Australian Government

Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology

Prioritising Summary

Autologous Haematopoietic Stem cell Transplantation (HSCT) for the regeneration of insulin-producing pancreatic cells in type 1 diabetics

March 2010

AHTA

Adelaide Health Technology Assessment

ISBN
Publications Approval Number:

Electronic copies can be obtained from http://www.horizonscanning.gov.au

Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

DISCLAIMER: This report is based on information available at the time of research cannot be expected to cover any developments arising from subsequent improvements health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

The Commonwealth does not guarantee the accuracy, currency or completeness of the information in this report. This report is not intended to be used as medical advice and intended to be used to diagnose, treat, cure or prevent any disease, nor should it be used therapeutic purposes or as a substitute for a health professional's advice. The Commonwealth does not accept any liability for any injury, loss or damage incurred by use of or reliance the information.

The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT). HealthPACT comprises representatives from departments in all states and territories, the Australia and New Zealand governments; and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This Horizon scanning prioritising summary was prepared by Linda Mundy and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, School of Population Health and Clinical Practice, Mail Drop DX 650 545, University of Adelaide, Adelaide, SA, 5005.

PRIORITISING SUMMARY

REGISTER ID: **000440**

NAME OF TECHNOLOGY: **AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)**

PURPOSE AND TARGET GROUP: **FOR THE REGENERATION OF INSULIN-PRODUCING PANCREATIC CELLS IN TYPE 1 DIABETICS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☒	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Brazil	✓		

IMPACT SUMMARY:

Autologous stem cell transfer aims to prevent the destruction of and preserve the function of remaining pancreatic beta cells in newly diagnosed type I diabetic patients. This technology would only be made available through specialist tertiary hospitals.

BACKGROUND

Diabetes mellitus is characterised by a total or near total insulin deficiency, resulting in an acute elevation of blood glucose levels (hyperglycaemia), rapid acidification of the blood (ketoacidosis), and death unless treated with insulin. Onset may occur at any age but usually in childhood or adolescence. Type 1 diabetes is often referred to as an auto-immune disease as in most cases it is caused by the immune system attacking and destroying the pancreatic beta-cells, which produce insulin. Although there is a basal release of insulin from the β-cells, insulin synthesis and secretion is mainly

controlled by concentration of glucose in the blood, ie a high blood glucose level leads to insulin secretion. Insulin is inhibited by a feedback mechanism controlled by the sympathetic nervous system. Insulin affects every tissue, in the body but particularly liver, muscle and fat cells. The overall function of the insulin is to facilitate the uptake, utilisation and storage of glucose, amino acids and fats after a meal; a fall in insulin causes a reduced uptake of these substances and an increase in the mobilisation of fuel stores. WHO criteria recommend that diagnosis should be based on a fasting plasma glucose level in excess of 126 mg/dL and/or a 2-hour plasma glucose level in excess of 200 mg/dL following an oral glucose tolerance test.(Richter et al 2007).

Complete immune-mediated β-cell destruction does not take place immediately after clinical onset of Type 1 diabetes. One technique proposed as a possible method for inducing remission in autoimmune diseases, including Type 1 diabetes, is a program of intense immunosuppression therapy, followed by the re-establishment of tolerance to pancreatic β-cells by the administration of autologous uncommitted haematopoietic[1] stem cells (Voltarelli et al 2008). This method has been used with mixed results in studies of multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and juvenile idiopathic arthritis (Openshaw et al 2002). The rationale of this method is that after the depletion of the cells deemed to have caused the diabetes by chemotherapy, the transplanted haematopoietic stem cells have the capacity to differentiate into a large number of β-cells. The exact mechanism for this process is unclear, although it has been suggested that autologous haematopoietic stem cell transplantation shifts the equilibrium from immune destruction to immune tolerance via clonal exhaustion, alterations in cytokines and changes in the types and numbers of T- and B-lymphocytes. Initial animal experiments demonstrated that the development of clinical Type 1 diabetes could be *prevented* by allogeneic[2], but not autologous, stem cell transplantation. However, once clinically overt Type 1 diabetes has been established in these animals it cannot be reversed by the administration of allogeneic stem cells, indicating that some pancreatic β-cells are required. Initial human trials in early-diagnosed Type 1 diabetic patients (within 8 weeks) demonstrated the continued secretion of insulin from the remaining β-cells after immunosuppression treatment with prednisone and cyclosporine. Although the β-cells were demonstrated to persist for a short period of time after clinical onset of diabetes, patients experienced serious side-effects with long-term immunosuppression (Voltarelli et al 2008).

[1] Autologous stem cell transplantation is a procedure in haematopoietic cells from which all blood cells develop, are removed, stored, and later transplanted back into the same person (Wikipedia 2010).

[2] Allogeneic stem cell transplantation is a procedure where stem cells are taken from a genetically non-identical member of the same species as the recipient (Wikipedia 2010).

CLINICAL NEED AND BURDEN OF DISEASE

In Australia during the period 2000-2006, the annual age-adjusted incidence rate of type I diabetes among children aged 0-14 years was 22.4 new cases per 100,000 population. There has been a slight increase in the incidence in this age group from 19.2 in 2000 to 22.6 in 2006, with the greatest increase occurring in 10-14 year olds (Catanzariti et al 2008). In comparison to other OECD countries, the incidence of type I diabetes in Australia is high, with only Norway, Sweden and Finland having a higher annual incidence. Amongst people aged 15-years and over at first insulin use, there were an average of 1,260 new cases per year. The rate of new cases amongst people aged over 15-years decreases dramatically with age and plateaus at aged 45-years. The peak incidence rate of type I diabetes occurs at age 15-years (Pieris-Caldwell et al 2008).

