Health Quality Ontario

The provincial advisor on the quality of health care in Ontario

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Composite Tissue Transplant of Hand or Arm: A Health Technology Assessment

KEY MESSAGES

A severe injury to an arm or hand can result in a loss of the limb. Having a limb amputated can affect how a person functions and how they feel about themselves. Hand and arm transplants—in which a limb from a deceased donor is grafted onto to a living person—are now possible. The complex procedure, called composite tissue transplant, involves connecting bone, muscles, nerves, skin, and other tissue. Transplant recipients must take medication to suppress their immune system for the rest of their lives, so that their body does not reject the new limb. This medication then puts them at risk for serious complications such as infections, heart disease, kidney damage, and some types of cancer.

Hand and arm transplants are now being done in many countries but nowhere in Canada. Several groups have proposed starting a hand and arm transplant program in Ontario. In this study, we looked at how safe and effective hand and arm transplants are for patients. We also looked at how much the transplants cost and whether they are cost-effective (good value for money).

We found that patients who received a hand or arm transplant were able to function better. However, these transplants are very expensive compared with the usual care that people with amputations receive in Ontario, and we are not sure whether they always work because the quality of the studies we could find was very low.

JUNE 2016
VOL. 16, NO. 13

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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We are grateful to Dr. Steve McCabe, Dr. Ronald Zuker, and Dr. Douglas Ross for their advice and guidance on hand and arm transplantation.

Citation
Health Quality Ontario. Composite tissue transplant of hand or arm: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2016 June;16(13):1-70. Available from: http://www.hqontario.ca/Evidence-to-Improve-Care/Journal-Ontario-Health-Technology-Assessment-Series/hand-arm-transplant

ABSTRACT

Background

Injuries to arms and legs following severe trauma can result in the loss of large regions of tissue, disrupting healing and function and sometimes leading to amputation of the damaged limb. People experiencing amputations of the hand or arm could potentially benefit from composite tissue transplant, which is being performed in some countries. Currently, there are no composite tissue transplant programs in Canada.

Methods

We conducted a systematic review of the literature, with no restriction on study design, examining the effectiveness and cost-effectiveness of hand and arm transplant. We assessed the overall quality of the clinical evidence with GRADE. We developed a Markov decision analytic model to determine the cost-effectiveness of transplant versus standard care for a healthy adult with a hand amputation. Incremental cost-effectiveness ratios (ICERs) were calculated using a 30-year time horizon. We also estimated the impact on provincial health care costs if these transplants were publicly funded in Ontario.

Results

Compared to pre-transplant function, patients' post-transplant function was significantly better. For various reasons, 17% of transplanted limbs were amputated, 6.4% of patients died within the first year after the transplant, and 10.6% of patients experienced chronic rejections. GRADE quality of evidence for all outcomes was very low.

In the cost-effectiveness analysis, single-hand transplant was dominated by standard care, with increased costs ($735,647 CAD vs. $61,429) and reduced quality-adjusted life-years (QALYs) (10.96 vs. 11.82). Double-hand transplant also had higher costs compared with standard care ($633,780), but it had an increased effectiveness of 0.17 QALYs, translating to an ICER of $3.8 million per QALY gained. In most sensitivity analyses, ICERs for bilateral hand transplant were greater than $1 million per QALY gained. A hand transplant program would lead to an estimated annual budget impact of $0.9 million to $1.2 million in the next 3 years, 2016 to 2018, to treat 3 adults per year.

Conclusions

Composite tissue transplant of the hand or arm may improve a patient's ability to function, but because the overall quality of evidence is of very low quality, there is considerable uncertainty as to whether benefits outweigh harms. Compared with standard care, both single- and double-hand transplants are not cost-effective.

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BACKGROUND

Health Condition

Severe injuries to arms and legs can result in the loss of large regions of tissue, disrupting healing and the function of the limb.[1] When the limb cannot be repaired, amputation (removal of the limb) becomes the best and only option, although this also causes significant distress and disability.[2] The most frequent causes of hand and arm amputation are trauma (such as from a severe fracture, or a blunt, penetrating or blast injury) and cancer, followed by damage to blood vessels from certain medical conditions.[3]

Clinical Need and Target Population

In Canada, an estimated 227,000 people have had either an arm or a leg amputated.[4] Among arm amputations worldwide, about 5% are done at the hand or wrist, 59% are below the elbow, 28% are through the elbow joint or above the elbow, and 8% are at the shoulder.[5]

Technology/Technique

The technology under review is called composite tissue transplantation—a surgical procedure in which a limb or body part from one person (a deceased donor) is transplanted or grafted to another person (a live recipient). It is extremely complex surgery that involves many kinds of tissue, including skin, muscle, tendon, nerves, bone, and blood vessels. The first successful composite tissue transplant was done in 1998, and the procedure has been used to transplant hands, face, abdominal wall, larynx, and other body parts. It offers hope to people who suffer severe disfigurement and functional impairment by restoring near-normal appearance and improving their ability to function.[6]

The procedure also involves some risks and can lead to complications. As with any transplant, patients must take immunosuppression therapy (drugs to suppress their immune system) so their body does not reject (attack) the transplant. After composite tissue transplant, patients must take these drugs for the rest of their lives, and this long-term use of immunosuppression puts them at risk for infections, heart disease, kidney damage, and some types of cancer. About 85% of hand transplant patients develop an acute rejection (when the body attacks the transplant soon after the surgery), but this common problem can be managed by established treatments.[7]

Composite tissue transplant programs are established worldwide, with sites now in the United States, France, China, Spain, Italy, Germany, Austria, Mexico, Malaysia, Belgium, Australia, the United Kingdom, and Poland.[8]

Ontario Context

There are no composite tissue transplant programs in Ontario or anywhere in Canada. Ontario's Ministry of Health and Long-Term Care has received a proposal from two groups that would like the government to fund a composite tissue transplant program for upper limbs (hands and arms). The Trillium Gift of Life Network has agreed to act as the source establishment for the proposed program, conducting donor suitability screening according to Health Canada requirements.

Regulatory Status

Health Canada classifies upper limbs as composite tissue rather than as a solid organ (such as a kidney, liver, or lungs). The drugs used to suppress the immune response so the body accepts the newly attached limb are only approved for solid organ transplants. There is no specific fee code in Ontario's Physician Schedule of Benefits for surgical procedures involved in a composite tissue transplant.

Research Questions

- What is the effectiveness of composite tissue transplants of the hand or arm in adults, as measured by rates of functional recovery, acute and chronic rejection, post-transplant amputation, complications, and mortality?
- What is the cost-effectiveness of composite tissue transplants of the hand?
- What is the potential budget impact of publicly funding a hand transplant program in Ontario?

Expert Consultation

In September and October 2015, we consulted several surgeons on the use of hand transplants and immunosuppression treatment. The role of the expert advisors was to contextualize the evidence and provide advice on composite tissue transplant of the hand or arm. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

CLINICAL EVIDENCE REVIEW

Objective

The objective of this part of the health technology assessment was to determine the effectiveness of hand or arm transplants in adults in terms of functional recovery, complications, acute and chronic rejection, amputation of the transplant, and mortality.

Methods

Literature Search

A literature search was performed on July 23, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and EBM Reviews, for studies published from January 1, 2010, to July 23, 2015. (Appendix 1 provides details of the search strategies.) A 2010 evidence review by the National Institute for Health and Care Excellence (NICE) captured the literature from 1998 to 2010.[9] We overlapped our search dates with the end date of the NICE review. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Published between January 1, 2010, and July 23, 2015
- Patients with an amputation of the arm or hand
- Patients with amputation of one or more limbs
- Limb amputation owing to trauma (injury)

Exclusion Criteria

- Amputations of other body parts, other than hand or arm
- Studies that focused on technical aspects of transplant procedure
- Editorials and letters to the editor

Outcomes of Interest

- Functional recovery
- Acute rejection (defined as a rapid reaction against the transplanted graft, generally occurring within 10 days after the surgery)
- Chronic rejection (defined as an immune rejection of the transplanted graft that may continue over several months)
- Amputation
- Complications
- Mortality

Statistical Analysis

A meta-analysis was not conducted because we did not have comparative data. Therefore, this is a narrative report describing the outcomes and rates of occurrence found in the literature.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodologic quality of systematic reviews.[10]

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[11] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Results

The database search yielded 476 citations published between January 1, 2010, and July 23, 2015 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis. In summary, one systematic review,[12] one retrospective registry with an update,[13,14] and one case series[15] met the inclusion criteria.

In our full-text review, we found that many of the relevant studies had duplicate information: they were case reports of hand or arm transplants that were included in the retrospective registry, and so were excluded. We hand-searched the reference lists of these studies to identify other relevant studies, and no other studies were identified.

Among our included studies is a 2014 abstract of an unpublished study by the International Registry on Hand and Composite Tissue Transplantation (IRHCTT).[13] The authors were contacted for more information. This registry collects information on a voluntary basis from teams performing hand transplants. Centres in the United States, Turkey, Belgium, Austria, the United Kingdom, France, Australia, Italy, Spain, Taiwan, Poland, and Germany provide detailed data on their patients. However, centres in Malaysia, Iran, and India are not captured in this registry. The 2014 registry includes data for about 48 patients, most of whom received hand or arm transplants between 2002 and 2014. Outcomes data were reported on 47 of the 48 patients; one patient who received a hand from a twin brother was excluded because the patient did not need immunosuppressant therapy. Table 1 summarizes the characteristics of the two studies from this international registry.

Although centres in China do contribute to the IRHCTT, Chinese cases are not covered in detail and the registry examines them separately. Data from the Chinese cohort may not be representative of limb transplants in North America and Europe. Patient selection criteria were not rigorously applied in Chinese centres, and not all patients received the necessary post-transplant medication and follow-up. Because of these differences, we did not include this case series in our analysis.[15] Instead, we provide a summary of the findings from the Chinese cohort in Appendix 3, Tables A4 and A5.

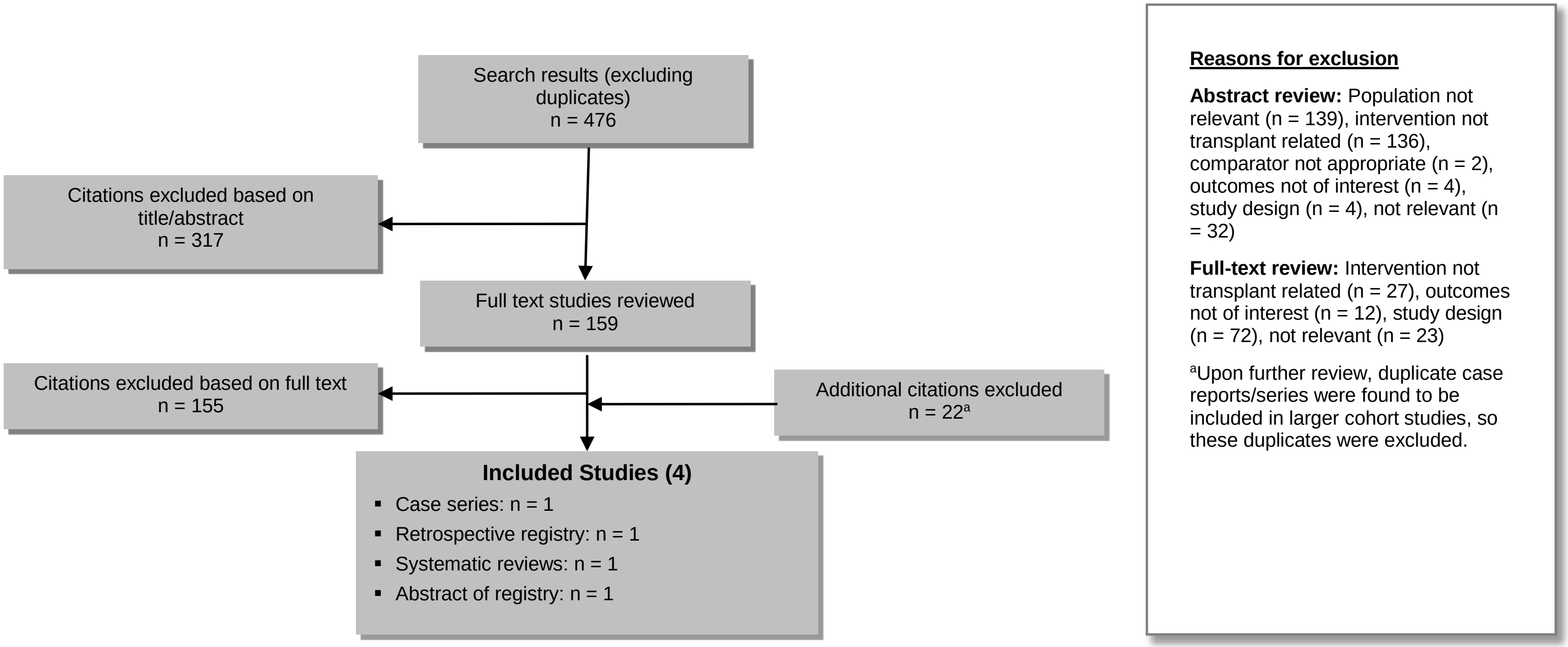

Figure 1: Citation Flow Chart for the Clinical Evidence Review

Table 1: Study Population Characteristics

Author, Year	N (% male)	Age,[a] Years (Range)	Type of Transplant, n	Level of Transplant, n	Cause of Amputation, n
Petruzzo et al, 2014[13]	47[b] (80.9%)	37.44 (17–65)	bilateral arm, 25 unilateral arm, 23 right-side,18 left-side, 5	palmar level, 13 wrist level, 18 distal forearm, 11 mid-forearm, 9 proximal forearm, 13 elbow level, 1 mid-arm, 2 proximal arm, 2 distal arm, 1	clean cut, 8 crush, 9 explosion, 12 electrical accident, 6 burn, 4 sepsis, 3 other, 3
Petruzzo et al, 2010[14]	33 (93.9%)	32 (19–54)	bilateral arm, 16 unilateral arm, 17	wrist level, 15 distal forearm, 6 mid-forearm, 6 proximal forearm, 5 elbow level, 1	clean cut, 3 crush, 12 explosion, 11 electric accident, 2 burn, 3 other, 2

[a]Articles did not state whether they were reporting mean or median age.
[b]Our analysis excludes 1 of the 48 study patients owing to lack of outcomes data on that patient.

Measures Used for Functional Recovery

Four assessments of disability were used in the studies included in our analysis:

- Disabilities of the Arm, Shoulder, and Hand (DASH) Score (higher score indicates worse function)
- Chen's Functional Grade (grade 1, good function; grade 4, poor function)
- Hand Transplantation Score System (lower score indicates worse function)
- Carroll test for global hand function (lower score is worse function)

Appendix 4 provides further details for these assessment tools.

Functional Recovery

A systematic review examined functional outcomes in 28 hand or arm transplant recipients.[12] These recipients were included in the International Registry on Hand and Composite Tissue Transplantation. Pre- and post-transplant function measured by the DASH score was recorded for 10 patients. The mean pre-transplant score was 71.01 (± 25.79) and the mean post-transplant score was 43.49 (± 26.48). The mean difference between DASH scores before and after the transplants (27.61 ± 19.04) was statistically significant (P = 0.005) and exceeded the minimum clinically important difference of 13 points.

This improvement in scores meant that muscle recovery in the transplanted hand or arm enabled patients to perform daily activities including eating, driving, grasping objects, riding a bicycle, shaving, using the telephone, and writing.[16] In addition, most patients were able to return to work.[14]

The systematic review also compared functional recovery for patients who had a unilateral (one side of the body) versus a bilateral (both sides of the body) transplant. There were no significant differences in their DASH scores either before or after the transplants. For patients with unilateral transplants, the mean pre-transplant score was 66.13, compared to 65.9 for bilateral transplant recipients (P = 0.93). Mean post-transplant scores were 59.4 for unilateral transplant patients and 36 for bilateral transplant patients (P = 0.14). Both groups improved, but the difference in the magnitude of their improvement (unilateral, 21.07; bilateral, 30.41) was not statistically significant (P = 0.66).

