
- 9 "Tissue and Organ Harvesting"/ (147451)
- 10 or/8-9 (162953)
- 11 Heart/ (432011)
- 12 and/10-11 (7549)
- 13 (heart* adj2 (donation* or procur* or harvest*)).ti,ab,kf. (2412)
- 14 or/1-7,12-13 (145700)
- 15 Organ Preservation/ (16472)
- 16 Organ Preservation Solutions/ (5175)
- 17 (organ adj2 (preservation or conservation or storage)).ti,ab,kf. (7731)
- 18 ((heart or cardiac or coronary) adj2 (preserv* or storag* or viabil*)).ti,ab,kf. (7501)
- 19 Perfusion/ (100229)
- 20 ((heart or cardiac or cardio* or coronary) adj4 perfusion).ti,ab,kf. (25149)
- 21 ((machine or mechanical or continuous) adj2 perfusion).ti,ab,kf. (5810)
- 22 (((normothermic or ex-vivo or exvivo or x-vivo or xvivo or warm) adj2 (perfusion or preserv* or extracorporeal* or extra corporeal*)) or NEVP).ti,ab,kf. (5068)
- 23 (paragonix or sherpapak or lifecradle or transmedics).ti,ab,kf. (78)
- 24 or/15-23 (154267)
- 25 14 and 24 (7204)
- 26 ((ocs adj1 heart*) or (organ adj1 (care or transport) adj1 (system* or console*))).ti,ab,kf. (210)

- 27 (beating heart adj2 box*).ti,ab,kf. (3)
- 28 or/25-27 (7313)
- 29 exp Animals/ not Humans/ (14284487)
- 30 28 not 29 (3713)
- 31 (Comment or Editorial or Letter).pt. (3184563)
- 32 30 not 31 (3615)
- 33 limit 32 to yr="1998 -Current" (2613)
- 34 limit 33 to english language [Limit not valid in CDSR; records were retained] (2470)
- 35 34 use medall,coch,cctr,clhta,cleed (1015)
- 36 heart transplantation/ (80560)
- 37 ((heart* or cardiac) adj1 (transplant* or graft* or allograft* or allotransplant*)).tw,kw. (81660)
- 38 ((donor or donors) adj2 (cardiectom* or heart*)).tw,kw. (10146)
- 39 heart death/ (24346)
- 40 (((donation* or donor*) adj3 (cardiac death* or cardiocirculatory death* or circulatory death*)) or DCD or DCDD).tw,kw. (9067)
- 41 brain death/ (21020)
- 42 (((brain* or cerebral*) adj1 (death or dead*)) or brain arrest or cerebral circulatory arrest* or irreversible coma* or DND or ((donation* or donor*) adj2 neurological death)).tw,kw. (20395)
- 43 (neurological determin* adj2 death).tw,kw. (77)
- 44 (heart* adj2 (donation* or procur* or harvest*)).tw,kw. (2445)
- 45 or/36-44 (163997)
- 46 organ preservation/ (16472)
- 47 heart preservation/ (1034)
- 48 (organ adj2 (preservation or conservation or storage)).tw,kw,dv. (8151)
- 49 ((heart or cardiac or coronary) adj2 (preserv* or storag* or viabil*)).tw,kw,dv. (7592)
- 50 organ perfusion/ (2308)
- 51 heart perfusion/ (7500)
- 52 ((heart or cardiac or cardio* or coronary) adj4 perfusion).tw,kw,dv. (25681)
- 53 ((machine or mechanical or continuous) adj2 perfusion).tw,kw,dv. (5852)
- 54 (((normothermic or ex-vivo or exvivo or x-vivo or xvivo or warm) adj2 (perfusion or preserv* or extracorporeal* or extra corporeal*)) or NEVP).tw,kw,dv. (5108)
- 55 organ transportation system/ (49)
- 56 (paragonix or sherpapak or lifecradle or transmedics).tw,kw,dv. (82)
- 57 or/46-56 (69485)
- 58 45 and 57 (6733)
- 59 ((ocs adj1 heart*) or (organ adj1 (care or transport) adj1 (system* or console*))).tw,kw,dv. (213)
- 60 (beating heart adj2 box*).tw,kw,dv. (3)
- 61 or/58-60 (6850)
- 62 (exp animal/ or nonhuman/) not exp human/ (10359147)
- 63 61 not 62 (4243)
- 64 Comment/ or Editorial/ or Letter/ (3143561)
- 65 63 not 64 (4083)
- 66 limit 65 to yr="1998 -Current" (3224)
- 67 limit 66 to english language [Limit not valid in CDSR; records were retained] (3028)
- 68 67 use emez (2082)
- 69 35 or 68 (3097)
- 70 69 use medall (932)
- 71 69 use emez (2082)
- 72 69 use coch (0)
- 73 69 use cctr (80)

- 74 69 use clhta (2)
- 75 69 use cleed (1)
- 76 remove duplicates from 69 (2409)

Economic Evidence Search

Search date: April 4, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 28, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 14>, Ovid MEDLINE(R) ALL <1946 to April 03, 2018>

Search Strategy:

