



Canadian Agency for  
Drugs and Technologies  
in Health

## RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL



**TITLE:** Islet Cell Transplantation in Patients with Unstable Diabetes: A Review of Clinical- and Cost-Effectiveness and Guidelines

**DATE:** 10 December 2014

### CONTEXT AND POLICY ISSUES

Diabetes is one of the most common chronic diseases in Canada. It was estimated that in the years of 2008 to 2009, 2.4 million Canadians had been diagnosed with diabetes, representing approximately 6.8% of the population including over 200,000 new diagnoses.<sup>1</sup> Disease management of diabetes consists of glycemic monitoring and glycemic control including education, lifestyle interventions such as nutrition therapy and physical activity, and pharmacotherapy.<sup>2</sup> Insulin and antidiabetic agents are the current standards of pharmacotherapy for type 1 and type 2 diabetes, respectively.<sup>2</sup> With the correct treatment and recommended lifestyle changes, many people with diabetes are able to adequately control their blood glucose levels and prevent or delay the onset of macrovascular and microvascular diabetic complications.<sup>2-4</sup> However, uncontrolled or unstable diabetes still happens despite treatments with insulin, diet, and suitable hygienic measures. There is no commonly accepted definition for “unstable” diabetes. It is usually described as a state of glycemic instability in different patterns: irregular and unpredictable hyperglycemia (frequently with ketosis), serious hypoglycemia, or alternating states of hyperglycemia and hypoglycemia.<sup>3,5</sup> This condition affects approximately 1 to 2% of patients with type 1 diabetes.<sup>6</sup> Whole pancreas transplantation (PT) is one method of beta cell replacement used currently to restore sustained normal glucose levels without the associated risk of severe hypoglycemia. This is a major surgical procedure relating to high risk of surgical complications and perioperative mortality; in addition, the lifelong immunotherapy after the transplantation usually has side effects, sometimes severe enough to adversely affect patient’s quality of life. Therefore, PT is generally recommended only in patients undergoing kidney transplantation and for patients with unstable diabetes (poor glycemic control accompanied by rapidly progressing diabetic complications).<sup>2,7-9</sup>

As a potential alternative for the whole organ transplantation, pancreatic islet transplantation (IT) has been investigated in clinical trials enrolling uncontrolled diabetic patients with serious progressive complications (type 1 diabetes and some type 2 diabetes).<sup>10,11</sup> The goals of IT are to restore glucose-regulated endogenous insulin secretion, halt the progression of diabetic

**Disclaimer:** The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

**Copyright:** This report contains CADTH copyright material and may contain material in which a third party owns copyright. **This report may be used for the purposes of research or private study only.** It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

**Links:** This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.

complications, and improve quality of life.<sup>11</sup> IT is less invasive than PT. It can be performed as islet transplantation alone (ITA) for patients without end-stage renal disease, islet after kidney transplantation (IAK), or simultaneous islet and kidney transplantation (SIK) for patients with end-stage renal disease.<sup>8</sup> During the procedure, the islet cells from a donor are infused to the portal vein of the recipient via a percutaneous catheter. After the procedure, lifelong immunosuppression is required to prevent rejection of the graft and recurrence of the autoimmune process.<sup>11</sup> More than one infusion may be required.<sup>12</sup> Previous research has demonstrated that IT is associated with improved insulin independence and other patient outcomes in the patients with poorly-controlled type 1 diabetes; in addition, its effectiveness has improved in recent years.<sup>13</sup> In one study, the proportion of patients achieving insulin independence three years post-transplant increased from 27% from 1999 to 2002, to 37% from 2003 to 2006, and to 44% from 2007 to 2010. Treatment with IT has beneficial effects on other clinical outcomes such as HbA1c levels and the risk of severe hypoglycemia.<sup>14</sup> The continuous evolving immunosuppressive regimens and technology for harvesting islet cells has contributed to the improving clinical outcomes related to IT.<sup>12</sup> Safety data has indicated that serious complications may occur as a result of the procedure (such as intraperitoneal bleeding, haemorrhage episodes, portal vein thrombosis, and injuries to the nearby organs). Long-term immunosuppression therapy has also been associated with a higher risk of adverse events such as serious infections.<sup>12</sup>

The purpose of this report is to summarize the evidence on the clinical effectiveness and the cost-effectiveness of islet cell transplantation compared with the current standards of treatment, and to summarize the guidelines that are relevant to the use of islet cell transplantation for patients with unstable diabetes.

## **RESEARCH QUESTIONS**

1. What is the clinical effectiveness of islet cell transplantation in patients with unstable diabetes?
2. What is the cost-effectiveness of using islet cell transplantation in patients with unstable diabetes?
3. What are the guidelines associated with the use of islet cell transplantation in patients with unstable diabetes?

## **KEY FINDINGS**

Limited evidence from one health technology assessment suggested that islet transplantation is effective in maintaining insulin independence, and associated with improved clinical outcomes in uncontrolled type 1 diabetic patients: reduced severe hypoglycemia, improved quality of life and reduced progression of diabetic complications were reported in small scale clinical trials with poor quality. The population was not clearly defined in the studies. There is a trend of increasing insulin independence and decreasing adverse events related to this evolving technology in recent years than earlier years. The cost-effectiveness of islet transplantation relative to the current treatment standards is undetermined based on the limited evidence. It has been recommended by evidence-based clinical practice guidelines to be used as an alternative intervention for unstable type 1 diabetes patients.