For 17 patients, the authors also reported the percentage of patients with various levels of functional recovery, using the Chen grade system. Before transplant, all of these patients (100%) had a Chen grade of 4 (poor function). After transplant, only one patient (5.9%) remained at grade 4; seven patients (41.2%) had improved to grade 3; eight patients (47.1%) had progressed to grade 2; and only one patient (5.9%) was improved to grade 1.

The Hand Transplantation Score System measure was reported for 14 patients with a transplant of the right hand or arm and seven patients who received a transplant of the left limb. Mean scores after transplant were in the "good" range: 74.21 (± 11.13) for right limb transplants and 71.85 (± 6.42) for the left limb transplants. Pre-transplant scores were not provided.

In the same systematic review, 15 patients received a secondary surgery owing to problems with the transplant. The mean post-transplant DASH scores for patients who had a second surgery was 36.41 (± 21.7), compared to 70 (± 14.73) for patients who did not undergo a second surgery. This difference in post-transplant function between the two groups was statistically significant (P = 0.036). However, the difference in the magnitude of improvement within each group was not statistically significant (P = 0.77).

Factors such as time of amputation (P = 0.9), the extent of tissue transplanted (P = 0.27), and the duration of ischemia (inadequate blood supply to the limb) (P = 0.41) were not statistically associated with better or worse post-transplant DASH scores.

In summary, patients' functional ability improves significantly after a composite tissue transplant of a hand or arm, compared with their pre-transplant function. GRADE quality of evidence is very low.

Acute Rejection

Acute rejection is the body's rapid reaction against the transplanted graft and generally occurs within 10 days post-transplant. In the 2014 study by IRHCTT, 76% of the 47 transplant recipients developed acute rejection in the first year after the procedure.[13] That study does not provide a breakdown of acute rejection episodes among patients, but the 2010 study from the same registry does.[14] In the 2010 dataset, 28 out of 32 patients (87.5%) experienced acute rejection within the first year, and patients had 1.8 episodes on average, ranging from a single episode (15 patients) to 5 episodes (1 patient). The cause of the acute rejections was a failure by patients to correctly take their immunosuppressive treatment or a decrease in immunosuppressive therapy owing to various side effects. However, all episodes of acute rejection were treated successfully. This study did not report on the frequency of acute rejection beyond the first year of the transplants.

Acute rejection is common post-transplant but manageable. GRADE quality of evidence is very low.

Chronic Rejection

Chronic rejection is a longer-term attack by the body's immune system against the transplanted graft. Chronic rejection can begin at any time and may continue over several months. In the 2014 IRHCTT study, 5 patients among the 47 recipients (10.6%) had a chronic rejection, 4 of which led to amputation of all or part of the new hand or arm.[13] These chronic rejections and subsequent amputations occurred at different time points. One patient was diagnosed 265 days after transplant because of acute ischemia of the transplanted hand. Another patient decided to have the new hand amputated more than two years (771 days) after transplant, because of chronic rejection. The third patient developed graft vasculopathy (disorder of the blood vessels) 11 years after transplant, resulting in amputation of two fingers. The fourth patient's chronic rejection and subsequent amputation 12 years after transplant occurred after multiple episodes of acute rejection and non-compliance with immunosuppressant therapy. Lastly, the fifth patient had no reported episodes of acute rejection but experienced chronic rejection 13 years after transplant, reportedly because of self-medication.

Chronic rejection of a composite tissue transplant can occur years after the procedure and can result in partial or total amputation of the transplanted limb. GRADE quality of evidence is very low.

Amputation of Transplanted Limb

Among the 47 transplant recipients in the 2014 IRHCTT study, 8 patients (17.0%) had the transplant partially or fully amputated for the following reasons (these patients overlap with the patients with chronic rejection described above, but because of differences in the way the report described these two groups, we cannot be sure where the duplication occurs):[13]

- Amputation of transplanted hand owing to bacterial infection and bleeding, 45 days after transplant, in a patient who had both a face and hand transplant
- Amputation of bilateral hand transplants owing to sepsis (blood infection) and necrosis (death of the limb or death of the tissue), 5 days after transplant, in a second patient who received both a face and hand transplant
- Amputation of bilateral hand transplants owing to necrosis of the fingers, 15 days after transplant
- Amputation of a transplanted hand owing to poor blood flow to the limb (poor vascularization), 3 days after transplant
- Amputation of transplanted hand, 29 months after transplant, because the patient did not take the immunosuppressant medicine
- Amputation of transplanted hand owing to intimal hyperplasia (thickening of the innermost layer of a blood vessel), 275 days after transplant)
- Amputation of transplanted hand owing to patient non-compliance with medical follow-up, ongoing rejections and patients decision to amputate, 12 years after transplant
- Amputation of transplanted hand owing to chronic rejection and patient's decision to amputate, 771 days after transplant

Amputation of the new limb for any reason occurs in less than 2 of every 100 hand or arm transplants. GRADE quality of evidence is very low.

Complications

Most complications experienced by hand or arm transplant patients were infections or metabolic complications (problems in the body's metabolism, such as the chemical processes that transform food into energy) and were related to the immunosuppression treatment that patients must take to reduce the risk of rejection. Post-transplant cancers, though less common, are also likely related to the use of immunosuppression drugs. Other complications—deep venous thrombosis (blood clot in a deep vein), arterial thrombosis (blood clot in an artery), pulmonary edema (fluid in the lungs), and congestive heart failure—were relatively rare, experienced by only 4 of 47 patients (8.5%), and only occurred within the first 3 months of the transplant. Table 2 summarizes the complications and number of episodes reported in the 2014 IRHCTT study (the authors did not report exact follow-up times or, for most types of complications, the number of patients affected).[13]

The abstract for the IRHCTT study separately reported complications for the first 3 months post-transplant. Most of the total episodes of infection occurred in this period. The same is true of the metabolic complications, including hyperglycemia (high blood sugar) where 13 of 21 cases were treated successfully, increased creatinine values (a measure of how well the kidney functions), arterial hypertension (high blood pressure), and leukopenia (low white blood cell count).

Because the study did not report the number of patients affected by each type of complication, we do not know whether the majority of hand or arm transplant recipients experience complications or only a small proportion of patients have many complications.

Most complications following composite tissue transplant of the hand or arm are owing to immunosuppression therapy but are managed. GRADE quality of evidence is very low.

Table 2: Transplant-Related Complications Following Hand or Arm Transplant

Complication	Total Episodes in Full Follow-Up,[a] n (Episodes in ≤ 3 Months Post-Transplant, n)
Infection	
Cytomegalovirus	6 (5)
Herpes virus	2 (2)
Herpes zoster	2 (1)
C. difficile infection	2 (2)
Condyloma	2
Epstein-Barr virus	1
Cutaneous mycosis	3 (3)
Bacterial infection	14 (11)
Osteitis	1 (1)
Pneumonia with sepsis	1 (1)
Infections of graft connective tissues	3
Metabolic Complications	
Hyperglycemia	21 (21)[b]
Post-transplant diabetes mellitus	4
Weight increase	2
Increased cholesterol	3
Increased creatinine values	8 (9)[c]
Arterial hypertension	6 (5)
Leukopenia	2 (2)
End-stage renal disease	1
Avascular necrosis of the hip	2
Hyperparathyroidism	1
Pulmonary embolism	1
Elevated transaminases + yGT	2
Other Complications	
Deep venous thrombosis	1 (1)[b]
Arterial thrombosis	2 (2)[b]
Pulmonary edema and congestive heart failure	1 (1)[b]
Cancer	
Basal cell carcinoma	1
Post-transplant lymphoproliferative disease	1

Abbreviations: yGT, gamma-glutamyltransferase
[a]Duration of follow-up beyond 3 months was not reported.
[b]Complications occurred only in the first 3 months post transplant.
[c]Authors did not explain why the number of episodes in the first 3 months is larger than the number of episodes in total follow-up.
Source: Petruzzo et al, 2014.[13]

Mortality

Among 47 transplant recipients in the IRHCTT study, 3 patients died (6.4%) within the first year after the procedure.[13] One patient died from cerebral anoxia (brain is deprived of oxygen) on post-transplant day 65 following a simultaneous face and bilateral hand transplants. The second patient died because of pulmonary edema and congestive heart failure on post-transplant day 1 (bilateral arm transplant). The third patient died of sepsis (blood infection) on post-transplant day 101 (type of transplant not reported).

Experts consulted for this review advised that the composite tissue transplant surgeries that resulted in death, as reported by the IRHCTT, would not be performed in Canada. Bilateral arm transplants or simultaneous face and hand transplants would not meet the patient selection criteria proposed for the Ontario program.

The mortality data are not generalizable to the Ontario context. GRADE quality of evidence is very low.

Limitations

These data have several limitations. First, follow-up times vary from a few months to 13 years, and the specific length of follow-up for each patient for the outcomes of interest was rarely stated.

Second, the overall quality of the evidence included was very low (Appendix 2, Tables A1 and A2), primarily because the evidence came from a voluntary registry and a low-scoring systematic review. In addition, these data are not completely generalizable to the Ontario population, as there are cases in the data (from the International Registry on Hand and Composite Tissue Transplantation) that would not be included under proposed patient selection criteria. Without access to patient-level data from the registry study, we were unable to tease out those patients.

Third, while no clinical trials on composite tissue transplant of the hand or arm have been published yet, three trials are registered on clinicaltrials.gov, an online registry of medical studies compiled by the US National Institutes of Health. These trials are currently recruiting patients, and the first trial is projected to be completed in 2018. These ongoing trials will examine similar important and meaningful outcomes (graft survival, functional recovery), as well as quality of life (one trial). They may produce higher-quality evidence than we were able to find for this review.

Finally, we were unable to examine data on all hand or arm transplants performed to date. According to Weissenbacher et al,[17] the total number of hand transplants performed worldwide by the end of 2014 was more than 100. Our report captures 88 procedures. This may be because centres in Malaysia, India, Iran, and one centre each in the US (California) and Italy (Milan) have not submitted data to the International Registry on Hand and Composite Tissue Transplantation. Also, we did not include the case of the 8-year-old boy in Maryland who received a bilateral hand transplant in July 2015.[18]

Patient Engagement

In health technology assessment, input from patients, caregivers, and the public can serve as a unique source of evidence about the personal impact of a disease or condition and how technologies can make a difference in people's lives. It can also identify gaps or limitations in the published research (for example, outcome measures that do not reflect what is important to patients and/or caregivers).[19-21] Patient, caregiver and public input can also provide additional information or perspectives on the more general ethical and social-values implications of technologies and treatments.

Primarily because of the time frame for this review, but also because there are no patients in Canada who have undergone hand or arm transplant, we did not undertake a patient engagement strategy for this report.

Patient Selection

Selecting suitable patients is critical for an effective hand and arm transplant program. This review did not examine patient selection criteria.

As noted above, experts consulted for this review stated that composite tissue transplant programs proposed in Ontario will not perform the transplant procedures associated with patient mortality (bilateral upper arm transplants and simultaneous face and hand transplants). The experts, who were involved in preparing the proposal for a hand and arm transplant program in Ontario, said that the proposed program has thoughtfully described criteria for donors and recipients and has developed a process to safely select and evaluate potential recipients and to execute the procedure and post-operative care, focusing on maximizing safety and effectiveness throughout the limb transplant process. The experts stated that the physicians involved in an Ontario composite tissue transplant program will learn from the world's experience to minimize complications and maximize function where the opportunity for patients is clear.

Conclusions

Based on data available from the International Registry on Hand and Composite Tissue Transplantation, the evidence supports the following conclusions about the effectiveness of composite tissue transplant of the hand or arm:

- Patients' ability to function improves significantly after transplant, compared with pre-transplant function (GRADE quality of evidence: very low)
- Acute rejection is common after a transplant but manageable (GRADE quality of evidence: very low)
- Chronic rejection can occur years after the procedure, resulting in partial or total amputation of the transplanted limb (GRADE quality of evidence: very low)
- Amputation of the new limb occurs in less than 2 of every 100 transplants, for any reason (GRADE quality of evidence: very low)
- Most complications are caused by immunosuppression therapy but are managed (GRADE quality of evidence: very low)
- The mortality data are not generalizable to the Ontario context (GRADE quality of evidence: very low)

ECONOMIC EVIDENCE REVIEW

Objectives

The objective of this analysis was to review the published economic evidence on the cost-effectiveness of composite tissue transplant of the hand or arm in patients with amputation of one or both upper limbs.

Methods

Sources

We performed an economic literature search on July 23, 2015, using Ovid MEDLINE, Ovid Embase, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Centre for Reviews and Dissemination Health Technology Assessment Database, and National Health Service Economic Evaluation Database, for English language studies published up to July 23, 2015. No date limits were used. The search was updated on a monthly basis through the AutoAlert function in Ovid up to October 1, 2015. Reference lists of identified studies were also examined for any additional relevant studies not found through the systematic search.

Literature Screening

We based our search terms on those used in the clinical evidence review in this report and applied economic filters to the search results. Study eligibility criteria for the literature search are listed below. Appendix 1 provides details of the search strategies. A single reviewer reviewed abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles.

Inclusion Criteria

- English-language full-text publications
- Studies published up to July 23, 2015
- Studies comparing composite tissue transplant of the hand or arm versus standard care (i.e., no transplant)
- Cost-utility analyses in any country
- Any type of economic studies in Canada (i.e., cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses, budget impact analyses, and cost analyses)

Exclusion Criteria

- Abstracts, letters, editorials, and unpublished studies

Outcomes of Interest

- Cost
- Quality-adjusted life-years (QALYs, a measure that combines the effect of an intervention on length of life and quality of life)
- Incremental cost-effectiveness ratio (ICER, a measure that compares the difference in costs and outcomes of two interventions)

Limitations

The economic literature review was conducted by a single reviewer.