-
- 1 Heart Transplantation/ (80567)
 - 2 ((heart* or cardiac) adj1 (transplant* or graft* or allograft* or allotransplant*)).ti,ab,kf. (80856)
 - 3 ((donor or donors) adj2 (cardiectom* or heart*)).ti,ab,kf. (10074)
 - 4 (((donation* or donor*) adj3 (cardiac death* or cardiocirculatory death* or circulatory death*)) or DCD or DCDD).ti,ab,kf. (8984)
 - 5 Brain Death/ (21020)
 - 6 (((brain* or cerebral*) adj1 (death or dead*)) or brain arrest or cerebral circulatory arrest* or irreversible coma* or DND or ((donation* or donor*) adj2 neurological death)).ti,ab,kf. (20065)
 - 7 (neurological determin* adj2 death).ti,ab,kf. (73)
 - 8 "Tissue and Organ Procurement"/ (124799)
 - 9 "Tissue and Organ Harvesting"/ (147454)
 - 10 or/8-9 (162959)
 - 11 Heart/ (432027)
 - 12 and/10-11 (7549)
 - 13 (heart* adj2 (donation* or procur* or harvest*)).ti,ab,kf. (2412)
 - 14 or/1-7,12-13 (145703)
 - 15 Organ Preservation/ (16473)
 - 16 Organ Preservation Solutions/ (5175)
 - 17 (organ adj2 (preservation or conservation or storage)).ti,ab,kf. (7733)
 - 18 ((heart or cardiac or coronary) adj2 (preserv* or storag* or viabil*)).ti,ab,kf. (7500)
 - 19 Perfusion/ (100233)
 - 20 ((heart or cardiac or cardio* or coronary) adj4 perfusion).ti,ab,kf. (25152)
 - 21 ((machine or mechanical or continuous) adj2 perfusion).ti,ab,kf. (5813)
 - 22 (((normothermic or ex-vivo or exvivo or x-vivo or xvivo or warm) adj2 (perfusion or preserv* or extracorporeal* or extra corporeal*)) or NEVP).ti,ab,kf. (5072)
 - 23 (paragonix or sherpapak or lifecradle or transmedics).ti,ab,kf. (78)
 - 24 or/15-23 (154279)
 - 25 14 and 24 (7205)
 - 26 ((ocs adj1 heart*) or (organ adj1 (care or transport) adj1 (system* or console*))).ti,ab,kf. (210)

- 27 (beating heart adj2 box*).ti,ab,kf. (3)
- 28 or/25-27 (7314)
- 29 economics/ (256421)
- 30 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (802498)
- 31 economics.fs. (402433)
- 32 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (792244)
- 33 exp "costs and cost analysis"/ (552414)
- 34 (cost or costs or costing or costly).ti. (242379)
- 35 cost effective*.ti,ab,kf. (284621)
- 36 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*).ab,kf. (186959)
- 37 models, economic/ (11214)
- 38 markov chains/ or monte carlo method/ (72024)
- 39 (decision adj1 (tree* or analy* or model*).ti,ab,kf. (36633)
- 40 (markov or markow or monte carlo).ti,ab,kf. (114964)
- 41 quality-adjusted life years/ (34954)
- 42 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (61135)
- 43 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (99725)
- 44 or/29-43 (2356324)
- 45 28 and 44 (122)
- 46 45 use medall,coch,cctr,clhta (46)
- 47 28 use cleed (1)
- 48 or/46-47 (47)
- 49 (Comment or Editorial or Letter or Congresses).pt. (3247683)
- 50 48 not 49 (47)
- 51 limit 50 to yr="1998 -Current" (32)
- 52 limit 51 to english language [Limit not valid in CDSR; records were retained] (30)
- 53 heart transplantation/ (80567)
- 54 ((heart* or cardiac) adj1 (transplant* or graft* or allograft* or allotransplant*).tw,kw. (81661)
- 55 ((donor or donors) adj2 (cardiectom* or heart*).tw,kw. (10146)
- 56 heart death/ (24346)
- 57 (((donation* or donor*) adj3 (cardiac death* or cardiocirculatory death* or circulatory death*)) or DCD or DCDD).tw,kw. (9064)
- 58 brain death/ (21020)
- 59 (((brain* or cerebral*) adj1 (death or dead*)) or brain arrest or cerebral circulatory arrest* or irreversible coma* or DND or ((donation* or donor*) adj2 neurological death)).tw,kw. (20394)
- 60 (neurological determin* adj2 death).tw,kw. (77)
- 61 (heart* adj2 (donation* or procur* or harvest*).tw,kw. (2445)
- 62 or/53-61 (163999)
- 63 organ preservation/ (16473)
- 64 heart preservation/ (1034)
- 65 (organ adj2 (preservation or conservation or storage)).tw,kw,dv. (8153)
- 66 ((heart or cardiac or coronary) adj2 (preserv* or storag* or viabil*).tw,kw,dv. (7591)
- 67 organ perfusion/ (2308)
- 68 heart perfusion/ (7500)
- 69 ((heart or cardiac or cardio* or coronary) adj4 perfusion).tw,kw,dv. (25684)
- 70 ((machine or mechanical or continuous) adj2 perfusion).tw,kw,dv. (5855)