## METHODS

### Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and November 12, 2014.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<b>Table 1: Selection Criteria</b>	
<b>Population</b>	Patients with unstable or uncontrolled diabetes
<b>Intervention</b>	Islet cell transplantation
<b>Comparator</b>	Standard treatment: insulin and/or other pharmaceutical therapies
<b>Outcomes</b>	Q1: Clinical effectiveness Q2: Cost-effectiveness Q3: Evidence-based clinical practice guidelines
<b>Study Designs</b>	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, non-randomized controlled studies, evidence-based clinical practice guidelines, and economic evaluations.

### Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, if they were already included in a systematic review or health technology assessment (HTA), or were published prior to January 2011.

### Critical Appraisal of Individual Studies

The included HTA was critically appraised using the AMSTAR instrument.<sup>15</sup> The cost-effectiveness component in the HTA was critically appraised using Drummond's checklist.<sup>16</sup> Clinical practice guidelines were critically appraised using the AGREE II instrument.<sup>17</sup> Numeric scores were not calculated for the included studies or guidelines. Instead, the strengths and limitations of each included study and guideline were described narratively.

## SUMMARY OF EVIDENCE

### Quantity of Research Available

A total of 375 citations were identified in the literature search. Following screening of titles and abstracts, 370 citations were excluded and five potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, six publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report: one was an HTA,<sup>7</sup> and two were evidence-based clinical practice guidelines.<sup>2,18</sup> No relevant systematic reviews or meta-analyses, randomized controlled trials, non-randomized controlled trials or economic evaluations were identified.

Appendix 1 describes the PRISMA flowchart of the study selection.

### Summary of Study Characteristics

A detailed summary of included studies is provided in Appendix 2.

#### Comparative clinical effectiveness and safety of islet cell transplantation versus standard treatment for unstable diabetes

##### *Study design*

One Canadian HTA evaluating the clinical effectiveness of IT was identified.<sup>7</sup> It exclusively included systematic reviews or meta-analyses published between 2008 and 2013 for patients with severe type 1 diabetes (“severe type 1 diabetes” was not defined in the HTA; characteristics of the patients involved were not described either). Data from the islet transplant registry were also searched to provide more recent clinical data for IT. Effectiveness of IT was measured using insulin independence, full graft function (patients were insulin independent), partial graft function (patients were protected from severe hypoglycemia and were less dependent on insulin than prior to IT) and patient-reported outcomes.

##### *Population*

Xie and colleagues in the McGill University Health Centre (MUHC) conducted an HTA of IT to review its clinical effectiveness and cost-effectiveness in patients with type 1 diabetes. This report focused on patients who had previously undergone a kidney transplant and therefore were already on immunosuppression therapy (IAK); evidence of patients who had simultaneous islet and kidney transplant (SIK) and islet transplant alone (ITA) were reviewed as well.

##### *Interventions and Comparators*

Islet cell transplantation was the intervention of interest in the HTA. The comparators were whole pancreas transplantation and insulin therapy.

### *Outcome Measures*

The clinical effectiveness of IT such as insulin independence, graft function and patient quality of life were evaluated. Safety related to the use of IT and subsequent immunosuppression therapy was reported in the HTA as well.

### Comparative cost-effectiveness of islet cell transplantation versus standard treatment for unstable diabetes

An economic evaluation was included in the HTA conducted by Xie et al.<sup>7</sup> Previously published economic evaluations of IT in patients with type 1 diabetes were reviewed. The comparative cost-effectiveness between IT and PT was evaluated from the perspective of the MUHC. A Markov decision-analytic model was developed to compare the long-term health-economic consequences of IT versus PT or versus intensive insulin treatment (IIT) in a subgroup of patients who previously underwent a kidney transplant. The costs of the procedure, procedure-related complications, and the cost of diabetes-related complications during follow-up were considered, while the immunosuppression related costs were ignored because it was assumed that patients in either the PT or IT arm received identical maintenance of immunosuppression therapy, thus these costs were same for patients receiving IT or PT. Other key assumptions were: except for the differences in procedure-related mortality of PT and IT (2% vs. 0%, respectively), patients in the PT arm and the IT arm had identical risks of mortality conditional on covariates; the age and sex-specific relative risk of mortality of the target patients was 7 times that in the general Canadian population in 2009; patients' baseline characteristics were not associated with the risk of graft loss; the risks of diabetic complications were related to graft function; and patients did not receive additional IT infusions or a repeat PT during follow up. The main outcome measure in the economic analysis was incremental cost per life-year gained. A discount rate of 3% was used in the base case. A time horizon of five years was chosen. Sensitivity analyses assuming 20 years follow up, discounting rate of 0 and 5% and different risk of mortality were performed.