Results

Literature Search

The database search yielded 48 citations after duplicates were removed (n = 13). Articles were excluded based on information in the title and abstract. Six full-text articles were retrieved for review, and one met the inclusion criteria. The article selection process is presented in Figure 2 using the flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[22]

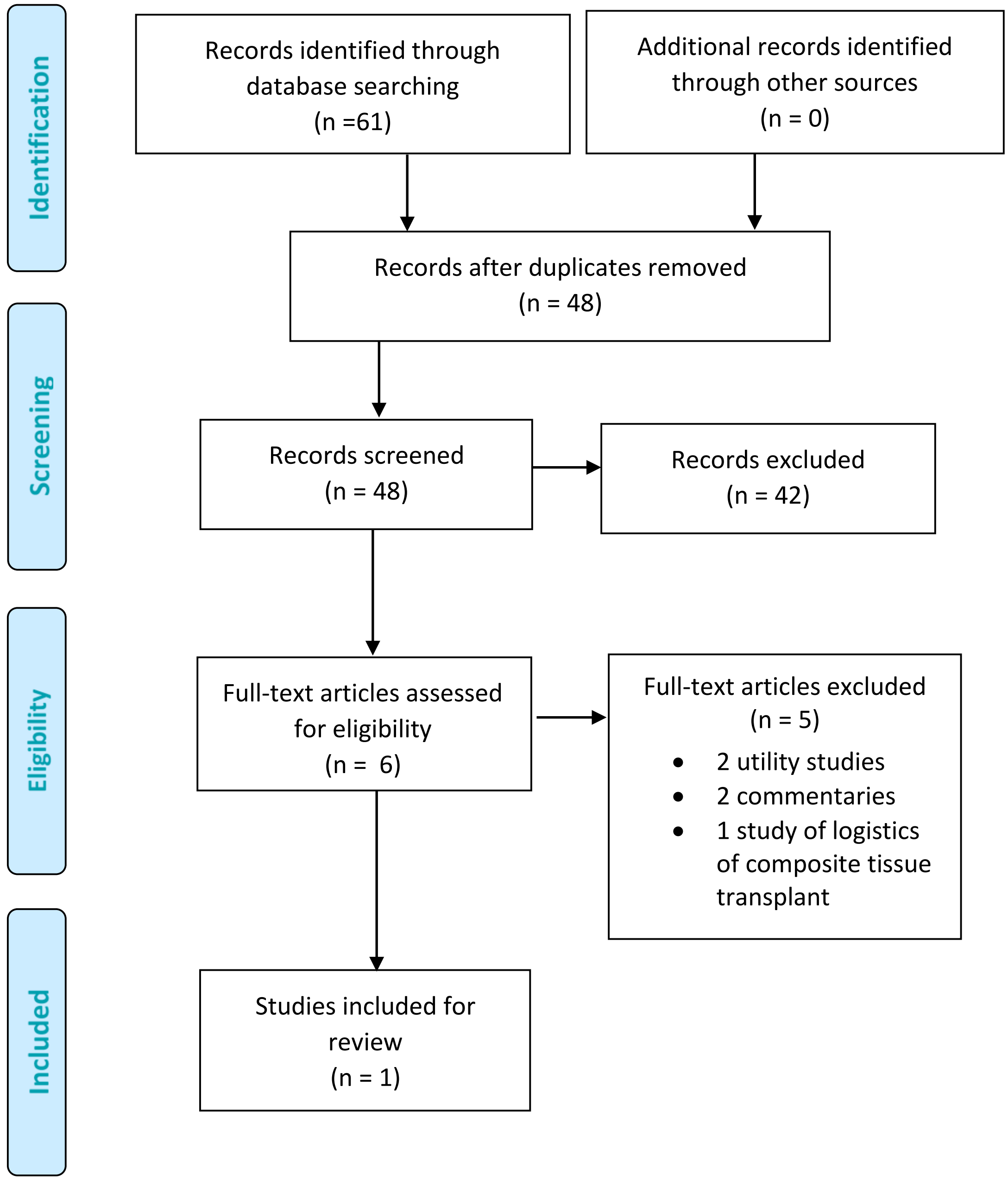

Figure 2: PRISMA Flow Diagram for the Economic Review

Source: Adapted from Moher et al, 2009.[22]

Critical Review

Table 3 provides a summary of the included study. Chung et al 2010[23] conducted a cost-utility analysis from the societal perspective in the United States, comparing two treatment strategies: patients who received composite tissue transplant of a single hand versus patients who received a prosthesis (artificial limb). The study also compared transplant of both hands versus prosthesis. The cost estimates were based on Medicare fee schedules plus the cost for productivity loss. The authors used the time trade-off approach to estimate the health-related utility for different health states. (Utility is a measure of people's preference for one state of health compared to others.) The eight health states in this study were minor complications related to immunosuppression for single- or double-hand transplant, major complications related to immunosuppression for single- or double-hand transplant, amputation of the transplanted hand or hands, and (for patients with no transplant) use of prosthesis for one or both hands. The single-hand transplant program was more expensive than the prosthesis strategy and was less effective in terms of QALY gained. Double-hand transplant was more expensive than standard care. The associated ICER was $318,961 USD per QALY gained.

We had several concerns about the design of this study. In estimating the utility of a composite tissue transplant, the authors assumed that complications from the procedure or from immunosuppression would last a lifetime; however, some major complications in their model, such as infection and acute rejection, usually have a temporary impact.

In addition, the authors applied an annual discount rate of 3% for the cost but not for the QALY. (Discounting is used to convert future values to an equivalent present value.) Although there is no consensus on whether the cost and health benefit should be discounted at the same rate,[24,25] most guidelines for economic evaluations use a common discount rate for both.[26] We replicated the model with discounting. When a discount rate of 3% was applied, the discounted incremental effectiveness of double-hand transplant was reduced to 1.06 QALYs compared with the prosthesis (double-hand transplant: 16.06 QALYs; prosthesis: 15 QALYs) and resulted in an even higher ICER, about $460,387 per QALY gained. Similarly, we applied the discount rate of 3% in the single-hand transplant scenario, the discounted QALY in the prosthesis group was still higher than in the single-hand transplant group (17.86 QALYs vs. 17.32 QALYs).

Finally, the authors assumed that the remaining life span of 40 years for a 35-year-old male would be equal for both treatment strategies. In reality, immunosuppression therapy, which is essential after a transplant, might reduce life expectancy for transplant recipients.

Table 3: Results of Economic Literature Review—Summary

Name, Year	Study Design and Perspective	Population	Interventions Comparators	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Chung et al, 2010[23]	Type of analysis: CUA Study design: decision-analytic model Perspective: societal perspective, the United States Time horizon: lifetime	Two scenarios: 35-year-old male with 1) unilateral hand amputation	Transplant of one hand versus prosthesis	Unilateral hand transplant: QALY gained: −1.19 Total QALYs: 28.81 (transplant); 30 (prosthesis) Annual discount rate: NA	Currency and year: US$, 2009 Unilateral hand transplant: Incremental cost: $507,640 Lifetime cost: $528,293 (transplant); $20,653 (prosthesis) Annual discount rate: 3%	Unilateral hand transplant: Transplant was dominated by prosthesis.
		2) bilateral hand amputation	Transplant of both hands versus prosthesis	Bilateral hand transplant: QALY gained: 1.53 Total QALYs: 26.73 (transplant); 25.2 (prosthesis) Annual discount rate: NA	Bilateral hand transplant: Incremental cost: $488,010 Lifetime cost: $529,315 (transplant); $41,305 (prosthesis) Annual discount rate: 3%	Bilateral hand transplant: ICER: $318,961 per QALY gained

Abbreviations: CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; NA, not available; QALY, quality-adjusted life-year.

Discussion and Conclusions

In this systematic review, we identified only one economic evaluation. Hand transplant and related immunosuppression treatment were costly and associated with considerable risks. Similarly, the rehabilitation necessary after the transplant was also very costly. Chung et al[23] concluded that composite tissue transplant of the hand was not cost-effective.

In addition to our concerns presented above (see Critical Review), we considered the source of the cost data to assess whether the results of this study could apply in Canada. The authors used costs from the perspective of a payer (the US Medicare fee schedule), and they probably underestimated the true health care cost associated with using the prosthetic hand. They assumed that the prosthesis would need to be replaced every four years, so one patient would require about 10 prostheses for the remaining life span of 40 years. In addition to the cost associated with the prostheses, there are usually costs for rehabilitation when patients receive the new prosthesis. Nevertheless, the lifetime costs for the single- and double-hand prosthesis strategies were rather low: $20,653 USD and $41,305 USD, respectively.

In summary, a single health economic study showed composite tissue transplant of the hand was not cost-effective in the United States. Results are not generalizable to the Ontario context.

PRIMARY ECONOMIC EVALUATION

The published economic evaluation identified in the literature review addressed the interventions of interest, but it was not conducted from a Canadian perspective.[23] Also, several key aspects of composite tissue transplant of hands and arms—immunosuppression therapy, surgical techniques, and patient management—have improved over time. Recognizing the importance of these changes and the need for locally useful information, we conducted a cost-utility analysis using updated scientific evidence and Ontario cost data.

Objectives

The objectives of this economic evaluation were to determine if unilateral (one hand) and bilateral (both hands) hand transplants are more or less expensive compared with standard care, and to assess the cost-effectiveness of hand transplant (incremental cost per quality-adjusted life-year [QALY] gained).

Methods

The information presented in this section of the report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.[27]

Type of Analysis

We conducted a cost-utility analysis comparing hand transplant and standard care (i.e., no transplant). (A cost-utility analysis is a type of economic evaluation that measures outcomes as health-related preferences, often expressed as quality-adjusted life-years [QALYs].)

Target Population

The target population in our model was adult patients who had one or both hands amputated more than 6 months earlier owing to trauma. They were generally healthy, both physically and psychologically. The age and gender of the population in our model—37 years old and 80% male—were the same as for 47 patients who received composite tissue transplant of a hand or arm, as described in the International Registry on Hand and Composite Tissue Transplantation.[13] Please note that the population in our economic model is slightly different than the population included in the clinical evidence review in this report.

In a separate scenario, we also considered a population of adult patients who were already undergoing immunosuppression therapy (e.g., from a previous organ transplant) and who had a relatively stable disease condition. This subgroup of patients would be likely to gain the most benefit from the hand transplant because they would not have the extra cost and extra risk of complication from immunosuppression.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care, the potential payer.

Interventions

The intervention of interest was composite tissue transplant of the hand, under contemporary immunosuppression regimens. See Background section above for details. In the standard care group, a proportion of patients used prostheses (artificial limbs).

Discounting and Time Horizon

We discounted future costs and QALYs to present values, and we applied an annual discount rate of 5% to both costs and QALYs, following guidelines from the Canadian Agency for Drugs and Technologies in Health.[26] All costs are expressed in 2015 Canadian dollars.[28] We selected a time horizon of 30 years for the base case analysis and up to 50 years for the sensitivity analysis.

Model Structure of the Analysis

We developed a Markov decision-analytic model to capture the long-term clinical and economic outcomes of hand transplant versus standard care. Figure 3 illustrates the model, simplified.

The model includes a one-year transition period in which the transplant recipients progress from the transplant procedure to a period of stable health. During this year, there is considerable risk of surgical complications, acute rejection and loss of the new hand; however, patients may gradually recover and gain hand function. After their condition stabilizes, transplant recipients enter states of minor or major complications. A lifetime of immunosuppression therapy is needed; therefore, transplant patients have a higher risk of developing various chronic diseases and a higher risk of dying from cardiovascular diseases (not shown in Figure 3). Using the categories defined by Chung et al,[23] we included the following major complications: cancer, diabetes, renal (kidney) failure, and infections. Minor complications were hypertension (high blood pressure), dyslipidemia (high blood fat and cholesterol levels), acute rejection of the new hand, and arterial or deep venous thrombosis (blood clot). During the follow-up period, patients in the minor complication states can move to the major complication states or amputation of the transplanted hand. Infection is defined as a temporary health state, and patients would transfer back to the minor complication state after the infection is successfully treated (one yearly Markov cycle).

In standard care, patients may either use a prosthesis or not, but they do not switch between prosthesis and no prosthesis during the follow-up.

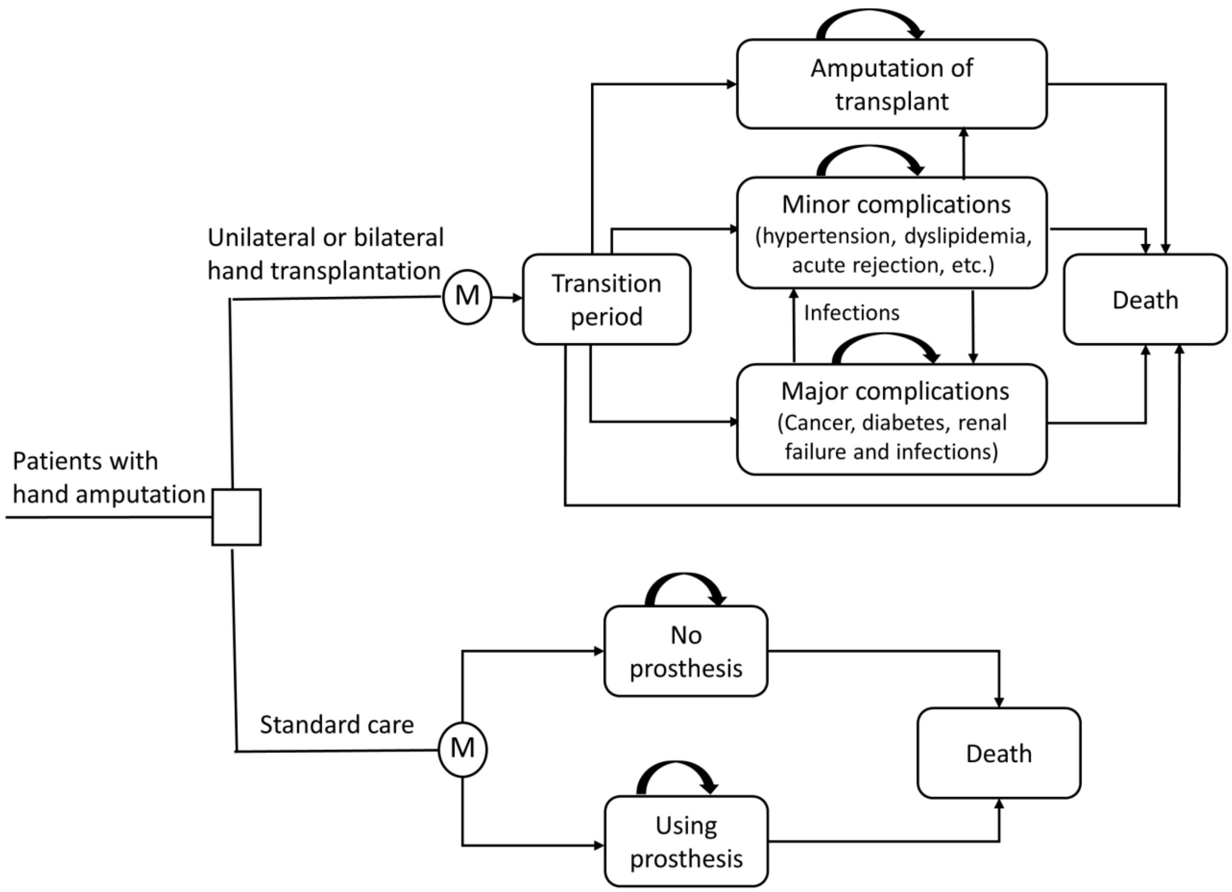

Figure 3: Composite Tissue Transplant of Hand Versus Standard Care, Simplified Decision-Analytic Model

Abbreviations: M, Markov model.

Main Assumptions

The goals of this analysis were to estimate the differences in costs and effectiveness between two treatments (hand transplant versus standard care) and to estimate the incremental cost-effectiveness ratio (ICER), a measure of value for money that estimates how much it will cost to gain one quality-adjusted life-year (QALY). A QALY is defined as one year of perfect health. For simplicity, we ignored certain clinical events and corresponding health care resource use that are likely to be similar in both treatment groups (transplant and standard care) or that would have a small impact on cost or effectiveness (i.e., minor complications such as hypertension and dyslipidemia caused by immunosuppression). We made the following assumptions that simplify the model but do not alter our primary goal:

- Transplant recipients would take immunosuppressant drugs for the rest of their lives, conditional on the survival of the transplanted hand
- After the transplant, no patients would have perfect health. That is, all transplant recipients would experience either minor or major complications or amputation of transplanted hand

- A unilateral hand transplant would be done for patients who had lost one hand, and patients who had lost both hands would receive a bilateral transplant in a single operation
- Amputation of the transplanted hand would only occur in the first three years after the transplant
- After losing the transplanted hand to amputation for any reason, people in the transplant group would be identical to people in standard care—that is, they would recover quickly from earlier complications and have no further risk of any complications from immunosuppression therapy; however, their health utility would be slightly lower than for patients in the standard care group
- Infection would have a temporary impact on health, although patients might experience more than one episode of infection during the long-term follow up
- Patients in the standard care group would have the same age- and sex-specific mortality as the general population, whereas mortality in the hand transplant group would be higher owing to the complications and risk of death associated with immunosuppression treatment
- Patients' age and sex would not be associated with their risk of surgical or immunosuppression-related complications or with the risk of loss of the transplanted hand

Assumptions for the Subgroup Analysis

In comparing hand transplant patients already undergoing immunosuppression treatment (i.e., previous organ transplant recipients) with patient with hand amputation receiving standard care, we assumed that:

- The hand transplant would not alter the ongoing maintenance of the immunosuppression treatment (we therefore excluded those treatment costs)
- Patients in both treatment strategies would have identical risks of complications from the immunosuppression treatment (we therefore excluded the costs of treating immunosuppression-related complications)
- Except for a 1% rate of surgical mortality associated with the hand-transplant procedure, the remaining lifespan of both groups (i.e., hand-transplant survivors and patients in standard care) would be the same: 32.8 years, similar to the life expectancy of 35- to 39-year-old patients with a kidney transplant in the US[29]

Clinical Outcomes, Utilities, and Cost Parameters

We used a number of different input parameters (the specific elements that go into the model). These included:

- Variables of clinical outcomes of the hand transplant, related to the surgical procedure and/or immunosuppression
- Utility values for the hand transplant and for standard care
- Various costs such as the costs of screening donors and recipients, the cost of the transplant procedure, and the cost of ongoing immunosuppression treatment

These parameters are described in more detail below. We derived many of the parameters from previous studies and, when necessary, we contacted authors of those studies to clarify information in their publications.