- 71 (((normothermic or ex-vivo or exvivo or x-vivo or xvivo or warm) adj2 (perfusion or preserv* or extracorporeal* or extra corporeal*)) or NEVP).tw,kw,dv. (5111)
- 72 organ transportation system/ (49)
- 73 (paragonix or sherpapak or lifecradle or transmedics).tw,kw,dv. (82)
- 74 or/63-73 (69493)
- 75 62 and 74 (6734)
- 76 ((ocs adj1 heart*) or (organ adj1 (care or transport) adj1 (system* or console*))).tw,kw,dv. (213)
- 77 (beating heart adj2 box*).tw,kw,dv. (3)
- 78 or/75-77 (6851)
- 79 Economics/ (256421)
- 80 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (130754)
- 81 Economic Aspect/ or exp Economic Evaluation/ (427709)
- 82 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (816860)
- 83 exp "Cost"/ (552414)
- 84 (cost or costs or costing or costly).ti. (242379)
- 85 cost effective*.tw,kw. (295610)
- 86 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*).ab,kw. (194509)
- 87 Monte Carlo Method/ (57838)
- 88 (decision adj1 (tree* or analy* or model*)).tw,kw. (40389)
- 89 (markov or markow or monte carlo).tw,kw. (119944)
- 90 Quality-Adjusted Life Years/ (34954)
- 91 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (64911)
- 92 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (119142)
- 93 or/79-92 (1998719)
- 94 78 and 93 (124)
- 95 Comment/ or Editorial/ or Letter/ or conference abstract.pt. (6116040)
- 96 94 not 95 (108)
- 97 limit 96 to yr="1998 -Current" (84)
- 98 limit 97 to english language [Limit not valid in CDSR; records were retained] (76)
- 99 98 use emez (44)
- 100 52 or 99 (74)
- 101 100 use medall (27)
- 102 100 use emez (44)
- 103 100 use coch (0)
- 104 100 use cctr (1)
- 105 100 use clhta (1)
- 106 100 use cleed (1)
- 107 remove duplicates from 100 (60)

Grey Literature Search

Search date: March 22–28, 2018

Websites searched: HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit,

National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, ClinicalTrials.gov, PROSPERO, EUnetHTA, Tufts CEA Registry

Keywords used: organ care system, OCS, heart transplantation, heart transplant, normothermic, perfusion, ex vivo

Results (included in PRISMA): 2

Ongoing clinical trials: 1

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias^a Among Comparative Cohort Studies (Newcastle-Ottawa Scale³⁷)

	Selection (rrr)	Comparability (rr)	Outcome (rrr)	Overall Judgement
Messer et al, 2017 ³⁶	rrr ^b	rr	rrr	Low risk of bias

^aWe judged the treated-cohort as somewhat representative of the average heart transplant candidate instead of truly representative because the study's eligibility criteria excluded high risk candidates on waitlist (see Table 1).

^bMore "r"s on the Newcastle-Ottawa Scale indicate high quality study features and likely lower risk of bias.

Table A2: GRADE Evidence Profile for Comparison of Heart Transplant With Hearts Donated After Cardiocirculatory Death Using a Portable Normothermic Cardiac Perfusion System Versus Hearts Donated After Neurological Determination of Death

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Survival at 90 days							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low
Survival at 30 days							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low
1-year cumulative survival							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low
Post-operative mechanical/inotropic support							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low
Early graft function							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low
ICU length of stay							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low
Hospital length of stay							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Acute rejection							
1 observational (comparative cohort) ³⁶	No serious limitations ^a	Not evaluable ^b	No serious limitations	Serious limitations (-1) ^c	Undetected	NA	⊕ Very Low

Abbreviations: ICU, intensive care unit; NA, not applicable.

^aRisk of bias was judged to be low for all considerations. The full risk-of-bias assessment is presented in Table A1 (Appendix 2).

^bThe presence or absence of inconsistency cannot be definitively assessed because the evidence is derived from a single study.

^cThe study had a small sample size, did not meet the optimal information size criterion, and did not adjust all analyses for multiple comparisons nor present both adjusted and unadjusted *P* values for all.

Appendix 3: Results of Applicability Checklists for Studies Included in the Economic Literature Review

Table A3: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of a Portable Normothermic Cardiac Perfusion System

Author, Year, Country of Publication	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are estimates of relative treatment effect from the best available source?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment ^a
New South Wales Ministry of Health, 2017, Australia	Yes	No	No	Yes, Australian public health care perspective	No	Yes	Yes	No	NA

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

Appendix 4: Routine Clinical Care After Heart Transplant

Table A4: Costs Associated With Routine Clinical Care After Heart Transplant

	Dosage ^a	Frequency per Year	Annual Cost ^b	Reference
Medical management for end-stage heart failure				
Angiotensin receptor-neprilysin inhibitor	200 mg bid	NA	3837.20	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
Beta-blocker			104.97	
Carvedilol	25 mg bid	NA	177.46	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
Bisoprolol	10 mg	NA	38.11	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
Metoprolol	200 mg	NA	99.35	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
Mineralocorticoid receptor antagonists	50 mg	NA	401.63	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
Spironolactone	50 mg	NA	77.16	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
Eplerenone	50 mg		726.10	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; Ezekowitz et al, 2017 ⁵⁰
Clinical care while on wait list for heart transplant				
Infectious disease profile	NA	1	21.86	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Routine blood and urine test	NA	4	30.40	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Electrocardiogram	NA	1	11.05	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Chest x-ray	NA	1	21.30	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹

	Dosage ^a	Frequency per Year	Annual Cost ^b	Reference
Non-invasive stress test	NA	1	238.00	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Cardiac catheterization	NA	2	166.90	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Cardiologist	NA	2	314.00	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Immunosuppression regimen, year 1				
Prednisone (7 months)	20 mg	NA	18.74	Ministry of Health and Long-Term Care 2016 ⁵⁹ , L. Mielniczuk, written communication, June 21, 2018
Mycophenolate mofetil	1,000 mg bid	NA	1,083.76	Ministry of Health and Long-Term Care 2016 ⁵⁹ , L. Mielniczuk, written communication, June 21, 2018
Tacrolimus	4 mg	NA	2,605.98	Ministry of Health and Long-Term Care 2016 ⁵⁹ , L. Mielniczuk, written communication, June 21, 2018
Sirolimus	3.7 mg at mo 3–7 2.7 mg thereafter	NA	7,141.37	Ministry of Health and Long-Term Care 2016 ⁵⁹ , L. Mielniczuk, written communication, June 21, 2018
Acyclovir (1 month)	400 mg bid	NA	38.10	Ministry of Health and Long-Term Care 2016 ⁵⁹ , L. Mielniczuk, written communication,, June 21, 2018
Nystatin (1 month)	qid	NA	8.88	Ministry of Health and Long-Term Care 2016 ⁵⁹ , L. Mielniczuk, written communication, June 21, 2018
Immunosuppression regimen, years 2–5				
Mycophenolate mofetil	1,000 mg bid	NA	632.44	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; L. Mielniczuk, written communication,
Tacrolimus	1 mg	NA	1,105.73	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; L. Mielniczuk, written communication,

	Dosage ^a	Frequency per Year	Annual Cost ^b	Reference
Sirolimus	2.7 mg	NA	8,201.63	Ministry of Health and Long-Term Care, 2016 ⁵⁹ ; L. Mielniczuk, written communication,
Follow-up care after heart transplant, year 1				
Cardiologist	NA	12	1,397.00	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Family physician	NA	16	1,235.20	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Electrocardiogram	NA	1	11.05	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Echocardiogram	NA	1	208.80	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Bone mineral density test	NA	1	82.80	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Non-invasive stress test	NA	1	238.00	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Coronary angiography/ intravascular ultrasound	NA	1	471.60	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Chest x-ray	NA	4	85.20	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Immunosuppression level	NA	30	240.90	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
HLA antibody screen	NA	4	9.36	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Routine blood test	NA	20	174.40	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Complete blood count	NA	18	71.64	Ministry of Health and Long-Term Care,

	Dosage ^a	Frequency per Year	Annual Cost ^b	Reference
				2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Liver function test	NA	2	10.24	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Lipid levels	NA	1	8.27	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Heart biopsy	NA	12	2,400.00	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Follow-up care after heart transplant, year 2 or 4				
Cardiologist	NA	1	105.25	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Family physician	NA	2	154.40	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Echocardiogram	NA	1	208.80	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Immunosuppression level	NA	1	8.03	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Routine blood test	NA	2	17.44	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Complete blood count	NA	2	7.96	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Liver function test	NA	2	10.24	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Lipid levels	NA	1	8.27	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Follow-up care after heart transplant, year 3				
Cardiologist	NA	1	105.25	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹

	Dosage ^a	Frequency per Year	Annual Cost ^b	Reference
Family physician	NA	2	154.40	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Echocardiogram	NA	1	208.80	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Coronary angiography/ intravascular ultrasound	NA	1	471.60	Ministry of Health and Long-Term Care, 2016 ⁵⁷ ; Trillium Gift of Life Network, 2018 ⁴⁹
Immunosuppression level	NA	1	8.03	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Routine blood test	NA	2	17.44	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Complete blood count	NA	2	7.96	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Liver function test	NA	2	10.24	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹
Lipid levels	NA	1	8.27	Ministry of Health and Long-Term Care, 2017 ⁶² ; Trillium Gift of Life Network, 2018 ⁴⁹

Abbreviations: bid, twice daily; qid, four times daily.

^aUnless otherwise noted, dosages are per day.

^bAll costs are reported in 2018 Canadian dollars.

Appendix 5: Results, Additional Sensitivity Analyses

Table A5: Results of the Budget Impact Sensitivity Analyses

	Total Budget Impact ^a					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Reference case analysis						
Net budget impact	2,033,776	1,005,097	659,506	852,828	1,056,299	5,607,506
Analysis 1a: 1.5 times greater probability of receiving VAD						
Current	329,742	1,717,930	2,338,022	2,510,207	2,819,628	9,715,530
Future	2,261,825	2,577,750	2,852,252	3,205,888	3,548,771	14,446,486
Net budget impact	1,932,082	859,820	514,230	695,681	729,143	4,730,956
Analysis 1b: 3 times greater probability of receiving VAD						
Current	631,747	1,955,500	2,546,444	2,749,960	3,125,020	11,008,672
Future	2,261,825	2,577,750	2,852,252	3,205,888	3,548,771	14,446,486
Net budget impact	1,630,078	622,250	305,808	455,927	423,751	3,437,814
Analysis 2: Post-surgical outcomes (optimistic scenario)						
Current	228,049	1,547,525	2,155,053	2,315,367	2,454,779	8,700,772
Future	2,242,400	2,548,613	2,823,114	3,176,750	3,509,920	14,300,797
Net budget impact	2,014,351	1,001,088	668,062	861,383	1,055,141	5,600,025
Analysis 3: Team labor costs						
Current	228,049	1,710,654	2,330,746	2,491,060	2,630,472	9,390,980
Future	2,468,825	2,784,750	3,128,252	3,481,888	3,824,771	15,688,486
Net budget impact	2,240,776	1,074,097	797,506	990,828	1,194,299	6,297,506
Analysis 4a: 1.5 times greater cost of ECMO vs reference case						
Current	228,049	1,572,654	2,192,746	2,353,060	2,492,472	8,838,980
Future	2,271,537	2,592,319	2,866,821	3,220,457	3,568,196	14,519,331
Net budget impact	2,043,489	1,019,666	674,075	867,397	1,075,724	5,680,350
Analysis 4b: 5 times greater cost of ECMO vs reference case						
Current	228,049	1,572,654	2,192,746	2,353,060	2,492,472	8,838,980
Future	2,339,526	2,694,302	2,968,804	3,322,439	3,704,173	15,029,244
Net budget impact	2,111,477	1,121,648	776,058	969,379	1,211,701	6,190,263
Analysis 5: Higher cost of disposables and lower cost of perfusion system maintenance						
Current	228,049	1,572,654	2,192,746	2,353,060	2,492,472	8,838,980
Future	2,339,526	2,720,598	3,008,085	3,374,707	3,730,576	15,183,315
Net budget impact	2,121,300	1,019,666	674,075	867,397	1,075,724	6,344,335
Analysis 6a: Medication cost-sharing, 10% MOH contribution						
Current	204,432	1,457,241	1,988,656	2,063,129	2,118,655	7,832,114
Future	2,180,151	2,524,076	2,718,065	2,991,188	3,244,613	13,658,093
Net budget impact	1,975,719	1,066,834	729,409	928,059	1,125,958	5,825,979