### Evidence-based guidelines and recommendations for islet cell transplantation for treatment of unstable diabetes

#### *Country of origin*

One clinical practice guideline was from the Canadian Diabetes Association (CDA) published in 2013,<sup>2</sup> and the other was from the Spanish National Health System (NHS) published in 2012.<sup>18</sup>

#### *Population*

The CDA guidelines and recommendations were meant for all diabetic patients, while the NHS guidelines were specific for patients with type 1 diabetes.<sup>2,18</sup>

#### *Interventions*

Pancreatic islet transplantation was the investigated intervention.

### *Grading of recommendations*

The recommendations in the CDA guidelines was assigned a grade from A through D.<sup>2</sup> The grade assigned to each recommendation is closely linked to the methodological rigour and robustness of the relevant clinical research:

- Grade A recommendations are generated based on level 1 evidence: systematic overview or meta-analysis of high quality RCTs; or appropriately designed RCT with adequate power to answer the question posed by the investigators; or nonrandomized clinical trial or cohort study with indisputable results.
- Grade B recommendations are supported by level 2 evidence: RCT or systematic overview that does not meet level 1 criteria.
- Grade C recommendations are made based on level 3 evidence: nonrandomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies.
- Grade D recommendations are made based on level 4 evidence (data that do not meet levels 1 to 3 criteria, or consensus).

The Spanish guidelines adopted a similar system to grade their recommendations:<sup>18</sup>

- Grade A recommendations are generated based on evidence rated as 1++ or 1+: high quality meta-analyses, systematic reviews clinical trials; or high quality clinical trials with very low risk of bias.
- Grade B recommendations are supported by evidence rated as 2++: high quality of systematic reviews of case-control or cohort studies, cohort or case-control studies with very low risk of bias and with high probability to establish a causal relationship; or extrapolated evidence from studies rated as 1++ or 1+.
- Grade C recommendations are made based on evidence rated as 2+: well-conducted case-control or cohort studies with low risk of bias and a moderate probability of establishing a causal relationship; or extrapolated evidence from studies rated as 2++.
- Grade D recommendations are made based on level evidence rated as 3 or 4: non-analytical studies such as case reports and case series, or expert opinion; or extrapolated evidence from studies rated as 2+.

### **Summary of Critical Appraisal**

A summary of critical appraisal of the included studies are provided in Appendix 3.

#### Comparative clinical effectiveness and safety of islet cell transplantation versus standard treatment for unstable diabetes

The HTA conducted by Xie et al.<sup>7</sup> described the study objectives and design. A search strategy was provided; however, it was unclear if there was a restriction on language. Only published evidence in the previous five years was included in this report. Methods of study selection and data extraction were not reported. It was also unclear if the quality of the included studies was examined. There were no detailed descriptions of the included studies and their trial characteristics and patient characteristics, such as the number of patients, medical history, severity of the disease, and the length of follow-up. Publication bias was not examined in this report.

### Comparative cost-effectiveness of islet cell transplantation versus standard treatment for unstable diabetes

An economic evaluation was included in the HTA conducted by Xie et al.<sup>7</sup> The research questions in this research were clearly stated, as well as the sources of effectiveness estimates and the cost estimates. It is noteworthy that the estimated cost data for IT were obtained from MUHC, and they differed considerably from the other centers. For example, the procedure cost for IT at the MUHC was C\$29,575 per patient; however it was C\$131,000 per infusion in Alberta, Canada. The difference in cost data between different centers may be due to the additional costs during the process of organ retrieval and the various islet laboratory costs. The choice of model and the key parameters were described. One assumption in this analysis was that the subsequent immunosuppression therapy was identical between PT and IT; however, the CDA guideline indicates that steroids are avoided in IT but may be used in PT.<sup>2</sup> Another assumption was that patient did not receive another islet cell infusion, but previous evidence suggested that most IT recipients need two or more infusions to achieve sufficient functioning islet mass; therefore, this assumption may lead to an underestimate of the cost for IT.<sup>8</sup> Sensitivity and scenario analyses were performed. This study was conducted in Canada; however, cost of the IT procedure may be estimated with different approaches from different centers. Therefore it is unclear if the findings from the cost-effectiveness performed from the perspective of MUHC can be generalized to other Canadian research centers.

### Evidence-based guidelines and recommendations for islet cell transplantation for treatment of unstable diabetes

CDA has performed a rigorous and comprehensive systematic review on diabetes to provide guidance on disease diagnosis and management.<sup>2</sup> In these guidelines, there was a clear description of scope, purpose, methodology, stakeholder involvement, evidence, safety issues, critical appraisal and formulation of recommendations. One limitation of these guidelines was that only English-language literature was searched and selected.

The clinical practice guidelines published by the Spanish National Health System (NHS) used a systematic review approach in guideline development.<sup>18</sup> Evidence from other guidelines and clinical studies was searched when they were published in Spanish, English, French or German from 1998 to March 2011. Data extraction was performed by two independent reviewers. Criteria for determining levels of evidence and grades of recommendations were clearly presented.

Both the CDA guidelines and the NHS guidelines were externally reviewed prior to publication. Updates of these guidelines are scheduled every five years. Conflicts of interest were declared in both guidelines.

### **Summary of Findings**

Details of the study findings are presented in Appendix 4.