Clinical Outcomes of Hand Transplants

We faced several considerations in deciding whether to use in our model the outcomes of 47 hand/arm transplant recipients (excluding 12 recipients from China[15]) in the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) from 1998 to 2014[13,14]:

- Our target patients are healthier than those in the registry
- The registry includes hand and arm transplant recipients; however, hand transplants have a higher chance of leading to improved function, compared with arm transplants (i.e., the degree of amputation is associated with functional outcomes[30])
- Patient selection strategies for hand transplant, surgical techniques, and protocols for immunosuppression treatment have all improved over time, so outcomes of earlier patients in the registry may not reflect the outcomes we could expect today

Based on these considerations, the outcomes in our hypothetical patients would be better than those in the international registry. Additionally, it is not realistic for the model to include all complications related to either the surgical procedure or immunosuppression treatment. We limited our model to the most common complications following the hand transplant procedure and/or immunosuppression but did not differentiate between the risk of complications in unilateral versus bilateral hand transplants.

Table 4 provides our estimates of clinical outcomes for the model parameters. We developed these in consultation with experts and using IRHCTT data and published data on complications associated with immunosuppression treatment following solid organ transplant as a reference.[31] The risk of mortality in the model's different health states is presented in Table 5.

Table 4: Clinical Outcomes for Hand Transplant Strategy in the Economic Model

Model Parameters	Estimates for Economic Model	Complications of Hand or Arm Transplant[a]	Immunosuppression-Related Complications of Solid Organ Transplant
Mortality			
Surgical mortality	0.5%	6%	NA
Increased cardiovascular mortality for those under immunosuppression therapy	2.5-fold higher than general population	NA	2.5-fold higher than general population[31]
Age- and sex-specific mortality of general population	Canadian Life Tables[32]	NA	NA
Amputation of transplant (owing to, e.g., infections, chronic rejection or non-compliance)			NA
1st year	5%	11%	
2nd year	1% for those at risk	0	
3rd year	1% for those at risk	4%	
≥ 4th year	0	2%	
Major complications			
Opportunistic infections			
Risk of infection requiring readmission	50% in first year and 3% annually for those at risk in subsequent years	Cytomegalovirus: 13%; bacterial infection: 30%; infections of graft connective tissues: 6%.	Cytomegalovirus: 25%–50%; PTLD: up to 15%–20%; pneumonia: 7.3%–36%; invasive fungal infections: up to 40%–59% (see Appendix 5 for further detail)[31]
Risk of all-cause mortality	Assuming no extra risk of mortality owing to infections	NA	NA
Cancer			
Risk of cancer	Incidence rate ratio, 3-fold higher than general population	4%	3-5-fold higher than general population; about half with cancer after 25 years of immunosuppression[31]

Model Parameters	Estimates for Economic Model	Complications of Hand or Arm Transplant[a]	Immunosuppression-Related Complications of Solid Organ Transplant
Incidence rate of cancer for general population	Canadian Cancer Statistics[33]		
Relative survival ratio,[b] conditional on having survived:	See Appendix 6 for details[33,34]	NA	NA
0 years	0.769		
1 year	0.921		
2 years	0.956		
3 years	0.967		
4 years	0.978		
5 years	0.989		
Diabetes			
Risk of diabetes	8% in first year, and no risk after first year	Diabetes: 8%; hyperglycemia: 44%	13.5% (based on meta-analysis of all types of solid organ transplants)[31]
Relative risk of all-cause mortality	1.8 (95% CI 1.71–1.9)[35b]	NA	NA
Renal failure			
Risk of renal failure	1% annually for those at risk	Renal failure: 2%; elevated creatinine: 17%	7%–21% in 5 years[36]
Relative risk of all-cause mortality	4.55 (95% CI 4.38– 4.74)[36]	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; PTLD, post-transplant lymphoproliferative disorders.
[a]Based on the International Registry on Hand and Composite Tissue Transplantation, reported in Petruzzo et al, 2014.[13]
[b]Relative survival ratio is the ratio of the observed survival in cancer patients to the expected survival of a group of similar people without cancer (in practice, the general population).[33,34]
[c]Authors reported the hazard ratio of any cause of mortality as 1.8 (95% CI 1.71–1.9) for diabetes versus non-diabetes.[35] We assumed that the relative risk is the same as the hazard ratio.
Note: Unilateral and bilateral hand transplants shared the same model inputs unless otherwise noted.

Table 5: Risk of Mortality in Different Health States in Markov Model

Health State	Risk of Morality
Hand transplant	
Transition period (the first year)	Surgical mortality + age- and sex-specific mortality of general population + added cardiovascular mortality[a]
Amputation of transplant	Age- and sex-specific mortality of general population
Minor complications	Age- and sex-specific mortality of general population + added cardiovascular mortality[a]
Opportunistic infections (major complication)	Age- and sex-specific mortality of general population + added cardiovascular mortality[a]
Diabetes and renal failure (major complication)	Age- and sex-specific mortality of general population × relative risk of any cause mortality
Cancer (major complication)	1 − relative survival ratio × (1 − age- and sex-specific mortality of general population); see Appendix 6 for details
Standard care	Age- and sex-specific mortality of general population

[a]Cardiovascular mortality includes death caused by heart disease and stroke. About 25% of deaths in Canada in 2011 were because of heart disease or stroke, for both sexes.[37] The added cardiovascular mortality = 1.5 × (25% × age- and sex-specific mortality of general population).

Clinical Outcomes of Standard Care

As noted above (see Main Assumptions), age- and sex-specific mortality in the standard care group is the same as that of the general Canadian population (Table 5). It is important to note that patients in the standard care group do not have any risk of complications related to hand transplant or immunosuppression treatment.

Utilities

Utilities are numbers that represent the strength of a person's preference for a certain health outcome (e.g., can walk, cannot walk) or health state (alive, dead). We used the health utilities determined by Chung et al[23] in their 2010 study of unilateral and bilateral hand transplant in the United States (Table 6). The authors conducted a time trade-off survey with 100 medical students to determine the utilities of various hypothetical health states related to living with a hand amputation: minor and major complications following hand transplant, amputation of the transplant, and use of prosthesis in the no-transplant group. We assumed that patients with or without prosthesis would have the same utility, as either option could reflect an individual's highest preference; there is no reason to assume that one approach is better than the other.

For our sensitivity analysis, we also used utilities derived from a time trade-off survey of a sample of people from the general public in Canada.[38] The authors measured utility by treatment—unilateral hand transplant and standard care (no transplant)—but not by the specific health states (such as amputation of the transplant or renal failure owing to immunosuppression). The utility of transplant of a single hand and the utility of standard care were 0.74 and 0.72, respectively.

Table 6: Utilities in the Economic Model

Health State	Utility (95% CI)	Author, Year
Unilateral hand amputation		
Unilateral hand transplant		
Minor immunosuppression complications	0.78 (0.75–0.81)	Chung et al, 2010[23]
Major immunosuppression complications	0.59 (0.55–0.63)	Chung et al, 2010[23]
Amputation of transplant	0.73 (0.69– 0.76)	Chung et al, 2010[23]
Transition period, the first year post-transplant	0.59 (0.55–0.63)	Estimate
Standard care (i.e., no transplant)		
Using prosthesis	0.75 (0.72–0.79)	Chung et al, 2010[23]
No prosthesis	0.75 (0.72–0.79)	Estimate
Bilateral hand amputation		
Bilateral hand transplant		
Minor immunosuppression complications	0.73 (0.69–0.77)	Chung et al, 2010[23]
Major immunosuppression complications	0.53 (0.49–0.58)	Chung et al, 2010[23]
Amputation of transplant	0.62 (0.58–0.66)	Chung et al, 2010[23]
Transition period, the first year post-transplant	0.53 (0.49–0.58)	Estimate
Standard care (i.e., no transplant)		
Using prosthesis	0.63 (0.59–0.67)	Chung et al, 2010[23]
No prosthesis	0.63 (0.59–0.67)	Estimate

Abbreviation: CI, confidence interval.

Costs

Table 7 presents the costs of a hand transplant program. University Health Network provided the detailed cost estimates (not including physician fees) of screening recipients, the transplant procedure, rehabilitation, and so on for bilateral hands transplantation. We estimated the physician fees based on Ontario's 2015 Schedule of Benefits for musculoskeletal system surgical procedures.[39] The cost of a single-hand transplant would be very similar to a bilateral procedure: we simply assumed that the operating room time would be 3 hours less for a single hand and that all other costs would be identical. We consulted experts to estimate the costs of donor screening, hand procurement, and prostheses for donors.[8] (For ethical reasons a prosthesis may be provided, depending on the family's wishes.) Based on published data, we estimated the attributable costs of immunosuppression-related complications, such as cancer and diabetes (Table 8).

Table 7: Cost of Hand Transplant, Including and Excluding Physician Fee

Variable	Cost, Including Physician Fee, $	Cost, Excluding Physician Fee, $	Cost Components and Sources
Screening recipient	38,713 (5 patients)	37,113 (5 patients)	Bioethics, laboratory service, hand/physical therapy, social work, physician fee, etc.; written communication[a]; Ministry of Health and Long-Term Care[39]
Screening donor	23,228 (3 donors)	22,268 (3 donors)	Assuming same per-person cost as to screen recipients
Pre-transplant	8,809	8,169	Hand/physical therapy, laboratory service, psychiatry, social work, physician fee, etc.[39]
Procurement			
Single hand	5,940	4,854	Assuming 2 hours in operating room, physician fee and prosthesis ($2,000) for the donor
Both hands	10,452	8,282	Assuming same cost components as for single-hand transplant
Transplant, peri-operative			
Single hand	93,510	79,929	Operating room, intensive care unit, ward stay, immunosuppression, laboratory service, pharmacy, occupational therapy, physician fee, etc.[39]
Both hands	101,187	84,211	Assuming same cost components as for single-hand transplant[39]
Post-transplant rehabilitation			Includes cost for readmission for various reasons (except cancer, diabetes and renal failure) within 2 years post-transplant
1st year post-transplant	133,042	130,333	Readmission episodes, immunosuppression, anti-infective therapy, laboratory service, psychiatry, social work, physician fee, etc.[39]
2nd year post-transplant	81,847	80,222	Readmission episodes, immunosuppression, laboratory service, psychiatry, social work, physician fee, etc.[39]
Annual fixed cost in 3rd year and later	22,144	21,060	Immunosuppression and physician fee, 1 visit per month. Assuming no rehabilitation after 2 years[39]

[a]Estimated cost of hand transplantation; written communication, July 2015.

Table 8: Cost of Immunosuppression-Related Complications

Variable	Cost, $	Notes and Sources
Amputation of transplant	20,160	Estimated at 3 hours of operating room time, 2 days in intensive care unit, 8 days in ward, and physician fee (assuming 10% of other costs included); written communication[a]
Opportunistic infections, after first 2 years	9,420	Cost for readmission and physician fee (assuming 10% of other costs included); written communication[a]
Cancer[b]		
First year	21,311	Total cost: $27,879 in the first year[40] minus the average cost of health care per capita, $6,568[41]
Annual cost in subsequent years	4,262	Estimated at 20% of the first year
Diabetes[b]		
First year	3,293	Goeree et al[42]
Annual cost in subsequent years	1,394	Goeree et al[42]
Renal failure, per year	66,892	Manns et al[43]

[a]Estimated cost of hand transplantation; written communication, July 2015.
[b]Attributable costs owing to the disease.

For standard care, there were costs incurred from prosthesis use, rehabilitation, and regular follow-up visits (Table 9). According to a survey by Raichle et al,[44] 56% of patients with an arm amputation used a prosthesis. One prosthesis can last an average of 3 years.[45] There was no cost for those not using a prosthesis.

Table 9: Resource Use and Cost of Using Prosthesis

Variable	Value	Notes and Sources
Proportion of patients using prosthesis	56%	Survey in the United States[44]
Average service life of prosthesis	3 years	Amputee Coalition, 2015[45]
Cost per externally powered prosthesis	$17,000	Including physician fee, the cost for the device and installation approved by the Assistive Devices Program, Ontario Ministry of Health and Long-Term Care[46]
Cost of occupational therapy when using new prosthesis	$1,813	Estimated at 10 visits with 2 hours per visit
Cost of routine outpatient follow up	$361.2	Estimated at 4 visits per year

Parameters for the Subgroup Analysis

For the hypothetical subgroup of patients already receiving immunosuppression treatment (e.g., because of an earlier organ transplant), we assumed that the probabilities for surgical mortality, amputation of the transplanted limb, and major complications were 0.01, 0.03 and 0.05, respectively. Adding these probabilities and subtracting from 1, we estimated that 91% of patients would live out their lives with good health outcomes (i.e., only minor complications). We also assumed that patients' health states would not change over their lifetimes. The remaining lifespan for this subgroup of patients was 32.8 years for both the standard care and hand transplant groups, except for a 1% surgical mortality associated with the transplants. There were no additional cost for the immunosuppression treatment and immunosuppression-related complications. However, we cannot verify these parameters as no published data are available on this subgroup of patients. Details of the model inputs for this subgroup are reported in Appendix 7, Table A8.

Analysis

Using our Markov decision analytic model, we compared the cost-effectiveness of unilateral and bilateral hand transplant and standard care, for both our primary target population and for the subgroup of patients already receiving immunosuppression treatment. Our main outcome was the ICER, measured as cost per QALY gained. We analyzed several scenarios to estimate the impact of various factors, such as including or excluding physician fees, having patients use a more expensive prosthesis, and including the cost for a personal support worker. We also conducted one-way and multi-way sensitivity analyses to assess other important factors that affect the incremental cost per QALY gained. In addition, we evaluated patient-level uncertainty using a first-order Monte Carlo simulation (also known as microsimulation or individual random walks). All analyses were conducted using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA) and Excel 2013 (Microsoft, Redmond, WA).

Generalizability

The findings of this economic analysis cannot be generalized to all adult patients with hand amputation. The results may, however, be used to guide decision-making about treatment options for healthy adults following a hand amputation.

Results

Base Case Analysis

Based on the model outlined in Figure 3 and using the parameter estimates in Tables 4 to 9, we calculated the cost and effectiveness of composite tissue transplant of one hand (unilateral) and both hands (bilateral) versus standard care over a 30-year period (Table 10). The unilateral hand transplant strategy was dominated by the standard care strategy, meaning the transplant was more costly and less effective (in terms of QALYs). Bilateral hand transplant was associated with an ICER of than $3.8 million per QALY gained, meaning it would cost roughly $3.8 million to gain one year of perfect health from this treatment. Although there is no universally accepted maximum amount that is considered reasonable to pay to gain a year of perfect health, thresholds commonly used in Canada range from $50,000 to $100,000 per QALY. Therefore, bilateral hand transplant was also not cost-effective compared with standard care.

Table 10: Base Case Analysis

Strategy	Average Total Costs, $[a]	Incremental Cost, $	QALYs	QALYs Gained	ICER,[b] $
Unilateral hand amputation					
Standard care	61,429	—	11.82	—	—
Hand transplant	735,647	674,218	10.96	−0.87	Dominated
Bilateral hand amputation					
Standard care	114,057	—	9.93	—	—
Hand transplant	747,837	633,780	10.10	0.17	3,765,037

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All costs are 2015 Canadian dollars.
[b]Incremental cost per QALY gained.
Note: numbers may appear inexact because of rounding.

We also explored the costs of bilateral transplant by treatment stages (Figure 4). In brief, the health care cost in the first year was very high, about $316,000 per patient, but after two years the treatment cost was much lower.