	Total Budget Impact ^a					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Analysis 6b: Medication cost-sharing, 25% MOH contribution						
Current	208,368	1,476,477	2,022,671	2,111,451	2,180,958	7,999,925
Future	2,276,200	2,592,319	2,740,430	3,026,971	3,295,306	13,789,492
Net budget impact	2,048,151	1,019,666	674,075	867,397	1,075,724	5,789,567
Analysis 6c: Medication cost-sharing, 50% public contribution						
Current	214,928	1,508,536	2,079,363	2,191,987	2,284,796	8,279,610
Future	2,216,451	2,547,931	2,777,704	3,086,610	3,379,794	14,008,490
Net budget impact	2,001,522	1,039,395	698,341	894,623	1,094,998	5,728,880
Analysis 6d: Medication cost-sharing, 75% public contribution						
Current	221,489	1,540,595	2,136,054	2,272,523	2,388,634	8,559,295
Future	2,239,138	2,562,841	2,814,978	3,146,249	3,464,283	14,227,488
Net budget impact	2,017,649	1,022,246	678,924	873,725	1,075,649	5,668,193
Analysis 7: Gradual annual increase of 10%: uptake of the procedure						
Current	65,157	583,526	1,198,031	1,864,555	2,457,686	6,168,955
Future	1,101,225	1,403,069	2,140,177	3,063,824	4,244,525	11,952,820
Net budget impact	1,036,068	819,544	942,145	1,199,269	1,786,840	5,783,865

Abbreviations: VAD, a ventricular assist device as the bridge to transplant, ECMO, extracorporeal membrane oxygenation; MOH, Ontario Ministry of Health.

^aAll costs are reported in 2018 Canadian dollars.

Appendix 6: Letter of Information



LETTER OF INFORMATION

Health Quality Ontario is conducting a review of **Organ Care System** for the **transportation of hearts for transplant**. The purpose is to understand whether these devices should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and families of those who may be impacted by heart transplantation. Our goal is to make sure the experiences of patients and caregivers are considered in the funding recommendations for this device.

WHAT DO YOU NEED FROM ME?

- ✓ 20-40 minutes of your time for a phone or in-person interview to share your story
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will likely last 20-40 minutes. It will be held in a private location or over the telephone. With your consent, the interview will be audio-taped. The interviewer will ask you questions about you or your loved one's condition and your perspectives about heart transplantation and the potential impact of the Organ Care System.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely.

RISKS TO PARTICIPATION:

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, please contact any staff.

If you are interested in participating, please contact Health Quality Ontario staff:

Appendix 7: Interview Guide

Interview for Organ Care System (OCS) Heart

Introduction

Explain Health Quality Ontario^a purpose, HTA process, and purpose of interview
History of heart failure (or need of heart transplantation) diagnosis and background (general only)

Lived Experience

Day-to-day routine
What has been the impact and its progression on quality of life?
(Loss of independence?)
Impact on loved ones/caregivers, work, etc.?

Therapies

What current therapies/treatments were used and their impact?
Cost of therapies attempted

Decision-Making

Decision-making surrounding heart transplantation, being on waitlist
Impact of waiting, anxiety, other?
Any factors that influence, affect choice?
Any concerns of heart type, 'extended criteria' or other?

Any familiarity with Organ Care System? If so, general thoughts or impressions?

^a Health Quality Ontario is now the Quality business unit at Ontario Health.