### Comparative clinical effectiveness and safety of islet cell transplantation versus standard treatment for uncontrolled diabetes

In the HTA report, two studies were included to provide evidence on clinical effectiveness of IT. One was a systematic review examining patient-reported outcomes (generic and diabetes-

specific health-related quality of life) including 12 studies, 10 for IT and 2 for PT.<sup>7</sup> The second study was an HTA report from the Institute of Health Economics (IHE) in Edmonton, Alberta. It was an update of previously published IHE reports and included six non-RCTs and 13 case series. Quality of the included individual studies were compromised due to small sample size (details not provided), results for mixed types of IT procedures (ITA, SIK or IAK versus PT or IIT) or patients (uremic or non-uremic) were reported, and insufficiently rigorous study design in the comparative studies of IT versus PT. Data in the included SR and the IHE report were not pooled due to the considerable heterogeneity of types of IT and patients' baseline characteristics. Evidence of effectiveness results was also identified from international registry data. Findings from this HTA suggested that treatment with IT was associated with improved insulin independence in more recent years (e.g. 2007 to 2009) compared with earlier years (e.g. 1999 to 2003, or 2004 to 2006); however insulin independence after IT was lower than that after PT. The risk of adverse events related to IT infusions and/or immunosuppression therapy reported in recent years was lower than those in earlier years: risk of severe adverse events decreased to 26% in 2007 to 2009, compared with 47% in 2004 to 2006 and 69% in 1999 to 2003. In addition, patient quality of life after the IT therapy was improved compared with before IT therapy.

#### Comparative cost-effectiveness of islet transplantation versus standard treatment for uncontrolled diabetes

##### *Review of previous economic evaluations*

In the HTA report, two economic evaluations of IT, one from the US and one from Canada (IHE report) were identified.<sup>7</sup> In the US study, the procedure cost of one IT infusion was estimated at US\$93,500 (including organ retrieval, islet isolation and screening and medical procedures). The cumulative cost and quality-adjusted life years (QALYs) of IT versus IIT over 20 years were US\$519,000 and 10.9 QALYs, and US\$ 663,000 and 9.3 QALYs, respectively. Therefore the study indicated that IT was more cost-effective than IIT. In the Canadian study, the cost of IT was approximate C\$131,000 per infusion (including costs of organ retrieval, isolation laboratory, clinical program and post-transplantation assessment). The cumulative costs over 20 years were C\$410,373 and C\$35,769 in the IT group and the IIT group, respectively. The IT group had an effectiveness of 2.06 QALYs gained and the incremental cost per QALY gained was C\$181,847. Therefore the study concluded that IT was not cost-effective compared with IIT in the study population.

##### *Cost-effectiveness analysis*

The average procedure cost of IT per patient at the MUHC was estimated as C\$29,575. This cost included costs for operating room, radiology, laboratory, pharmacy (induction of immunosuppression therapy), intensive care unit and inpatient costs; while the physician fee, the costs for organ retrieval and the maintenance of immunosuppression therapy were excluded. Compared to PT, the incremental cost per life-year gained for IT was C\$66,552 at five years follow up. The incremental cost per life-year gained in the sensitivity analyses and scenario analyses ranged from C\$50,000 to C\$80,000.

### Evidence-based guidelines and recommendations for islet cell transplantation for treatment of unstable diabetes

The CDA recommended that individuals with type 1 diabetes with preserved renal function, or who have undergone successful kidney transplantation but have persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control, may be considered for pancreas or islet allotransplantation.<sup>2</sup> This was a Grade D recommendation based on consensus.

In the Spanish NHS guidelines, islet transplantation was recommended in the context of controlled trials only, but not for routine use in clinical practice.<sup>18</sup> This was a Grade C recommendation.

### **Limitations**

The literature search did not identify randomized or non-randomized controlled trials regarding the comparative clinical effectiveness of islet transplantation relative to insulin or other antidiabetic agents for patients with uncontrolled diabetes. In the included HTA report and economic evaluation, islet transplantation was compared with current standards such as intensive insulin therapy or whole pancreas transplantation. Evidence from small observational studies or registry databases was reported. There is no commonly accepted definition for unstable diabetes; therefore there may be heterogeneity in terms of baseline patient characteristics across the individual studies included in the HTA report. Effectiveness and safety of mixed types of IT procedures were evaluated in patients with various baseline characteristics. Therefore it is challenging to compare the findings across the studies. Important health outcomes such as change in health-related quality of life or functional status, severe hypoglycemia episodes, rates of diabetes complications and risks of adverse events were not reported in sufficient detail. In addition, the long-term consequences of immunosuppression therapy after the procedure may have an impact on the effect of islet transplantation and patient's quality of life, but this was not reported in the HTA report.

In the cost-effectiveness analysis of islet transplantation, the costs were estimated from the perspective of MUHC; therefore it is uncertain if the study results can be generalized to other healthcare facilities in Canada.