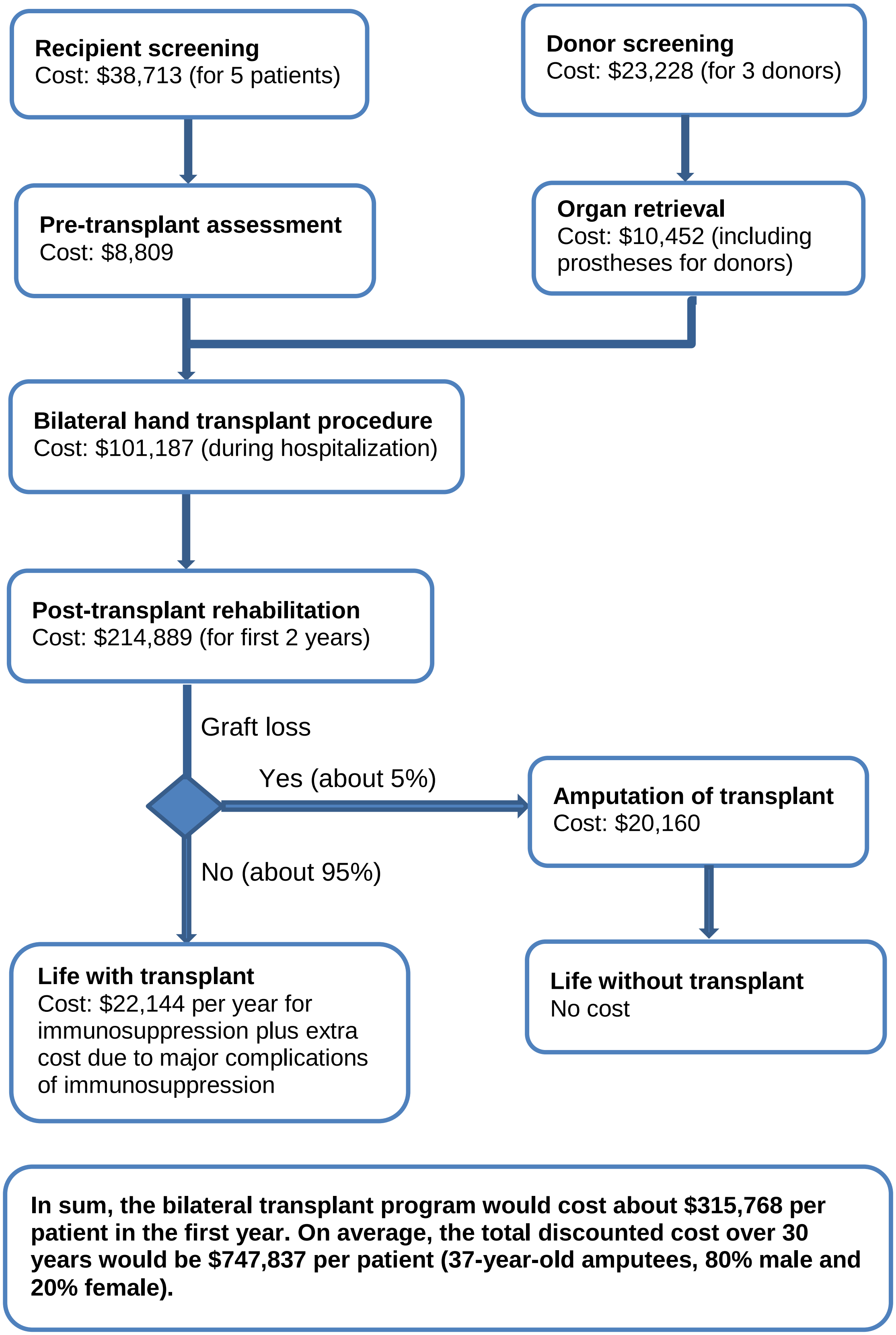

Figure 4: Summary of Treatment Stage and Cost of Bilateral Hand Transplant

Subgroup Analysis

We present the results for the subgroup—adult patients already undergoing immunosuppression treatment—in Table 11. Compared with the base case, the subgroup yielded more favourable results for the hand transplant program. However, the ICER for unilateral hand transplant was still high ($1.4 million per QALY gained) and the ICER for bilateral hand transplant was $162,426 per QALY gained, higher than the commonly used threshold in Canada. When we reduced surgical mortality rate to 0.5%, the ICER for a single-hand transplant decreased to $1.03 million per QALY gained (incremental cost: $260,699; incremental effectiveness: 0.25 QALY), and the ICER for double-hand transplants decreased to $155,855 per QALY gained (incremental cost: $216,947; incremental effectiveness: 1.39 QALYs).

Table 11: Subgroup Analysis for the Adult Patients Already Undergoing Immunosuppression Therapy

Strategy	Average Total Costs, $[a]	Incremental Cost, $	QALYs	QALYs Gained	ICER,[b] $
Unilateral hand amputation[c]					
Standard care	65,308	—	12.57	—	—
Hand transplant	325,218	259,910	12.76	0.19	1,384,561
Bilateral hand amputation[c]					
Standard care	121,251	—	10.56	—	—
Hand transplant	337,407	216,157	11.89	1.33	162,426

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All costs are 2015 Canadian dollars.
[b]Incremental cost per QALY gained.
[c]Remaining lifetime of 32.8 years.
Note: numbers may appear inexact because of rounding.

Deterministic Sensitivity Analysis

We examined several factors that could affect the ICER values of hand transplant versus standard care (Appendix 8, Table A9). Exclusion of physician fees had a marginal impact on results for both unilateral and bilateral hand transplant. Without discounting, both transplant strategies were dominated by (more expensive and less effective) the standard care strategy. However, for the subgroup of patients already taking immunosuppression drugs, the ICERs of unilateral and bilateral hand transplant versus standard care were reduced to $582,104 and $46,581 per QALY gained, respectively, without discounting. Using the utility data from the survey of the general public in Canada, unilateral hand transplant was still dominated by standard care.

The costs and QALYs of both treatment strategies (transplant and standard care) for patients with bilateral hand transplant over a 50-year period are presented in Figures 5 and 6. The difference in cost between the two treatments increased over time. Compared with standard care, the bilateral hand transplant program resulted in the highest QALY gained (0.37) at 17 years of follow up, with a corresponding ICER of $1.5 million per QALY gained, whereas after 36 years, the standard care group was associated with higher QALYs than the hand transplant group.

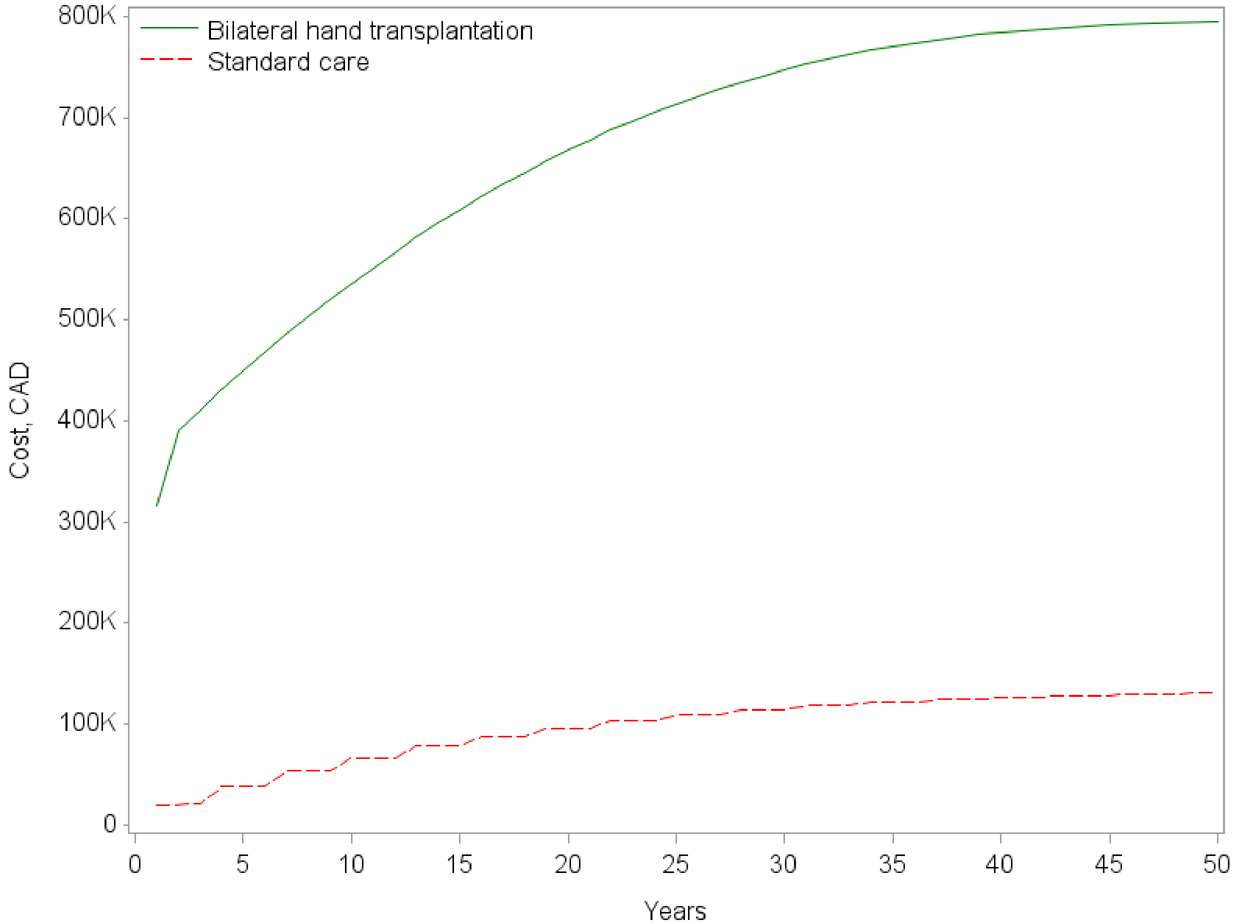

Figure 5: Total Costs of Bilateral Hand Transplant and Standard Care by Follow-Up Time

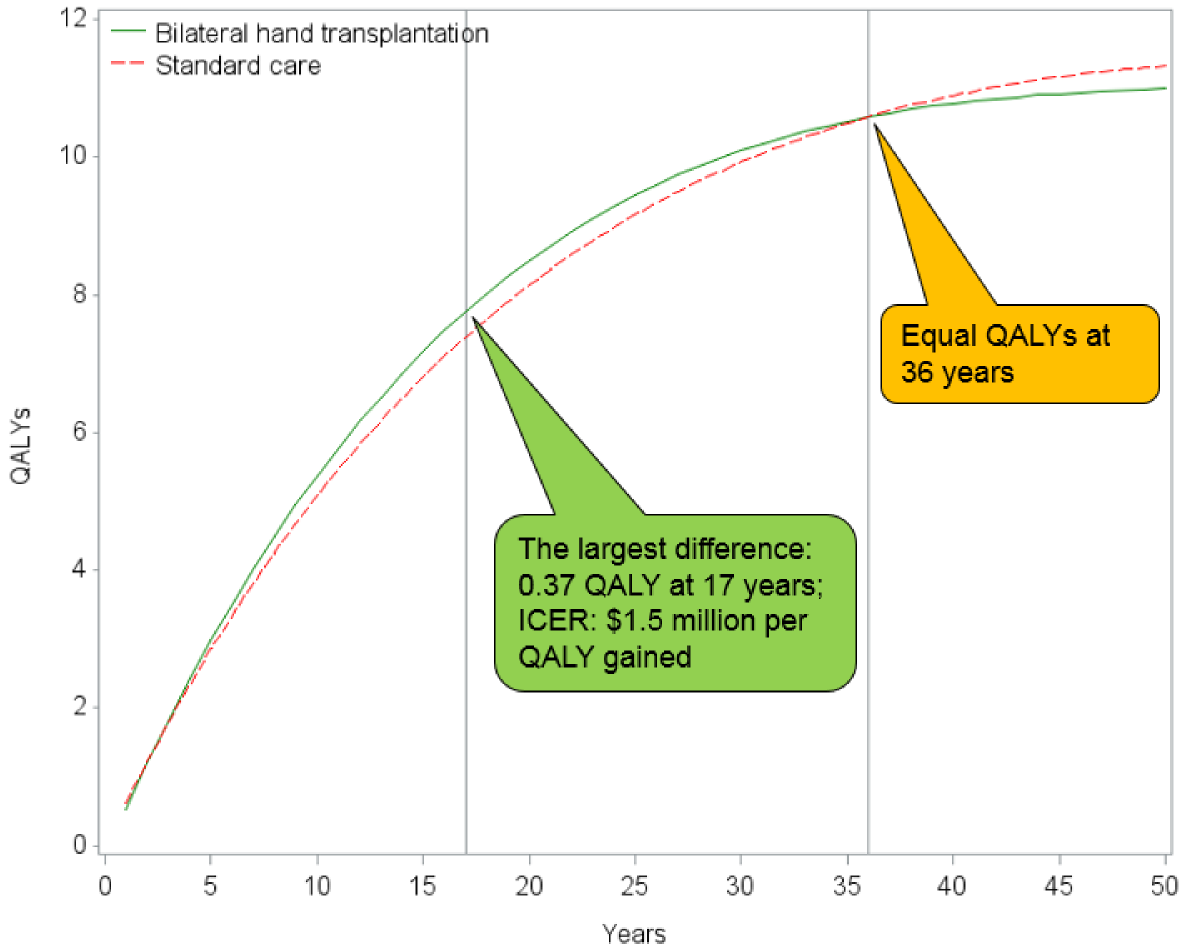

Figure 6: Quality-Adjusted Life-Years in Bilateral Hand Transplant and Standard Care by Follow-Up Time

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

When we reduced the risk of major complications (cancer, diabetes, renal failure, and infections) to 50% of the risk in the base case, the QALY gained with bilateral hand transplants increased to 0.59 and the corresponding ICER was about $1 million per QALY gained. Excluding the cost of transplant (i.e., if that cost were included in the hospital's global budget), the ICER for a bilateral transplant was $3.2 million per QALY gained. If we included the cost of a personal support worker for patients with bilateral hand transplant in the standard care group (2 hours/day, $17.52/hour; 2×17.52×365 = $12,790/year),[47] the ICER would decrease to $2.6 million per QALY gained. If a sophisticated prosthesis costs $80,000 (more expensive than our base case prosthesis) and 80% of patients in standard care use a prosthesis, the incremental cost of bilateral hand transplant compared to standard care was $27,659 (much lower than in the base case), with a corresponding ICER of $164,309 per QALY gained.

Unilateral hand transplant was dominated by standard care in most of our one-way sensitivity analyses (detailed results not reported). For bilateral hand transplants, the one-way sensitivity analyses showed that the ICERs were greater than $1 million per QALY gained in all scenarios examined (Table 12).

Table 12: One-Way Sensitivity Analysis, Bilateral Hand Transplant Versus Standard Care

Variable (Range)	Incremental Cost Per QALY Gained, $
Base case analysis (reference)	**3,765,037**
Age of target patient (30 to 50 years old)	1,692,690 to dominated[a]
Proportion of male in target patients (50% to 100%)	4,418,927 to 3,425,972
Proportion of patients using prosthesis in standard care group (40% to 100%)	3,958,629 to 3,232,661
Risk of surgical mortality (0% to 1%)	2,905,873 to 5,365,808
Incidence rate ratio of cancer because of immunosuppression therapy (2- to 4-fold higher than general population)	2,326,106 to 9,049,492
Risk of diabetes in the first year (6% to 10%)	2,993,421 to 5,078,606
Annual risk of renal failure for those at risk (0% to 2%)	1,333,807 to dominated[a]
Total cost of screening, pre-treatment assessment and transplant (excluding physician fee) for bilateral hand transplant ($120,032 to $200,053)	3,527,350 to 4,002,725
Annual cost of post-transplant care (excluding physician fee) for bilateral hand transplant (75% to 125% of base case)	3,054,887 to 4,475,188
Price per prosthesis ($12,750 to $21,250)	3,921,359 to 3,608,716
Utility of using prostheses or not for patients with bilateral hand amputation in standard care group (0.59 to 0.67)	793,374 to dominated
Utility of major complication of bilateral hand transplant (0.49 to 0.58)	Dominated [a] to 1,663,571
Utility of minor complication of bilateral hand transplant (0.69 to 0.77)	Dominated[a] to 1,120,415

[a]Bilateral hand transplant was more expensive and less effective compared to standard care.