REFERENCES

- (1) National Institute for Health and Care Excellence. OCS Heart system for heart transplant: Medtech innovation briefing [MIB86] [Internet]. London: The Institute; 2016 [cited 2018 Dec]. Available from: <https://www.nice.org.uk/advice/mib86>
- (2) Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ*. 2012;184(14):E765-73.
- (3) Messer SJ, Axell RG, Colah S, White PA, Ryan M, Page AA, et al. Functional assessment and transplantation of the donor heart after circulatory death. *J Heart Lung Transplant*. 2016;35(12):1443-52.
- (4) HealthConsult. Organ perfusion systems for solid organs [Internet]. North Sydney (New South Wales, Australia): New South Wales Ministry of Health; 2017 [cited 2018 Dec]. Available from: <https://trove.nla.gov.au/version/248762500>
- (5) Health Quality Ontario. Left ventricular assist device for destination therapy: a health technology assessment [Internet]: Health Quality Ontario; 2016 [cited 2018 18 Sep]. Available from: <http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/hta-lvad>
- (6) Health Quality Ontario. Left ventricular assist devices for destination therapy: Health Quality Ontario recommendation [Internet]. Toronto (ON): Queen's Printer for Ontario; 2016 [cited 2018 Dec]. Available from: <http://www.hqontario.ca/Portals/0/Documents/evidence/reports/recommendation-lvad-1602-en.pdf>
- (7) Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report--2014; focus theme: retransplantation. *J Heart Lung Transplant*. 2014;33(10):996-1008.
- (8) Isaac D, Chan M, Haddad H, Cheung A, West L, Rao V, et al. Cardiac transplantation: eligibility and listing criteria in Canada 2012 [Internet]. Ottawa (ON): Canadian Cardiac Transplant Network; 2011 [cited 2017 Oct 11]. Available from: https://www.ccs.ca/images/Affiliates/CCTN/FINAL_Cardiac_Transplant_Eligibility_and_Listing_Criteria_20121.pdf
- (9) Canadian Institute for Health Information. e-Statistics report on transplant, waiting list and donor statistics: 2016 summary statistics, January 1 to December 31, 2016 [Internet]. Ottawa (ON): The Institute; 2017 [cited 2018 Dec]. Available from: https://www.cihi.ca/sites/default/files/document/corr_ar-estatistics-2016-en.xlsx
- (10) Trillium Gift of Life Network. Statistics [Internet]. Toronto (ON): The Network; 2017 [cited 2017 Oct 11]. Available from: <http://www.giftoflife.on.ca/en/publicreporting.htm>
- (11) Steinbrook R. Organ donation after cardiac death. *N Engl J Med*. 2007;357(3):209-13.
- (12) Ardehali A, Esmailian F, Deng M, Soltesz E, Hsich E, Naka Y, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet*. 2015;385(9987):2577-84.
- (13) Rao V, Dhanani S, MacLean J, Payne C, Paltser E, Humar A, et al. Effect of organ donation after circulatory determination of death on number of organ transplants from donors with neurologic determination of death. *CMAJ*. 2017;189(38):E1206-E11.
- (14) Shemie SD. Brain arrest to neurological determination of death to organ utilization: the evolution of hospital-based organ donation strategies in Canada. *Can J Anaesth*. 2006;53(8):747-52.

- (15) Venkateswaran RV, Bonser RS, Steeds RP. The echocardiographic assessment of donor heart function prior to cardiac transplantation. *Eur J Echocardiogr.* 2005;6(4):260-3.
- (16) Yeter R, Hubler M, Pasic M, Hetzer R, Knosalla D. Organ preservation with the organ care system. *Appl Cardiopulm Pathophysiol.* 2011;15:207-12.
- (17) Russo MJ, Chen JM, Sorabella RA, Martens TP, Garrido M, Davies RR, et al. The effect of ischemic time on survival after heart transplantation varies by donor age: an analysis of the United Network for Organ Sharing database. *J Thorac Cardiovasc Surg.* 2007;133(2):554-9.
- (18) Dhital KK, Chew HC, Macdonald PS. Donation after circulatory death heart transplantation. *Curr Opin Organ Transplant.* 2017;22(3):189-97.
- (19) Shemie SD, Baker AJ, Knoll G, Wall W, Rocker G, Howes D, et al. National recommendations for donation after cardiocirculatory death in Canada: donation after cardiocirculatory death in Canada. *CMAJ.* 2006;175(8):S1.
- (20) Mehra MR. Challenges, diligence, and a breakthrough in donation after circulatory death in heart transplantation. *J Heart Lung Transplant.* 2017;36(12):1319-21.
- (21) Wagner FM. Donor heart preservation and perfusion. *Appl Cardiopulm Pathophysiol.* 2011;15:198-206.
- (22) Barnard MS. Heart transplantation: an experimental review and preliminary research. *S Afr Med J.* 1967;41(48):1260-2.
- (23) Monteagudo Vela M, Garcia Saez D, Simon AR. Current approaches in retrieval and heart preservation. *Ann Cardiothorac Surg.* 2018;7(1):67-74.
- (24) Dalle Ave AL, Shaw D, Bernat JL. An analysis of heart donation after circulatory determination of death. *J Med Ethics.* 2016;42(5):312-7.
- (25) TransMedics, Inc. Organ Care System: What is the Transmedics Organ Care System? [Internet]. Andover (MA): TransMedics, Inc.; 2017 [cited 2017 Oct 11]. Available from: http://www.transmedics.com/wt/page/organ_care.html.
- (26) Tsukashita M, Naka Y. Organ Care System for heart procurement and strategies to reduce primary graft failure after heart transplant. *Oper Tech Thorac Cardiovasc Surg.* 2016;20:322-34.
- (27) Bell RM, Mocanu MM, Yellon DM. Retrograde heart perfusion: the Langendorff technique of isolated heart perfusion. *J Mol Cell Cardiol.* 2011;50(6):940-50.
- (28) Connellan M, Dhital KK. Donor heart procurement from the donation after circulatory death pathway. *Oper Tech Thorac Cardiovasc Surg.* 2017;22:58-67.
- (29) Chan JL, Kobashigawa JA, Reich HJ, Ramzy D, Thottam MM, Yu Z, et al. Intermediate outcomes with ex-vivo allograft perfusion for heart transplantation. *J Heart Lung Transplant.* 2017;36(3):258-63.
- (30) National Institute for Health and Care Excellence. Normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death: interventional procedures guidance (IPG549) [Internet]. London: The Institute; 2016 [cited 2018 Dec]. Available from: <https://www.nice.org.uk/guidance/ipg549>
- (31) Medical Devices Regulations, SOR/98-282 (October 17, 2018).
- (32) McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-6.
- (33) O'Neill J, Tabish H, Welch V, Petticrew M, Pottie K, Clarke M, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. *J Clin Epidemiol.* 2014;67(1):56-64.
- (34) Koerner MM, Ghodsizad A, Schulz U, El Banayosy A, Koerfer R, Tenderich G. Normothermic ex vivo allograft blood perfusion in clinical heart transplantation. *Heart Surg Forum.* 2014;17(3):E141-5.