### **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

Evidence regarding the comparative effectiveness of islet cell transplantation in treatment of unstable diabetes was limited. The included health technology assessment examined clinical and cost-effectiveness of islet cell transplantation in type 1 diabetes patients with unstable metabolic control. In its included individual studies, islet transplantation was compared with whole pancreas transplantation or intensive insulin therapy. Data from a registry database suggests an increase in the rates of insulin independence and decrease in risks of adverse events in recent years compared with earlier years, although the rates of insulin independence after IT was lower than that achievable with whole pancreas transplantation. In one cost-effective analysis, the incremental cost per life-year gained for islet transplantation comparing with whole pancreas transplantation was C\$66,552. This was close to the threshold value of cost-effectiveness (US\$50,000). Conflicting results were found in previous economic evaluations with respect to the relative cost-effectiveness between islet transplantation and intensive insulin therapy.

Islet transplantation was recommended by one Canadian guideline as an option for patients with unstable type 1 diabetes. In another guideline, this procedure was recommended only in the context of controlled trials.

In conclusion, limited evidence suggests that islet transplantation is effective in maintaining insulin independence and is associated with improved clinical outcomes for unstable type 1 diabetes. There is a trend of increasing insulin independence and decreasing risks of adverse events related to this evolving technology. The cost-effectiveness of islet transplantation relative to the current treatment standards is undetermined based on the limited evidence.

**PREPARED BY:**

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

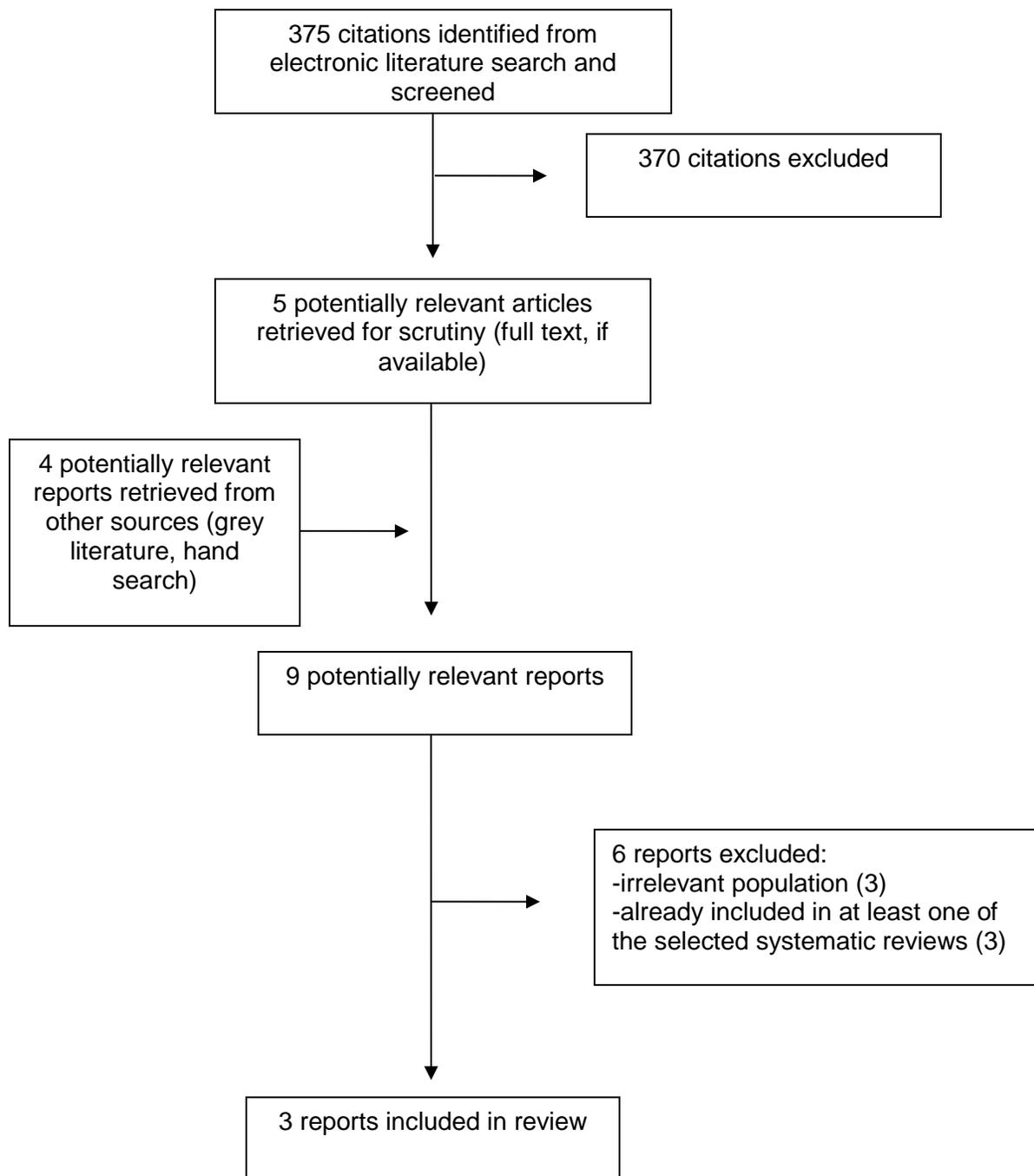
[www.cadth.ca](http://www.cadth.ca)