First-Order Monte Carlo Simulation

We generated 100,000 hypothetical patients to explore patient-level uncertainty in our model. Table 13 presents the results of the Monte Carlo simulations, which were consistent with the base case (see Table 10). However, the uncertainty in QALYs (e.g., the coefficient of variation, the ratio of the standard deviation to the mean) in the unilateral and bilateral hand transplant strategies was greater than in the standard care group. About 39% of patients with a single-hand transplant and 65% of patients with a double-hand transplant would have higher QALYs than the standard care group.

Table 13: Results of First-Order Monte Carlo Simulation

Strategy	Average Total Costs, $[a] (SD)	Incremental Cost, $ (SD)	QALYs (SD)	QALYs Gained (SD)	ICER,[b] $
Unilateral hand amputation					
Standard care	61,416 (54,953)	—	11.82 (1.14)	—	—
Hand transplant	735,836 (236,968)	674,420 (242,575)	10.97 (1.99)	−0.85 (1.72)	Dominated
Bilateral hand amputation					
Standard care	113,486 (102,090)	—	9.93 (0.97)	—	—
Hand transplant	748,035 (238,477)	634,549 (257,757)	10.10 (1.91)	0.17 (1.67)	3,691,961

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SD, standard deviation.
[a]All costs are 2015 Canadian dollars.
[b]Incremental cost per QALY gained, calculated using the mean.
Notes: Results are expressed as the mean with standard deviation. Numbers may appear inexact because of rounding.

Discussion and Conclusions

Our economic analysis demonstrates that a hand transplant program is extremely unlikely to be cost-effective according to commonly used cost-effectiveness thresholds. The costs of bilateral and unilateral hand transplant were fairly close, but only bilateral hand transplant resulted in greater QALYs compared with standard care. Transplant for the subgroup of patients who were already using immunosuppression therapy was more cost-effective than in the base case because they did not have the additional risk of complications and costs related to taking that medication. Nevertheless, even in the most favourable scenario for hand transplants (i.e., bilateral hand transplant for people already on immunosuppression drugs), the ICER was still as high as $162,426 per QALY gained, exceeding the common thresholds in Ontario.

Our conclusions are consistent with those of Chung et al 2010,[23] the only published cost-effectiveness study of hand or arm transplants that we found. Although our modelling strategy, parameter inputs, and discounting rate differed (for example, we used a dynamic Markov model instead of a decision tree with static health states over time), both studies were based on overlapping scientific evidence, and we applied the health utilities from Chung et al[23] in our model.

It is important to note that the target population of the economic model is not the same as the actual patients included in our clinical evidence review. A 2007 paper on patient selection for hand transplants suggested that only about one-third of patients who had received the procedure met the criteria for being good candidates.[30] Our model assumed there would be careful patient selection and optimal post-transplant management, so the risks of surgical mortality, amputation of the transplant, and complications from immunosuppression in our model were much lower than in the observed data (i.e., 47 cases in the International Registry on Hand and Composite Tissue Transplantation[13,14]). However, even under these optimal conditions, the hand transplant strategy was still not cost-effective compared with standard care (with or without prosthesis). Although not formally evaluated, hand transplants for less healthy adult patients or arm transplants for our healthy target population would be unlikely to be cost-effective as well, since clinical outcomes and health utilities in these patients would be worse than in the model's optimal hand transplant patients. The uncertainty around cost-effectiveness is even greater for children since it is unclear whether a transplanted hand or arm would continue to function and develop as children grow; it is also unclear how immunosuppression impacts life expectancy and quality of life for healthy child patients.

In the future, it may be that less toxic, less expensive immunosuppressant drugs will be developed and that patient selection and treatment strategies will improve. However, this would not necessarily mean that hand transplant would become cost-effective, since prosthesis techniques are improving at the same time. For example, it has been reported that an advanced bionic hand can be produced by 3D-printing for less than £1,000 GBP (about $2,000 CAD).[48]

Strengths and Limitations

Our study has several strengths: the use of modelling techniques to capture the major benefits of hand transplants (i.e., improved health utility, conditional on a good outcome) and the harm from long-term immunosuppression therapy (e.g., increased risk of chronic disease and of death); comprehensive analyses to examine the cost-effectiveness of various scenarios; and expert consultation for the model assumptions and inputs.

Our study also encounters several limitations. In our model, we defined mutually exclusive health states and did not allow patients to transition between the major complication states. We did not consider patients' motivation to choose one treatment option over another and their compliance in follow-up. We also limited the model to a few of the most common complications related to immunosuppression but ignored others. We made some effort to develop reliable parameters for our hypothetical healthy adults, but the model inputs may still be imprecise, and some model assumptions are difficult to verify. We estimated costs conservatively, and the real resources and costs for a hand transplant program may be much higher than our estimates. For instance, the 2015 surgery for a bilateral hand transplant for an 8-year-old boy in the US lasted 10 hours and involved 40 medical personnel including 12 surgeons, according to a news report.[49] In addition, we did not include the cost of post-transplant rehabilitation beyond two years,[8] and we ignored the cost of minor complications such as hypertension and dyslipidemia. Our cost estimates for the standard care group may also be conservative. For example, our model may not have fully captured the cost of rehabilitation programs and adaptive aids that patients with hand amputation need in their lifetimes.

Summary

- Unilateral hand transplant (transplant of one hand) is an expensive treatment with reduced effectiveness (lower quality-adjusted life-years [QALYs]) compared with standard care
- Bilateral hand transplant (transplant of two hands) is unlikely to be cost-effective as it is associated with a small gain in QALYs and substantially increased costs compared with standard care
- Further investigation is needed into the appropriate economic thresholds for non-drug treatments for rare conditions to better inform decision-making about publicly funding these treatments

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to determine the estimated cost burden over the next 3 years, from 2016 to 2018, of a composite tissue transplant program for selected patients with hand amputation. All costs are reported in 2015 Canadian dollars.[28]

Objectives

The objective of this analysis was to assess the potential budget impact of adopting composite tissue transplant of the hand as a treatment option in Ontario.

Methods

Target Population

Although there are a large number of adults with hand or arm amputation in Ontario, transplants would be performed in a very small group of patients. According to the composite tissue transplant program proposal, the annual volume of hand or arm transplants in Ontario would be about 3. Because our cost-utility analysis, above, showed that there was no gain in quality-adjusted life-years (QALY) for unilateral hand transplant (transplant of one hand) compared with standard care, we limited our target population to adults needing a bilateral hand transplant (transplant of both hands).

Canadian Costs

Based on undiscounted results from the base case model in the cost-utility analysis, we estimated the average cost in Canadian dollars for each year after the transplant procedure, for three years (Table 14). Table 15 presents the undiscounted cost for each post-transplant year for the subgroup of patients already taking immunosuppression drugs (people who previously had an organ transplant and were already taking immunosuppression therapy would not incur the cost of those drugs for a hand transplant).

Table 14: Average Cost Per Patient for Each Post-Transplant Year, Base Case

Strategy[a]	Post-Transplant Costs, $[b]		
	Year 1	Year 2	Year 3
Standard care	20,258	202	202
Bilateral hand transplant	315,768	78,428	22,476

[a]The risk of mortality was very low for both treatments in the first 3 years (> 99% survival), so we approximated the average cost per patient as the average cost for those at risk.
[b]2015 Canadian dollars.

Table 15: Average Cost Per Patient for Each Post-Transplant Year, Subgroup Analysis

Strategy	Post-Transplant Costs, $[a]		
	Year 1	Year 2	Year 3
Standard care	20,258	202	202
Bilateral hand transplant[b]	273,887	58,586	520

[a]2015 Canadian dollars.
[b]Subgroup is adult patients already undergoing immunosuppression therapy because of an earlier organ transplant.

Analysis

We included both new patients and those treated previously and, for simplicity, assumed that all patients would survive beyond the 3 years covered by this analysis. We used the following formula to estimate the net budget impact of bilateral hand transplants, relative to standard care (standard care includes patients with or without prostheses):

$$\text{Budget impact } = \sum_{i=1}^{k}(Cost_{CTTi} \times N - Cost_{SCi} \times N)$$

i: year post transplant; i = 1, 2, 3.
k: total follow-up time, up to 3 years.
N: number of patients, 3 in base case analysis.
Cost $_{CTTi}$: annual cost at year i in the hand transplant group.
Cost $_{SCi}$: annual cost at year i in the standard care group.

We conducted a base case analysis and sensitivity analyses, varying the number of transplant recipients and the mix of patients (in one scenario, 1 of 3 patients were already undergoing immunosuppression therapy).

We conducted the budget impact analysis using Excel 2013 (Microsoft, Redmond, WA).

Results

Base Case

Adopting a hand transplant program would lead to a moderate cost increase (Table 16). If 3 patients per year received bilateral hand transplants, the net budget impact in 2016, 2017, and 2018 would be about $0.9 million, $1.1 million and $1.2 million, respectively.

Table 16: Budget Impact of Adopting Hand Transplant Program in Ontario, Base Case

Year	Strategy	Program Cost, $			Sum
		Year 1	Year 2	Year 3	
2016	Standard care	60,774	—	—	60,774
	Bilateral hand transplant	947,304	—	—	947,304
	Net budget impact, 2016	886,530	—	—	**886,530**
2017	Standard care	60,774	606	—	61,380
	Bilateral hand transplant	947,304	235,284	—	1,182,588
	Net budget impact, 2017	886,530	234,678	—	**1,121,208**
2018	Standard care	60,774	606	606	61,986
	Bilateral hand transplant	947,304	235,284	67,428	1,250,016
	Net budget impact, 2018	886,530	234,678	66,822	**1,188,030**

Sensitivity Analysis

If 2 of the 8 patients expected to receive a hand transplant each year were already undergoing immunosuppression therapy, the budget impact would be marginally less than in the base case. As expected, the budget impact would vary with the volume of hand transplant procedures (Table 17).

Table 17: Budget Impact of Adopting Hand Transplant Program in Ontario, Sensitivity Analysis

Scenario	Net Budget Impact, $		
	2016	2017	2018
1 of 3 patients per year already undergoing immunosuppression therapy	844,649	1,059,485	1,104,351
4 patients in 2016, 6 patients in 2017, and 8 patients in 2018[a]	1,182,040	2,085,964	2,922,532
2 patients per year[a]	591,020	747,472	792,020

[a]The analysis was based on undiscounted results from the base case in the cost-utility analysis.

Conclusion

A hand transplant program in Ontario would lead to a moderate cost increase: about $0.9 million in 2016 to treat 3 adult patients.

ABBREVIATIONS

AMSTAR	Assessment of Multiple Systematic Reviews
DASH	Disabilities of the Arm, Shoulder, and Hand
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
IRHCTT	International Registry on Hand and Composite Tissue Transplantation
QALY	Quality-adjusted life-year

GLOSSARY

Cost-utility analysis	A type of analysis that estimates the value for money of an intervention by weighing the cost of the intervention against the improvements in length of life and quality of life. The result is expressed as a dollar amount per "quality-adjusted life-year" or QALY.
Deterministic sensitivity analysis	A type of analysis that changes the variables to determine if the final answer will change. The analysis is done by first setting values for each factor, and then substituting other possible values for one (in a one-way sensitivity analysis) or more (in a multi-way sensitivity analysis) factors to test how these changes affect the result.
Discounting	A method that considers that costs and health benefits are worth more today than in the future.
Dominance	A test or treatment is in a state of dominance over another when it is both more effective and less costly than the other treatment option.
Incremental cost	The extra cost associated with using one test or treatment instead of another.
Incremental cost-effectiveness ratio (ICER)	A ratio that compares the extra costs of a treatment with the additional benefits of the treatment.
Markov model	A type of modelling that measures the health state of a patient over the course of treatment. A patient may stay in one health state or move from one health state to another, depending on the effect of the treatment and the progression of the disease.
Monte Carlo simulation	Determines the uncertainty in an economic model by running many trials of the model. In each trial, random numbers are assigned wherever values are uncertain to see how the model result changes.
Quality-adjusted life-year (QALY)	A measure of health outcome that includes both the quality and the quantity of life.
Sensitivity analysis	Every evaluation contains some degree of imprecision. Study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact on study results. There are various types of sensitivity analyses. Examples include deterministic, probabilistic, and scenario.

APPENDICES

Appendix 1: Literature Search Strategies

Strategy for the Clinical Evidence Review

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <2nd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 29>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Upper Extremity/ (313496)
2 (upper extremit* or arm$1 or forearm* or limb$1 or hand$1).tw. (1449806)
3 or/1-2 (1579713)
4 Amputation, Traumatic/ (6139)
5 Amputation/ (33852)
6 Disarticulation/ (16991)
7 Amputation Stumps/ (4382)
8 Amputees/ (29112)
9 (amputat* or amputee* or macroamputat* or disarticulation* or bilateral or unilateral).tw. (669626)
10 or/4-9 (709702)
11 3 and 10 (96794)
12 exp Upper Extremity Deformities, Congenital/ (20739)
13 ((upper extremit* or arm$1 or forearm* or limb$1 or hand$1) adj2 (congenital or deformit* or malform*)).tw. (7313)
14 or/11-13 (120950)
15 Vascularized Composite Allotransplantation/ (204)
16 Composite Tissue Allografts/ (1928)
17 Allografts/ (27060)
18 (allotransplant* or (allograft* adj2 composite) or CTA or CTAs or VCA or VCAs).tw. (30266)
19 Transplantation, Homologous/ (110997)
20 ((upper extremit* or arm$1 or forearm* or limb$1 or hand$1) adj3 (transplant* or allograft*)).tw. (3120)
21 or/15-20 (165256)
22 14 and 21 (1258)
23 Hand Transplantation/ (533)
24 Upper Extremity/tr or Arm/tr or Forearm/tr or Hand/tr (57)
25 or/22-24 (1616)
26 exp Animals/ not (exp Animals/ and Humans/) (8221976)
27 25 not 26 (1500)
28 limit 27 to (english language and yr="2010 -Current") [Limit not valid in CDSR,DARE; records were retained] (632)
29 28 use pmoz,cctr,coch,dare,clhta,cleed (246)
30 exp arm/ (198395)
31 (upper extremit* or arm$1 or forearm* or limb$1 or hand$1).tw. (1449806)

32 or/30-31 (1516194)
33 traumatic amputation/ (6206)
34 amputation/ (33852)
35 limb amputation/ (3359)
36 amputation stump/ (5195)
37 (amputat* or amputee* or macroamputat* or disarticulation* or bilateral or unilateral).tw. (669626)
38 exp limb malformation/ (35425)
39 (congenital or deformit* or malform*).tw. (625704)
40 or/33-39 (1290436)
41 32 and 40 (137586)
42 hand amputation/ (533)
43 arm amputation/ (1169)
44 or/41-43 (138121)
45 vascularized composite allotransplantation/ (204)
46 allotransplantation/ (32674)
47 allograft/ (27109)
48 composite graft/ (1875)
49 (allotransplant* or (allograft* adj2 composite) or CTA or CTAs or VCA or VCAs).tw. (30266)
50 ((upper extremit* or arm$1 or forearm* or fore-arm$1 or limb$1 or hand$1) adj3 (transplant* or allograft*)).tw. (3120)
51 or/45-50 (89817)
52 44 and 51 (1251)
53 hand transplantation/ (533)
54 or/52-53 (1579)
55 (exp animal/ or nonhuman/) not exp human/ (9396760)
56 54 not 55 (1459)
57 limit 56 to (english language and yr="2010 -Current") [Limit not valid in CDSR,DARE; records were retained] (658)
58 57 use emez (424)
59 29 or 58 (670)
60 59 use pmoz (232)
61 59 use emez (424)
62 59 use cctr (5)
63 59 use coch (8)
64 59 use dare (0)
65 59 use clhta (0)
66 59 use cleed (1)
67 remove duplicates from 59 (489)

Strategy for the Economic Review

Databases searched included: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <2nd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 29>, All Ovid MEDLINE(R) <1946 to Present>"

Search Strategy:

----

1 exp Upper Extremity/ (313496)
2 (upper extremit* or arm$1 or forearm* or limb$1 or hand$1).tw. (1449806)
3 or/1-2 (1579713)
4 Amputation, Traumatic/ (6139)
5 Amputation/ (33852)
6 Disarticulation/ (16991)
7 Amputation Stumps/ (4382)
8 Amputees/ (29112)
9 (amputat* or amputee* or macroamputat* or disarticulation* or bilateral or unilateral).tw. (669626)
10 or/4-9 (709702)
11 3 and 10 (96794)
12 exp Upper Extremity Deformities, Congenital/ (20739)
13 ((upper extremit* or arm$1 or forearm* or limb$1 or hand$1) adj2 (congenital or deformit* or malform*)).tw. (7313)
14 or/11-13 (120950)
15 Vascularized Composite Allotransplantation/ (204)
16 Composite Tissue Allografts/ (1928)
17 Allografts/ (27060)
18 (allotransplant* or (allograft* adj2 composite) or CTA or CTAs or VCA or VCAs).tw. (30266)
19 Transplantation, Homologous/ (110997)
20 ((upper extremit* or arm$1 or forearm* or limb$1 or hand$1) adj3 (transplant* or allograft*)).tw. (3120)
21 or/15-20 (165256)
22 14 and 21 (1258)
23 Hand Transplantation/ (533)
24 Upper Extremity/tr or Arm/tr or Forearm/tr or Hand/tr (57)
25 or/22-24 (1616)
26 exp Animals/ not (exp Animals/ and Humans/) (8221976)
27 25 not 26 (1500)
28 economics/ (246834)
29 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (696277)
30 economics.fs. (368739)
31 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (634825)
32 exp "costs and cost analysis"/ (484991)
33 cost*.ti. (218587)
34 cost effective*.tw. (227768)
35 (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. (142523)
36 models, economic/ (126668)
37 markov chains/ or monte carlo method/ (115776)
38 (decision adj1 (tree* or analy* or model*)).tw. (30955)
39 (markov or markow or monte carlo).tw. (92036)
40 quality-adjusted life years/ (25933)
41 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (44380)

42 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (87543)
43 or/28-42 (2146092)
44 27 and 43 (59)
45 limit 44 to english language [Limit not valid in CDSR,DARE; records were retained] (58)
46 45 use pmoz,cctr,coch,dare,clhta (30)
47 27 use cleed (2)
48 exp arm/ (198395)
49 (upper extremit* or arm$1 or forearm* or limb$1 or hand$1).tw. (1449806)
50 or/48-49 (1516194)
51 traumatic amputation/ (6206)
52 amputation/ (33852)
53 limb amputation/ (3359)
54 amputation stump/ (5195)
55 (amputat* or amputee* or macroamputat* or disarticulation* or bilateral or unilateral).tw. (669626)
56 exp limb malformation/ (35425)
57 (congenital or deformit* or malform*).tw. (625704)
58 or/51-57 (1290436)
59 50 and 58 (137586)
60 hand amputation/ (533)
61 arm amputation/ (1169)
62 or/59-61 (138121)
63 vascularized composite allotransplantation/ (204)
64 allotransplantation/ (32674)
65 allograft/ (27109)
66 composite graft/ (1875)
67 (allotransplant* or (allograft* adj2 composite) or CTA or CTAs or VCA or VCAs).tw. (30266)
68 ((upper extremit* or arm$1 or forearm* or fore-arm$1 or limb$1 or hand$1) adj3 (transplant* or allograft*)).tw. (3120)
69 or/63-68 (89817)
70 62 and 69 (1251)
71 hand transplantation/ (533)
72 or/70-71 (1579)
73 (exp animal/ or nonhuman/) not exp human/ (9396760)
74 72 not 73 (1459)
75 Economics/ (246834)
76 Health Economics/ or exp Pharmacoeconomics/ (208728)
77 Economic Aspect/ or exp Economic Evaluation/ (374317)
78 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (634825)
79 exp "Cost"/ (484991)
80 cost*.ti. (218587)
81 cost effective*.tw. (227768)
82 (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. (142523)
83 Monte Carlo Method/ (47134)
84 (decision adj1 (tree* or analy* or model*)).tw. (30955)
85 (markov or markow or monte carlo).tw. (92036)
86 Quality-Adjusted Life Years/ (25933)

87 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (44380)
88 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (87543)
89 or/75-88 (1755711)
90 74 and 89 (59)
91 limit 90 to english language [Limit not valid in CDSR,DARE; records were retained] (56)
92 91 use emez (29)
93 46 or 47 or 92 (61)
94 93 use pmoz (21)
95 93 use emez (29)
96 93 use cctr (0)
97 93 use coch (9)
98 93 use dare (0)
99 93 use clhta (0)
100 93 use cleed (2)
101 remove duplicates from 93 (48)

Appendix 2: Evidence Quality Assessment in Clinical Evidence Review

Table A1: AMSTAR Scores of Included Systematic Reviews

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
NICE, 2010[9b]	7	✓	?[c]	✓	✓	✗	✓	✓[d]	✓[e]	✗[f]	✗[g]	✓
Landin et al, 2012[12]	5	✓	✗[h]	✗	✓	✗	✓	✗	✗	✓	✗	✓

[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al.[10]
[b]Included to provide guidance on the start date for our literature search.
[c]Does not state how many individuals screened articles.
[d]Studies included were case series and case reports, with no formal quality assessment, but issues with follow-up, study design, study population, and other issues are documented.
[e]States shortcomings of research in “efficacy” and “safety’ sections (e.g., timing not stated, absolute figures not reported).
[f]Does not state that it was not appropriate to combine results from case series and case reports.
[g]Does not state that publication bias was not assessed because there were fewer than 10 studies.
[h]Does not state how many individuals screened articles, but the methodology paper they cite states two authors extracted data.

Table A2: GRADE Evidence Profile for Composite Tissue Transplant of Hand or Arm

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Functional Recovery							
1 (Systematic review)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[a]	Undetected	No other considerations	⊕ Very low
Acute Rejection							
1 (Case series)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	No other considerations	⊕ Very low
Chronic Rejection							
1 (Case series)	No serious limitations	No serious limitations	Serious limitations (–1)[b]	No serious limitations	Undetected	No other considerations	⊕ Very low
Amputation							
1 (Case series)	No serious limitations	No serious limitations	Serious limitations (–1)[c]	No serious limitations	Undetected	No other considerations	⊕ Very low
Complications							
1 (Case series)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	No other considerations	⊕ Very low
Mortality							
1 (Case series)	No serious limitations	No serious limitations	Serious limitations (–1)[d]	No serious limitations	Undetected	No other considerations	⊕ Very low

[a]The interval around the estimate is rather large and if the upper limit represented the true effect, a different clinical course may be taken (if the limb is not functioning properly, this may lead to a more extensive rehabilitation regimen or may lead to a decision to amputate).
[b]Patients who developed chronic rejection based on noncompliance would not get through the rigorous patient screening proposed for Ontario.
[c]Some patients who had transplant amputated may not represent procedures that would be done in Ontario (simultaneous face/arm transplant, bilateral arm transplant).
[d]Some patients who died may not represent procedures that would be done in Ontario (simultaneous face/arm transplant, bilateral arm transplant).

Table A3: Risk of Bias Among Case Series of Composite Tissue Transplant of Hand or Arm

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Petruzzo et al, 2014[12]	Limitations[a]	No limitations	No limitations	Limitations[b]	No limitations

[a]Some patients included in this case series would not meet the patient selection criteria in the proposed Ontario transplant programs; therefore, results may not be generalizable.
[b]As this paper was a case series, there was no control for confounding.

Appendix 3: Results From Chinese Case Series

Pei et al[15] describe transplants performed on 12 patients in China with 15 hand or arm transplants from 1999 to 2006. Table A4 summarizes the characteristics of the study population and Table A5 summarizes the findings from this case series.

Table A4: Study Population Characteristics, Chinese Case Series

N (% male)	Age, years, mean ± SD	Type of Transplant	Level of Transplant	Cause of Amputation (n)
12 (91.7%)	34 ± 11.13 Range: 19 – 52	3 bilateral transplants 9 unilateral transplants 7 right-side transplants 2 left-side transplants	1 thumb 1 palm 6 wrist level 5 forearm level	traumatic amputation (3) machine injury (3) explosion (5) cold injury (1)

Abbreviations: SD, standard deviation
Source: Pei et al, 2012[15]

Table A5: Summary of Outcomes, Chinese Case Series

Acute Rejection	Chronic Rejection	Complications	Amputation	Mortality
11 of the 12 transplant patients (91.6%) experienced acute rejection, 4.1 episodes on average. Among the 11 patients, 1 patient had 10 episodes of acute rejection (once a year after transplant), 1 had 9 episodes (once a year after transplant), 1 had 8 episodes (once a year after transplant), 1 had 7 episodes (once a year after transplant), 1 had 4 episodes, 1 had 2 episodes, and 5 patients each had 1 episode of acute rejection. The causes of acute rejection were not reported.	2 of the 12 patients (16.7%) experienced chronic rejection. Case 2 had a rejection15 months post-transplant, with severe continuous pain on radial side of the wrist. Ischemic changes and necrosis of the dorsal skin were noted, surgery was done but the pain continued and the wound did not heal. Case 8 had a rejection episode at 2 years characterized by swelling and rash that did not improve.	Opportunistic infections among the 12 transplant patients included 1 episode each of eczema, pulmonary infection, steroid-induced dermatitis, and fungal infection. Among metabolic complications were 4 episodes of elevated transaminases + yGT, 3 episodes of elevated glucose, and 1 episode of arterial hypertension and hypoproteinemia.	In the 12 transplant recipients, 7 transplants (58.3%) resulted in amputation. Reasons varied: pain and non-healing wound, necrosis owing to rejection, non-compliance with immunosuppressive treatment, and rejection owing to decreased immunosuppressive treatment because of pulmonary infection.	No deaths were reported.

Abbreviations: yGT, gamma-glutamyltransferase.
Source: Pei et al, 2012.[15]

Appendix 4: Measures of Functional Recovery

Disabilities of the Arm, Shoulder, and Hand (DASH) is scored in two components: the disability/symptom section (30 items, scored 1 –5) and the optional high-performance sport/music or work section (4 items, scored 1–5). Higher scores on the DASH represent higher levels of disability.[50] This measure is the most commonly used in examining functional recovery in hand and arm transplant patients. The minimum clinically important difference ranges from 8 to 17 DASH points (with a mean of 13).[51]

Chen's Functional Grade is a grading scheme with four levels of functional recovery:

- Grade 1: good function, able to resume original work, range of motion exceeds 60% of normal, complete or nearly complete recovery of sensation, muscle power of grades 4 and 5
- Grade 2: able to resume some suitable work, range of motion exceeds 40% of normal, nearly complete recovery of sensation, muscle power of grades 3 and 4
- Grade 3: able to carry on normal life, range of motion exceeds 30% of normal, partial recovery of sensation, muscle power of grade 3
- Grade 4: almost no function in survived limb[50]

Hand Transplantation Score System has six domains: appearance, sensibility, movement, psychological and social acceptance, daily activities and work status, and patient satisfaction and general well-being. The score system is based on a value of 100 points where 81–100 points is graded as excellent, 61–80 as good, 31–60 as fair, and 0–30 as poor.[50]

The Carroll test integrates mobility, motor function, and sensation to assess global hand function that are required for activities of daily living. It consists of tasks such as moving objects of different sizes and weights, writing one's name, and pouring water.[52] The score system is out of 99 and higher scores represent better function.[53] An excellent functional outcome score is 85 or higher, good scores are 75–84, fair scores are 51–74, and a poor score is less than 51.[52]

Appendix 5: Complications of Immunosuppression Following Organ Transplant

Table A6: Rates of Infections, Diabetes, and Kidney Failure Associated With Immunosuppression Following Solid-Organ Transplant, by Organ

Complication	Overall	Transplant Type					
		Kidney	Pancreas	Liver	Lung	Heart	Intestinal
Infections, %							
Cytomegalovirus	25–50						
PTLD		1–5					15–20
Bacterial urinary tract infections	4.4 in non-kidney transplants	7					
Skin and wound		up to 45 in kidney-pancreas transplants					
Pneumonia in first year		7.3		22	36		
Invasive fungal infections			7–14	5–42	15–35		40–59
Diabetes, %	13.5 (meta-analysis)	20–50 in first year		9–21 in first year	20 in first year		
Kidney failure, % (cumulative incidence at 5 years)[36]				18	16	11; 7 in heart-lung transplants	21

Abbreviations: PTLD: Post-transplant lymphoproliferative disease.
Data source: Girlanda R, 2013.[31]

Appendix 6: Estimating One-Year Relative Survival Ratio for Patients With Cancer

In the model developed for our cost-utility analysis, we needed to estimate the increased risk of death from cancers that transplant patients may develop as a result of the immunosuppression treatment they must take to prevent rejection of the transplanted limb. A relative survival ratio for cancer is the ratio of the observed survival in cancer patients to the expected survival of a group of similar non-cancer individuals (in practice, the general population). Relative survival ratio is the preferred measure for cancer survival, and the 5-year ratio is often chosen as the primary duration of analysis.[33] But our Markov model used a yearly cycle, so the time-dependent 1-year relative survival ratio for patients at risk is the desired parameter input for this model. Based on the 5-year relative survival ratio conditional on surviving from year 0 to year 5 and on the 1-year relative survival ratio at year 0 (see Table A7a), we approximated the conditional 1-year relative survival ratio from year 1 to year 5.

Table A7a: Published Unadjusted Conditional Relative Survival Ratios

Variable	Value	Source
5-year relative survival ratio, conditional on having survived		Canadian Cancer Statistics, 2015[33]
0 years	0.63	
1 years	0.81	
2 years	0.87	
3 years	0.90	
4 years	0.92	
5 years	0.93	
1-year relative survival ratio, conditional on having survived 0 years	0.769	Ellison, 2014[34]
10-year relative survival ratio, conditional on having survived 0 years	0.589	Ellison, 2014[34]

Note: The adjusted 5-year relative survival ratios, conditional on having survived from year 1 to year 5, were not available.

Let $S_C(t)$ and $S_G(t)$ be the probability of surviving exceeding time t for cancer patients and for the general population, respectively. Then, the relative survival ratio (RSR) to time t is:

(1) $\text{RSR}\ (t) = S_C(t)\ /\ S_G(t)$

(2) Also, the probability of survival to time t ($S[t]$) = $S_1 \times S_2 \times S_3 \times \ldots \times S_t$
$S_1, S_2, S_3 \ldots S_t$: the conditional probability of survival in a given time unit

Thus, formula (1) can be expressed as
(3) $\text{RSR}\ (t) = (S_{C1} \times S_{C2} \times S_{C3} \times \ldots \times S_{Ct})\ /\ (S_{G1} \times S_{G2} \times S_{G3} \times \ldots \times S_{Gt})$

Formula (3) can be re-written as
(4) $\text{RSR}\ (t) = (S_{C1}\ /\ S_{G1}) \times (S_{C2}\ /\ S_{G2}) \times (S_{C3}\ /\ S_{G3}) \times \ldots . \times (S_{Ct}\ /\ S_{Gt})$
(5) $= \text{RSR}_1 \times \text{RSR}_2 \times \text{RSR}_3 \times \ldots \times \text{RSR}_t$
$\text{RSR}_1, \text{RSR}_2, \text{RSR}_3 \ldots \text{RSR}_t$: relative survival ratio in each time unit, conditional on survival at the start point of the time unit

We selected 1 year as the time unit and assumed that the 1-year relative survival ratio at 5 years (i.e., conditional on surviving 5 years) was same as that at 6 years and later.
Based on formula (5),

(6) 5-year relative survival ratio at time 0 ($RSR_{\_5y\_T0}$) = $RSR_{\_1y\_T0} \times RSR_{\_1y\_T1} \times RSR_{\_1y\_T2} \times RSR_{\_1y\_T3} \times RSR_{\_1y\_T4}$
$RSR_{\_1y\_T0}$, $RSR_{\_1y\_T1}$ … : the 1-year relative survival ratio for those who survive at time 0, 1 year …

(7) 5-year relative survival ratio at year 1 ($RSR_{\_5y\_T1}$) = $RSR_{\_1y\_T1} \times RSR_{\_1y\_T2} \times RSR_{\_1y\_T3} \times RSR_{\_1y\_T4} \times RSR_{\_1y\_T5}$

Let formula (6) be divided by formula (7). Then,
(8) $(RSR_{\_5y\_T0} / RSR_{\_5y\_T1}) = RSR_{\_1y\_T0} / RSR_{\_1y\_T5}$

Then, $RSR_{\_1y\_T5} = (RSR_{\_5y\_T1} \times RSR_{\_1y\_T0}) / RSR_{\_5y\_T0} = (0.81 \times 0.769) / 0.63 = 0.989$

Using the same method, we estimated the 1-year relative survival ratio, conditional on having survived years from year 1 to year 4. See Table A7b.