- (35) Stamp NL, Shah A, Vincent V, Wright B, Wood C, Pavey W, et al. Successful heart transplant after ten hours out-of-body time using the TransMedics Organ Care System. *Heart Lung Circ.* 2015;24(6):611-3.
- (36) Messer S, Page A, Axell R, Berman M, Hernandez-Sanchez J, Colah S, et al. Outcome after heart transplantation from donation after circulatory-determined death donors. *J Heart Lung Transplant.* 2017;36(12):1311-8.
- (37) Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- (38) Schünemann H, Brožek J, Guyatt G, Oxman A, editors. GRADE handbook [Internet]. Hamilton (ON): GRADE Working Group; 2013 [cited 2017 Dec]. Available from <http://gdt.guidelinedevelopment.org/app/handbook/handbook.html>.
- (39) Dhital KK, Iyer A, Connellan M, Chew HC, Gao L, Doyle A, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. *Lancet.* 2015;385(9987):2585-91.
- (40) Garcia Sáez D, Bowles CT, Mohite PN, Zych B, Maunz O, Popov AF, et al. Heart transplantation after donor circulatory death in patients bridged to transplant with implantable left ventricular assist devices. *J Heart Lung Transplant.* 2016;35(10):1255-60.
- (41) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Med.* 2009;6(6):e1000097.
- (42) Chaudhry SP, Stewart GC. Advanced heart failure: prevalence, natural history, and prognosis. *Heart Fail Clin.* 2016;12(3):323-33.
- (43) Health Policy Advisory Committee on Technology. Technology overview: new and emerging organ perfusion systems [Internet]. Herston (Queensland, Australia): Queensland Department of Health; 2014 [cited 2018 Dec]. Available from: <https://www.coaghealthcouncil.gov.au/Portals/0/HealthPACT/New%20and%20Emerging%20Organ%20Perfusion%20System%20Technology%20Overview%20July%202014.pdf>
- (44) Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential improvements. *Transplantation.* 2014;97(3):258-64.
- (45) Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Statist Soc B.* 1995;57(1):289-300.
- (46) Knight SR, Morris PJ, Schneeberger S, Pengel LH. Trial design and endpoints in clinical transplant research. *Transpl Int.* 2016;29(8):870-9.
- (47) National Institute for Health and Care Excellence. Process and methods guides. Appendix I quality appraisal checklist—economic evaluations. London (UK): National Institute for Health and Care Excellence; 2012.
- (48) Messer S, Large S. Resuscitating heart transplantation: the donation after circulatory determined death donor. *Eur J Cardiothorac Surg.* 2016;49(1):1-4.
- (49) Trillium Gift of Life Network. Clinical handbook for heart transplantation. Toronto (ON): The Network; 2018.
- (50) Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. *Can J Cardiol.* 2017;33(11):1342-433.
- (51) Venkateswaran RV. Functional restoration, transportation and transplantation of human hearts from donation after circulatory death (DCD) organ donors [Internet]. Manchester (UK): Wythenshawe Hospital; n.d. [cited 2018 Dec]. Available from: https://nhsbt.dbe.blob.core.windows.net/umbraco-assets-corp/3601/wythenshawe_dcd_heart_version_1.pdf