## REFERENCES

1. Public Health Agency of Canada. The burden of diabetes in Canada. Diabetes prevalence [Internet]. In: Diabetes in Canada: facts and figures from a public health perspective. Ottawa: The Agency; 2011 Dec 15. Chapter 1 [cited 2014 Nov 28]. Available from: <http://www.phac-aspc.gc.ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/chap1-eng.php#DIA>.
2. Canadian Diabetes Association Clinical Practice Guidelines. Can J Diabetes [Internet]. 2013 [cited 2014 Nov 28];37(S1):S1-S212. Available from: [http://guidelines.diabetes.ca/App\\_Themes/CDACPG/resources/cpg\\_2013\\_full\\_en.pdf](http://guidelines.diabetes.ca/App_Themes/CDACPG/resources/cpg_2013_full_en.pdf)
3. Duncan GG., Guest GM., Jackson R.L., Marble A., Sheridan E.P. Unstable diabetes; panel discussion. Diabetes. 1956 Nov;5(6):475-83.
4. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014 Jan;37 Suppl 1:S14-S80.
5. Benbow SJ, Walsh A, Gill GV. Brittle diabetes in the elderly. J R Soc Med [Internet]. 2001 Nov [cited 2014 Dec 9];94(11):578-80. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1282243>
6. Dorner M, Pinget M, Brogard JM. [Essential labile diabetes (author's transl)]. MMW Munch Med Wochenschr. 1977 May 13;119(19):671-4.
7. Xie X, Rich B, Dendukuri N. Islet transplantation in patients with type 1 diabetes mellitus [Internet]. Montreal (QC): McGill University Health Centre; 2014 Apr 18. [cited 2014 Nov 27]. (Report no. 66). Available from: [http://www.mcgill.ca/tau/files/tau/muhc\\_tau\\_2014\\_66\\_islet\\_transplantation.pdf](http://www.mcgill.ca/tau/files/tau/muhc_tau_2014_66_islet_transplantation.pdf)
8. Corabian P, Guo B, Harstall C, Yan C, Chuck A. Islet transplantation for the treatment of type 1 diabetes [Internet]. Edmonton: Institute of Health Economics; 2013 Feb. [cited 2014 Nov 27]. (Alberta STE report). Available from: <http://www.ihe.ca/documents/Islet%20Transplantation%202013.pdf>
9. Zinger A, Leibowitz G. Islet transplantation in type 1 diabetes: hype, hope and reality - a clinician's perspective. Diabetes Metab Res Rev. 2014 Feb;30(2):83-7.
10. Pancreatic islet cell transplantation [Internet]. New York: Mount Sinai Hospital; 2014. [cited 2014 Nov 27]. Available from: <http://www.mountsinai.org/patient-care/health-library/treatments-and-procedures/pancreatic-islet-cell-transplantation>
11. Robertson RP. Pancreas and islet transplantation in diabetes mellitus. 2014 Feb 3 [cited 2014 Nov 27]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: [www.uptodate.com](http://www.uptodate.com) Subscription required.
12. National Institute for Health and Care Excellence. Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus [Internet]. London: The Institute; 2008 Apr. [cited 2014 Nov 27]. (NICE interventional procedures guidance 257). Available from: <http://www.nice.org.uk/guidance/ipg257>

13. Tiwari JL, Schneider B, Barton F, Anderson SA. Islet cell transplantation in type 1 diabetes: an analysis of efficacy outcomes and considerations for trial designs. *Am J Transplant*. 2012 Jul;12(7):1898-907.
14. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, et al. Improvement in outcomes of clinical islet transplantation: 1999-2010. *Diabetes Care* [Internet]. 2012 Jul [cited 2014 Nov 17];35(7):1436-45. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3379615>
15. 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* [Internet]. 2007 [cited 2014 Dec 9];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>
16. Drummond checklist, figure 15.5.a [Internet]. Version 5.1.0 [updated March 2011]. In: *Cochrane handbook for systematic reviews of interventions*. London: Cochrane Collaboration; 2011 Mar [cited 2014 Dec 1]. Available from: [http://handbook.cochrane.org/chapter\\_15/figure\\_15\\_5\\_a\\_drummond\\_checklist\\_drummond\\_1996.htm](http://handbook.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm).
17. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. *CMAJ* [Internet]. 2010 Dec [cited 2014 Apr 9];182(18):E839-E842. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf>
18. Clinical practice guideline for diabetes mellitus type 1 [Internet]. 2012 May 1. [cited 2014 Nov 27]. Available from: [http://www.quiasalud.es/GPC/GPC\\_513\\_Diabetes\\_1\\_Osteba\\_compl\\_en.pdf](http://www.quiasalud.es/GPC/GPC_513_Diabetes_1_Osteba_compl_en.pdf)

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Characteristics of Included Studies