Table A7b: Estimated One-Year Relative Survival Ratio

Variable	Value
1-year relative survival ratio, conditional on having survived	
0 years	0.769
1 years	0.921
2 years	0.956
3 years	0.967
4 years	0.978
5 years	0.989

To validate our findings, we compared the estimated 5-year and 10-year relative survival ratios using formula (5) and the published 1-year relative survival ratio.[34] The projected 5-year and 10-year relative survival ratios were 0.64 and 0.60, respectively, which were close to the observed values (0.63 for 5 years and 0.589 for 10 years, see Table A7a), indicating the validity of the estimated 1-year relative survival ratios.

Furthermore, we estimated the probability of death for patients with cancer, given the 1-year relative survival ratio and the annual probability of death in the general population in Canada.[32]

Formula (1) also can be expressed as
(9) $RSR = (1 - P_C) / (1 - P_G)$
Pc: the probability of death for patients with cancer; P_G: the age- and sex-specific probability of death in the general population, based on Canadian life tables.

(10) Then, $P_C = 1 - RSR \times (1 - P_G)$

The estimated probability of death for patients with cancer is conditional on the number of years they have survived and on their age and sex.

Appendix 7: Details of Model Inputs for the Subgroup Analysis

Table A8: Model Inputs for the Subgroup of Hand Transplant Recipients Already Undergoing Immunosuppression Therapy

Variable	Value	Notes and Sources
Hand transplant		
Post-transplant outcome		Utility values for post-transplant outcomes were same as in base case;[23] see Table 7
Surgical mortality	0.01	Estimate
Amputation of transplant	0.03	Estimate
Major complication	0.05	Estimate; we did not assign extra cost for major complications
Minor complication	0.91	Estimate
Total cost of transplant		
1 hand	$170,199	Written communication[a] and MOHLTC[39]
2 hands	$182,388	Written communication[a] and MOHLTC[39]
Cost of post-transplant care		
1st year post transplant	$91,812	Rehabilitation; assumes no readmission and no extra cost for immunosuppression and anti-infective therapy[39]
2nd year post transplant	$61,027	Rehabilitation; no extra cost for immunosuppression[39]
Annual cost, after 2 years	$542	6 physician visits per year; no extra cost for immunosuppression[39]
Cost of standard care		Same as in base case; see Table 9

Abbreviations: MOHLTC, Ministry of Health and Long-Term Care.

[a]Estimated cost of hand transplantation; written communication, July 2015.

Notes: Hand transplant recipients are adults with remaining life time of 32.8 years. Unilateral and bilateral hand transplants share the same parameter values, unless otherwise noted.

Appendix 8: Detailed Results of the Sensitivity Analysis

Table A9: Detailed Results of Sensitivity Analyses Comparing Hand Transplant and Standard Care

Strategy	Average Total Costs, $[a]	Incremental Cost, $	QALYs	QALYs Gained	ICER, $[b]
Sensitivity Analysis, Excluding Physician Fees					
Unilateral hand amputation					
Standard care	58,241	—	11.82	—	—
Hand transplant	699,939	641,698	10.96	−0.87	Dominated
Bilateral hand amputation					
Standard care	110,869	—	9.93	—	—
Hand transplant	707,649	596,780	10.10	0.17	3,545,238
Base Case Model, Undiscounted Results					
Unilateral hand amputation					
Standard care	107,901	—	21.71	—	—
Hand transplant	1,097,553	989,653	19.63	−2.07	Dominated
Bilateral hand amputation					
Standard care	200,113	—	18.23	—	—
Hand transplant	1,109,743	909,630	18.08	−0.15	Dominated
Subgroup Analysis Results for Adults With Amputations[c] Who Are Already Undergoing Immunosuppression Therapy, Undiscounted Results					
Unilateral hand amputation					
Standard care	122,566	—	24.6	—	—
Hand transplant	336,408	213,842	24.97	0.37	582,104
Bilateral hand amputation					
Standard care	227,286	—	20.66	—	—
Hand transplant	348,597	121,311	23.27	2.60	46,581
Results Based on the Utilities from the General Public in Canada					
Unilateral hand amputation					
Standard care	61,429	—	11.35	—	—
Hand transplant	735,647	674,218	11.20	−0.14	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All costs are 2015 Canadian dollars.
[b]Incremental cost per QALY gained.
[c]Remaining life time: 32.8 years.
Note: Some numbers may appear inexact because of rounding.

REFERENCES

(1) Armed Forces Institute of Regenerative Medicine [Internet]. Fort Detrick (MD): Medical Research and Material Command; c2000 [updated 2010 Mar 22; cited 2015 Oct 2]. Available from: http://mrmc.amedd.army.mil/index.cfm?pageid=medical_r_and_d.afirm.overview

(2) Bhuvaneswar CG, Epstein LA, Stern TA. Reactions to amputation: recognition and treatment. J Clin Psychiatry. 2007;9(4):303-8.

(3) Hand prosthetics [Internet]. Providence (RI): Brown University; c2003. Statistics: causes leading to amputation. 2003 Apr 28 [cited 2015 Oct 2]; [about 1 screen]. Available from: http://biomed.brown.edu/Courses/BI108/BI108_2003_Groups/Hand_Prosthetics/stats.html

(4) Active Living Alliance for Canadians with a Disability. Helping Canadians with disability/chronic disease get physically active: tip sheets for intermediaries [Internet]. Ottawa: Active Living Alliance for Canadians with a Disability; 2013 [cited 2015 Oct 2]. Available from: http://www.ala.ca/Images/TipSheets/pdfs/Amputations_tip_sheet.pdf

(5) LeBlanc M. Give hope - give a hand - the LN-4 prosthetic hand [Internet]. Stanford (CA): Stanford University; 2008 [cited 2015 Oct 2]. Available from: https://web.stanford.edu/class/engr110/2011/LeBlanc-03a.pdf

(6) Schuind F. Hand transplantation and vascularized composite tissue allografts in orthopaedics and traumatology. Orthop Traumatol Surg Res. 2010;96(3):283-90.

(7) Fischer S, Lian CG, Kueckelhaus M, Strom TB, Edelman ER, Clark RA, et al. Acute rejection in vascularized composite allotransplantation. Curr Opin Organ Transplant. 2014;19(6):531-44.

(8) MacKay BJ, Nacke E, Posner M. Hand transplantation–a review. Bull Hosp Jt Dis (2013). 2014;72(1):76-88.

(9) National Institute for Health and Clinical Excellence. Interventional procedure overview of hand allotransplantation [Internet]. London: National Institute for Health and Clinical Excellence; 2010 [cited 2015 Oct 5]. Available from: https://www.nice.org.uk/guidance/ipg383/evidence/hand-allotransplantation-overview2

(10) Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.

(11) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

(12) Landin L, Bonastre J, Casado-Sanchez C, Diez J, Ninkovic M, Lanzetta M, et al. Outcomes with respect to disabilities of the upper limb after hand allograft transplantation: a systematic review. Transpl Int. 2012;25(4):424-32.

(13) Petruzzo P, Lanzetta M, Dubernard J. International registry on hand and composite tissue transplantation. Transplantation. 2014;98:44.

(14) Petruzzo P, Lanzetta M, Dubernard JM, Landin L, Cavadas P, Margreiter R, et al. The international registry on hand and composite tissue transplantation. Transplantation. 2010;90(12):1590-4.

(15) Pei G, Xiang D, Gu L, Wang G, Zhu L, Yu L, et al. A report of 15 hand allotransplantations in 12 patients and their outcomes in China. Transplantation. 2012;94(10):1052-9.

(16) Lanzetta M, Nolli R, Vitale G, Magni F, Radaelli I, Stroppa L, et al. Hand transplantation: the Milan experience. Polish Journal of Surgery. 2007;79(12):762-72.

(17) Weissenbacher A, Hautz T, Pierer G, Ninkovic M, Zelger BG, Zelger B, et al. Hand transplantation in its fourteenth year: the Innsbruck experience. Vascularized Composite Allotransplantation. 2014;1(1-2):11-21.
(18) Matheson K. Eight-year-old boy becomes youngest double-hand transplant recipient. The Globe and Mail [Internet]. 2015 Jul 29. [cited 2015 Oct 2]. Available from: http://www.theglobeandmail.com/news/world/eight-year-old-boy-becomes-youngest-double-hand-transplant-recipient/article25748566/
(19) Barham L. Public and patient involvement at the UK National Institute for Health and Clinical Excellence. Patient. 2011;4(1):1-10.
(20) Messina J, Grainger DL. A pilot study to identify areas for further improvements in patient and public involvement in health technology assessments for medicines. Patient. 2012;5(3):199-211.
(21) Tjornhoj-Thomsen T, Hansen HP. Knowledge in health technology assessment: who, what, how? Int J Technol Assess Health Care. 2011;27(4):324-9.
(22) Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
(23) Chung KC, Oda T, Saddawi-Konefka D, Shauver MJ. An economic analysis of hand transplantation in the United States. Plast Reconstr Surg. 2010;125(2):589-98.
(24) Claxton K, Paulden M, Gravelle H, Brouwer W, Culyer AJ. Discounting and decision making in the economic evaluation of health-care technologies. Health Econ. 2011;20(1):2-15.
(25) Hammitt JK. Discounting health and cost-effectiveness analysis: a response to Nord. Health Econ. 2012;21(7):878-82.
(26) Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. 3rd ed. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
(27) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)–explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.
(28) Statistics Canada. Consumer Price Index, health and personal care [Internet]. Ottawa: Statistics Canada; 2015. [updated 2015 Aug 21; cited 2015 Oct 15] Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/cpis01a-eng.htm
(29) Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2015;66(1 Suppl 1):Svii, S1-305.
(30) Schuind F, Abramowicz D, Schneeberger S. Hand transplantation: the state-of-the-art. J Hand Surg Eur Vol. 2007;32(1):2-17.
(31) Girlanda R. Complications of post-transplant immunosuppression. 2013. In: Andrades JA, editor. Regenerative medicine and tissue engineering [Internet]. InTech. Available from: http://www.intechopen.com/books/regenerative-medicine-and-tissue-engineering
(32) The Human Mortality Database Research Teams. Life tables in 2011 in Canada [Internet]. Berkeley (CA): The Human Mortality Database Research Teams. c2013. [cited 2015 Oct 15]; Available from: http://www.mortality.org/
(33) Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2015. Toronto: Canadian Cancer Society; 2015.
(34) Ellison LF. Adjusting relative survival estimates for cancer mortality in the general population. Health Rep. 2014;25(11):3-9.

(35) Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364(9):829-41.

(36) Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349(10):931-40.

(37) Statistics Canada. The 10 leading causes of death, 2011 [Internet]. Ottawa: Statistics Canada; 2014 [updated 2014 Jan 28; cited 2015 Oct 15]. Available from: http://www.statcan.gc.ca/pub/82-625-x/2014001/article/11896-eng.htm

(38) Alolabi N, Chuback J, Grad S, Thoma A. The utility of hand transplantation in hand amputee patients. J Hand Surg Am. 2015;40(1):8-14.

(39) Ministry of Health and Long-Term Care in Ontario. Schedule of benefits for physician services under the Health Insurance Act [Internet]. Toronto: Queen's Printer for Ontario; 2015 [updated 2015 May 1; cited 2015 Oct 15]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html

(40) de Oliveira C, Bremner KE, Pataky R, Gunraj N, Chan K, Peacock S, et al. Understanding the costs of cancer care before and after diagnosis for the 21 most common cancers in Ontario: a population-based descriptive study. CMAJ Open. 2013;1(1):E1-8.

(41) Canadian Institute for Health Information. National health expenditure trends, 1975 to 2014. Ottawa: Canadian Institute for Health Information; 2014 [cited 2015 Oct 15]. Available from: https://www.cihi.ca/en/nhex_2014_report_en.pdf

(42) Goeree R, Lim ME, Hopkins R, Blackhouse G, Tarride J, Xie F, et al. Prevalence, total and excess costs of diabetes and related complications in Ontario, Canada. Can J Diabetes. 2009;33(1):35-45.

(43) Manns BJ, Mendelssohn DC, Taub KJ. The economics of end-stage renal disease care in Canada: incentives and impact on delivery of care. Int J Health Care Finance Econ. 2007;7(2-3):149-69.

(44) Raichle KA, Hanley MA, Molton I, Kadel NJ, Campbell K, Phelps E, et al. Prosthesis use in persons with lower- and upper-limb amputation. J Rehabil Res Dev. 2008;45(7):961-72.

(45) Amputee Coalition of America. Prosthetic FAQs for the new amputee [Internet]. Manassas (VA): Amputee Coalition of America. c2015 [updated 2015 May; cited 2015 Oct 15]. Available from: http://www.amputee-coalition.org/resources/prosthetic-faqs-for-the-new-amputee/

(46) Assistive Devices Program, Ministry of Health and Long-Term Care. Limb prostheses policy and administration manual [Internet]. 2015 [updated 2015 Sep; cited 2015 Oct 15]. Available from: http://www.health.gov.on.ca/en/pro/programs/adp/policies_procedures_manuals/docs/limb_prosthesis_manual.pdf

(47) PayScale, Inc. Health care aide salary (Canada) [Internet]. Seattle: PayScale, Inc.; 2015 [cited 2015 Oct 15]. Available from: http://www.payscale.com/research/CA/Job=Health_Care_Aide/Hourly_Rate

(48) Griffiths S. The cheap robotic hand set to revolutionise prosthetics: 3D-printed device performs advanced tasks for a fraction of the cost. Daily Mail Online [Internet]. 2015 Sep 8 [cited 2015 Oct 15]. Available from: http://www.dailymail.co.uk/sciencetech/article-3211347/The-cheap-robotic-hand-set-revolutionise-prosthetics-3D-printed-device-performs-advanced-tasks-fraction-cost.html

(49) McLaughlin E. All grins, Baltimore boy becomes 1st to receive new hands. CNN http://www.cnn.com/2015/07/29/us/baltimore-boy-zion-harvey-first-double-hand-transplant-recipients/

(50) McCabe S, McClelland B. Measuring outcome in upper-extremity transplantation. Curr Transpl Rep. 2014;1:211-4.

(51) The DASH outcome measure [Internet]. Toronto: Institute for Work and Health; c2006 [updated 2006 Jan 1; cited 2015 Oct 2]. Available from: http://dash.iwh.on.ca/faq

(52) Breidenbach WC, Gonzales NR, Kaufman CL, Klapheke M, Tobin GR, Gorantla VS. Outcomes of the first 2 American hand transplants at 8 and 6 years posttransplant. J Hand Surg Am. 2008;33(7):1039-47.

(53) Hung TH. Long-term prevention of rejection and combination drug therapy. In: Hewitt CW and Lee WPA, editors. Transplantation of composite tissue allografts [Internet]. New York: Springer; 2008. p. 150-163 [cited 2015 Oct 2]. Available from: https://books.google.ca/books?id=IkTgIYbmIIMC&pg=PA156&lpg=PA156&dq=carroll+test+hand+function&source=bl&ots=mn5EORt-ra&sig=D1XvwExQpf7koNLTq3TDbL9ut_c&hl=en&sa=X&ved=0CDkQ6AEwBmoVChMI2vC42Pz4xwIV0EmSCh0nCgil#v=onepage&q=carroll%20test%20hand%20function&f=false

About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

About the Ontario Health Technology Advisory Committee (OHTAC)

About OHTAS

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ISSN 1915-7398 (online)
ISBN 978-1-4606-8031-5 (PDF)