- (52) Trillium Gift of Life Network. Organ Care System for DCD heart transplantation. Toronto (ON): The Network; 2017.
- (53) Bank of Canada. Annual exchange rates [Internet]. Ottawa (ON): Bank of Canada; 2018 [cited 2018 Oct 18]. Available from: <https://www.bankofcanada.ca/rates/exchange/annual-average-exchange-rates/>
- (54) Statistics Canada. Table 36-10-0100-01: Purchasing power parities of gross domestic product, Organisation for Economic Co-operation and Development countries [Internet]. Ottawa (ON): Statistics Canada; 2018 [cited 2018 Oct 18]. Available from: <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=3610010001>
- (55) Statistics Canada. Table 326-0020: Consumer price index [Internet]. Ottawa (ON): Statistics Canada; 2018 [cited 2018 Apr]. Available from: <http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=3260020&&pattern=&stByVal=1&p1=1&p2=-1&tabMode=dataTable&csid=>
- (56) Ministry of Health and Long-Term Care. Ontario case costing initiative [Internet]. Toronto (ON) Queen's Printer for Ontario. c2017. Available from: <https://www.ontario.ca/data/ontario-case-costing-initiative-occi>
- (57) Ministry of Health and Long-Term Care. Schedule of benefits: physician services under the Health Insurance Act [Internet]. Toronto (ON): Ministry of Health and Long-Term Care; 2016 Mar 1. Available from: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20160401.pdf
- (58) St-Onge M, Fan E, Megarbane B, Hancock-Howard R, Coyte PC. Venoarterial extracorporeal membrane oxygenation for patients in shock or cardiac arrest secondary to cardiotoxicant poisoning: a cost-effectiveness analysis. *J Crit Care*. 2015;30(2):437.e7-14.
- (59) Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto (ON): Queen's Printer for Ontario; 2016 [cited 2018 Jun 15]. Available from: <https://www.formulary.health.gov.on.ca/formulary/>
- (60) Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Circ Heart Fail*. 2017;10(1):pii: e003529.
- (61) McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.
- (62) Ministry of Health and Long-Term Care. Schedule of benefits for laboratory services [Internet]. Toronto (ON): Queen's Printer for Ontario; 2017 [cited 2017 Nov 7]. Available from: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn.pdf
- (63) Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report--2014; focus theme: retransplantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2014;33(10):996-1008.
- (64) Government of Ontario. Get help with high prescription drug costs [Internet]. Toronto (ON): Queen's Printer for Ontario; 2018 [cited 2018 Oct 18]. Available from: <https://www.ontario.ca/page/get-help-high-prescription-drug-costs>
- (65) Barnieh L, Clement F, Harris A, Blom M, Donaldson C, Klarenbach S, et al. A systematic review of cost-sharing strategies used within publicly funded drug plans in member countries of the Organisation for Economic Co-operation and Development. *PLoS One*. 2014;9(3):e90434.

- (66) Toronto Liver Transplant Program. Pre-liver transplant manual [Internet]. Toronto (ON): University Health Network; 2011 [cited 2018 Dec]. Available from: https://www.uhn.ca/Transplant/PatientsFamilies/Clinics_Tests/Liver_Transplant/Documents/MOT_PF_CC_Liver_PreMANUAL.pdf
- (67) Sutherland G, Dinh T. Understanding the gap: a pan-Canadian analysis of prescription drug insurance coverage [Internet]. Ottawa (ON): Conference Board of Canada; 2017 [cited 2018 Apr 6]. Available from: <http://innovativemedicines.ca/wp-content/uploads/2017/12/20170712-understanding-the-gap.pdf>
- (68) Henriksen M, Klokke L, Bartholdy C, Schjoedt-Jorgensen T, Bandak E, Bliddal H. No effects of functional exercise therapy on walking biomechanics in patients with knee osteoarthritis: exploratory outcome analyses from a randomised trial. *BMJ Open Sport Exerc Med*. 2016;2(1):e000230.
- (69) Yilmaz Yelvar GD, Cirak Y, Dalkilinc M, Demir YP, Baltaci G, Komurcu M, et al. Impairments of postural stability, core endurance, fall index and functional mobility skills in patients with patello femoral pain syndrome. *J Back Musculoskelet Rehabil*. 2016;30:30.
- (70) OHTAC Public Engagement Subcommittee. Public engagement for health technology assessment at Health Quality Ontario—final report from the Ontario Health Technology Advisory Committee Public Engagement Subcommittee [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015 [cited 2016 Jan]. Available from: <http://www.hqontario.ca/Portals/0/documents/evidence/special-reports/report-subcommittee-20150407-en.pdf>
- (71) Kvale S. Interviews: an introduction to qualitative research interviewing. Thousand Oaks (CA): Sage; 1996.
- (72) Kuzel AJ. Sampling in qualitative inquiry. In: Miller WL, Crabtree BF, editors. *Doing qualitative research*. Thousand Oaks (CA): Sage; 1999. p. 33-45.
- (73) Morse J. Emerging from the data: cognitive processes of analysis in qualitative research. In: Morse J, editor. *Critical issues in qualitative research methods*. Thousand Oaks (CA): Sage; 1994. p. 23-41.
- (74) Patton MQ. *Qualitative research and evaluation methods*. 3rd ed. Thousand Oaks (CA): Sage; 2002.
- (75) Strauss AL, Corbin JM. *Basics of qualitative research: techniques and procedures of developing a grounded theory*. 2nd ed. Thousand Oaks (CA): Sage; 1998.
- (76) Health Technology Assessment International Interest Group on Patient and Citizen Involvement in HTA. Introduction to health technology assessment [Internet]. Edmonton (AB): Health Technology Assessment International; 2015 [cited 2016 Jan]. Available from: http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/v2_files/Resource/PCI_SG-Resource-Intro_to_HTA_KFacey_Jun13.pdf
- (77) Strauss AL, Corbin JM. Grounded theory research: procedures, canons, and evaluative criteria. *Qual Sociol*. 1990;13(1):3-21.
- (78) Strauss AL, Corbin JM. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. *Handbook of qualitative research*. Thousand Oaks (CA): Sage; 1994. p. 273-85.
- (79) NVivo qualitative data analysis software. QSR International. Doncaster, Victoria (Australia). Available at: <https://www.qsrinternational.com/nvivo/home>.

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This health technology assessment was produced by the Quality business unit at Ontario Health, the government agency that when fully established will be responsible for ensuring all Ontarians receive high-quality health care where and when they need it.

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