Characteristics of Included Health Technology Assessment

First Author, Publication Year, Country	Study design, Length of Follow-up	Patients Characteristics, Sample Size (n)	Intervention	Comparator(s)	Outcomes
Xie <i>et al.</i> , 2013 <sup>7</sup>  Canada	Clinical: Published HTAs and SRs were searched in multiple databases from 2008 to Nov. 2013. CITER database was searched as well.  Economic previously published EE were reviewed; an economic model has been developed to assess the cost-effectiveness.	Clinical: 1 HTA and 1 SR were included.  Economic: 1 HTA and 1 EE were included.	IT	PT  IIT	Clinical: <ul style="list-style-type: none"> <li>▪ Insulin independent</li> <li>▪ Full/partial graft function</li> <li>▪ Patient-reported outcomes</li> <li>▪ Safety:</li> </ul> Cost-effectiveness <ul style="list-style-type: none"> <li>▪ ICER</li> </ul>

CITER=The Collaborative Islet Transplant Registry; EE=economic evaluation; HTA=health technology assessment; ICER=incremental cost per life-year gained; IIT=intensive insulin therapy; IT=islet transplantation; PT=pancreas transplantation; SR=systematic review;

**Characteristics of Included Clinical Practice Guidelines**

Author, Year, Origin	Objective of Guideline	Evidence Collection, Selection and Synthesis
CDA guidelines, 2013, Canada <sup>2</sup>	To provide a useful reference tool to help healthcare professionals translate the best available evidence into practice; to update the 2008 CDA guidelines.	<ul style="list-style-type: none"> <li>• Evidence was identified through comprehensive literature search of English-language literature; updated literature searches were performed at regular intervals through the development process.</li> <li>• Level of evidence was determined based on study's objectives, methodological rigour, susceptibility to bias and generalizability.</li> </ul>
NHS guidelines, 2012, Spain <sup>18</sup>	To improve the quality, efficiency and equity of care for people with type 1 diabetes in the NHS; to provide guidance on the various alternatives for the care provided to people with type 1 diabetes, establishing the most relevant and up-to-date evidence-based recommendations	<ul style="list-style-type: none"> <li>• Evidence was identified through comprehensive literature search of Spanish/ English/ French/ German-language literature, from 1998 to March 2011</li> <li>• Relevant clinical practice guidelines and clinical studies were identified</li> <li>• Data extraction were performed by 2 independent reviewers</li> <li>• Quality of the included literature was assessed using AGREE or SIGN instruments for guidelines and clinical trials, respectively</li> <li>• Classification of levels of evidence and grades of recommendations was based on the SIGN scale</li> </ul>

CDA=Canadian Diabetes Association; NHS=National Health System (Spain)

APPENDIX 3: Critical Appraisal of Included Studies

First Author, Publication Year, Country	Strengths	Limitations
<b>Health Technology Assessments</b>		
<p>Xie, 2013<sup>1</sup> Canada</p>	<ul style="list-style-type: none"> <li>• Review (clinical and economic): Objectives and inclusion/exclusion criteria were stated.</li> <li>• Economic model: Study had a well-defined question, description of the competing treatments and established effectiveness of the therapies.</li> </ul> <p>Perspective, time horizon, discounting were stated.</p> <p>Costs with their references were disclosed and appropriate.</p> <p>Sensitivity analyses were performed and conclusions were adequate.</p>	<ul style="list-style-type: none"> <li>• Literatures were searched in the last 5 years; not clear if there was a restriction on language; only published studies were searched.</li> <li>• Unclear if study selection and data extraction were conducted by 2 independent reviewers; no description on the methods of quality assessment for the included studies.</li> <li>• No list of all included studies with their characteristics and appraisal.</li> <li>• No list of excluded studies.</li> <li>• No declaration of conflict of interest or sources of funding.</li> <li>• Publication bias was not examined.</li> <li>• Economic model: Cost-effectiveness was assessed from the perspective of a local health authority; the generalizability of the study results to a different setting was unclear.</li> </ul>
<b>Clinical Practice Guidelines</b>		
<p>CDA guidelines, 2013, Canada<sup>2</sup></p>	<ul style="list-style-type: none"> <li>• The objective of the guideline was clearly specified</li> <li>• The health topic was clearly specified</li> <li>• The population to which the guideline applies was clearly mentioned, and the views and preferences of the target population have been sought</li> <li>• Methods for formulating recommendations were reported</li> <li>• Recommendations were specific and unambiguous</li> <li>• Key recommendations were easily identifiable</li> <li>• Conflicts of interest were declared</li> </ul>	<ul style="list-style-type: none"> <li>• Only English-language literatures were identified</li> <li>• The guideline did not provide advice on how the recommendations can be put into practice</li> <li>• The potential resource implications of applying the recommendations have not been considered</li> </ul>

First Author, Publication Year, Country	Strengths	Limitations
<p>NHS guidelines, 2012, Spain<sup>18</sup></p>	<ul style="list-style-type: none"> <li>• The overall aim of the guideline was clearly described</li> <li>• The health topic was clearly specified</li> <li>• The population to which the guideline applies was clearly mentioned, and the views and preferences of the target population have been sought</li> <li>• Methods for formulating recommendations were reported</li> <li>• Recommendations were specific and unambiguous</li> <li>• A procedure for updating the guideline was specified</li> <li>• Competing interests of guideline authors were reported</li> </ul>	<ul style="list-style-type: none"> <li>• The guideline did not provide advice on how the recommendations can be put into practice</li> <li>• The potential resource implications of applying the recommendations have not been considered</li> </ul>

APPENDIX 4: Summary of Study Findings

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
<b>Health Technology Assessments</b>		
<p>Xie, 2014, Canada<sup>7</sup></p>	<ul style="list-style-type: none"> <li>• <i>Clinical effectiveness and safety:</i> 1 SR, 1 HTA and CITR were identified.</li>   <li><i>Data from the included SR and HTA:</i> <ul style="list-style-type: none"> <li>○ 5 year insulin independence rates was 50%;</li> <li>○ Reduced severity of hypoglycemia episodes, reduced progression of diabetic microvascular complications, and improved cardiovascular function was reported;</li> <li>○ Patient survival was 96% at 12 years in a large case series;</li> <li>○ Post-operative complications: Hematoma, paresthesia, infection, phlebitis were commonly reported, but overall event numbers were small. DVT and PE were rare.</li> <li>○ Diabetes-specific QOL following IT was improved compared with before IT; the effect was maintained over 3 years.</li> </ul> </li>   <li><i>CITR data:</i> <ul style="list-style-type: none"> <li>○ Full and partial graft function rates: 3 years after the last IT infusion: 44% and 21%, respectively; 5 years after the last IT infusion: 24% and 19%, respectively. (compared to various types of PT: 1-year insulin independence: 82-89% 5-year insulin independence: 58-71%)</li> <li>○ Risk of AEs and severe AEs due to IT infusions and/or immunosuppression therapy in recent years was lower than those in earlier years (decreased from 69% in 1999-2003 to 47% in 2004-2006 and to 26% in 2007-2009)</li> <li>○ Most common procedure-related complications: intraperitoneal bleeding (2%), partial branch-vein occlusion (8%) and liver abnormality (40%); most severe AEs were related to immunosuppression.</li> </ul> </li>   <li>• <i>Cost-effectiveness:</i> 1 US study and 1 Canadian HTA report assessed the cost-effectiveness of IT.</li> </ul>	<p>“For type 1 diabetes with unstable metabolic control who have previously undergone a kidney transplant, IT therapy can improve glycemic control and reduce the risk of hypoglycemia.</p> <p>PT is associated with a risk of procedural mortality and of serious post procedural complications. IT is associated with a negligible risk of procedural mortality or complications. Both procedures carry a high risk of severe adverse events that are associated primarily with the immunosuppression therapy.</p> <p>Compared with PT, IT leads 0.092 life-years or approximately one month gained in 5 years follow up. This translates into a relatively high incremental cost-effectiveness ratio of IT vs PT of \$66,552 per life-year gained at 5 years post-transplant. Compared with IIT, IT is associated a significantly higher cost, but also with a significantly reduced risk of diabetes-related complications.</p> <p>There is as yet insufficient evidence that IT is equal or superior to PT to justify its routine use when PT is the contemplated procedure.” (p. xii)</p>

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	<ul style="list-style-type: none"> <li>○ From literature review: 2 economic studies were identified (1 from US, 1 from Canada)                             <ul style="list-style-type: none"> <li>▪ One time cost of an IT infusion was ~US\$93,500 in the US study, and was C\$131,000 in the Canadian study.</li> <li>▪ The US study: cumulative cost and QALY of IT vs. IIT over 20 years were US\$519,000 and 10.9 QALYs and US\$663,000 and 9.3 QALYs.</li> <li>▪ The Canadian study: cumulative cost in 20 years was C\$410,373 for IT and C\$35,769 for IIT; IT was superior in effectiveness with 2.06 QALYs gained and the incremental cost per QALY gained was \$181,847.</li> </ul> </li> <li>○ From economic model:                             <ul style="list-style-type: none"> <li>▪ Compared to PT, IT resulted in 0.092 life-years gained at a higher incremental cost of C\$6,120 in 5 years per procedure.</li> <li>▪ Corresponding ICER was C\$66,552 per life-year gained at 5 years follow-up.</li> <li>▪ ICER in sensitivity and scenario analyses ranged from C\$50,000 to C\$80,000 per life-year gained.</li> <li>▪ Compared to IIT, the incremental cost of IT was C\$28,383 at 1-year follow up, and C\$23,023 at 5-year follow up.</li> </ul> </li> </ul>	
<b>Clinical Practice Guidelines</b>		
CDA guidelines 2013, Canada <sup>2</sup>	Recommendation: "individuals with type 1 diabetes with preserved renal function, or who have undergone successful kidney transplantation but have persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control, may be considered for pancreas or islet allotransplantation." (Grade D, Consensus) – page S95	
NHS guidelines 2012, Spain <sup>18</sup>	Recommendation: "Nowadays, islet transplantation is only recommended in the context of controlled trials" (Grade C) – page 160	

AE=adverse event; CITR=The collaborative islet transplant registry; HTA=health technology assessment; ICER=incremental cost-effectiveness ratio; IIT=intensive insulin therapy; IT=islet transplantation; NHS=National Health System (Spain); PT=pancreas transplantation; QALY=quality-adjusted life years; QOL=quality of life; SR=systematic review;