There is little information available on the quality of life of people with Type 1 diabetes in Australia. A study of children and young people with Type 1 diabetes in Melbourne found that their general health and quality of life were poorer than their peers in the general population. Lower quality of life was found to be related to poor blood glucose control in children aged 5–11 years, but not in adolescents aged 12–18 year-olds, however the presence of diabetes-related symptoms and concerns was associated with poorer psychosocial functioning for both age groups (Pieris-Caldwell et al 2008).

In New Zealand the incidence of type I diabetes appears to be increasing and in the year 2000 it was estimated that the number of people with type I diabetes was 10,564[3] (Health Funding Authority 2000). The estimated incidence of Type-1 juvenile diabetes in New Zealand was 25.8 cases per 100,000 persons aged up to 19 years in 2001.

DIFFUSION

Although there is no evidence of the use of this technique to treat new-onset of Type 1 diabetes, there is a lot of research being conducted in Australia on the use of haematopoietic stem cell transplantation (HSCT) for autoimmune diseases. World-wide, over 400 patients have been treated using HSCT for a range of diseases including rheumatoid arthritis, scleroderma, multiple sclerosis and SLE. If the use of HSCT to treat new-onset diabetes is shown to be effective, Australia would have the appropriate skill base to conduct this therapy (NSW Stem Cell Network 2007).

COMPARATORS

Although treatment regimens and types of insulin available have developed over time, once diagnosed individuals with Type 1 diabetes are required to self inject with insulin to control their blood sugar levels for life. A subcutaneous infusion of insulin

[3] Estimated population of New Zealand in 2000 was 3,857,800 (Statistics New Zealand 2008).

may also be delivered via a pump permanently attached to the patient. Insulin doses must be adjusted according to carbohydrate intake and the degree of physical activity being undertaken. Hypoglycaemia, or low blood sugar levels, is one of the most common side effects among individuals with Type I diabetes and is a barrier to achieving and maintaining tight glycaemic control. Tight glycaemic control (maintaining glycaemic levels to a target HbA_{1c}[4] level of seven per cent has been demonstrated to lower the risk of developing retinopathy by 47 per cent, nephropathy by 54 per cent and neuropathy by 60 per cent (Nguyen et al 2008).

In 2008, ASERNIP-S wrote a Prioritising Summary on "Allogeneic pancreatic islet cell transplantation". This summary concluded that there was insufficient evidence to determine the safety and effectiveness of allogeneic pancreatic islet cell transplantation for the treatment of type 1 diabetes mellitus. The technology appeared to be effective in a subset of patients in the short-term (1-2 years), and was associated with serious adverse events.

Several trials are currently underway which aim to investigate other methods for preventing further destruction of β-cells and to maintain the production of insulin from the remaining β-cells in newly diagnosed Type 1 diabetics and hence delay or reduce the risk of developing the long-term, diabetes-related health problems. All patients must be newly diagnosed with Type 1 diabetes within the past three months, still actively secreting insulin and have antibodies against insulin and the insulin producing cells. Three studies have ceased recruiting and one study examining injection of glutamic acid decarboxylase or the GAD protein, is still recruiting. Patients in this two-year trial are being randomised to receive either the GAD protein or placebo. Patients are required to present for 13 study visits, however injections of GAD or placebo are only given at three of these visits. One of the closed trials is a randomised controlled trial (RCT) with patients being assigned to be administered with either placebo or treatment with rituximab, which reduces the number of B-lymphocytes, preventing further destruction of the β-cells. Rituximab has been approved by the FDA for the treatment of B-cell lymphoma and is listed on the Australian PBS for the treatment of Non-Hodgkin's Lymphoma, chronic lymphocytic leukaemia (authority required) and rheumatoid arthritis (public and private hospital authority required). Another of the closed RCTs involves the infusion of CTLA-4 Ig or abatacept versus an infusion of a placebo. The two-year study required participants to undergo 27 infusions every 28 days. Abatacept is listed on the PBS (public and private hospital authority required) for the treatment of the pain and joint inflammation associated with rheumatoid arthritis. The remaining closed RCT studied the effect of two drugs, mycophenolate mofetil (MMF/CellCept®) and daclizumab (DZB/Zenapax®), over a two-year period on the ability to reduce immune system activity. Participants were randomised to three groups: active MMF with DZB

[4] HbA_{1c} = glycolsylated haemoglobin

placebo, active MMF plus active DZB and MMF placebo plus DZB placebo. MMF (placebo or drug) was administered as a pill taken 2-3 times per day, however DZB (drug or placebo) was administered intravenously twice during the first month of study participation. MMF, an immunosuppressant, is listed on the PBS (authority required) for the prevention of transplant rejection. DZB is not listed on the PBS (PBS 2010; Type 1 Diabetes TrialNet 2010).

SAFETY AND EFFECTIVENESS ISSUES

Voltarelli et al (2007) screened 100 patients with newly diagnosed Type 1 diabetes for participation in their study using the transplantation of haematopoietic stem cells (level IV intervention evidence). Patients were required to have a diagnosis of disease onset during the previous six weeks as demonstrated by measurable levels of antibodies against glutamic acid decarboxylase (anti-GAD) (Voltarelli et al 2007). Although 10 per cent of Type 2 diabetics may have antibodies to GAD, the enrolled patients all had genotypes consistent with Type 1 diabetes (Skyler 2007). Of the 100 potential patients, 15 satisfied the inclusion criteria and agreed to participate. The mean age of all patients was 19.2 years (range 14-31 years). All patients reported at diagnosis with symptoms of hyperglycaemia including weight loss. The mean body mass index at diagnosis was 19.8 (range 16.6-23.4) and the mean plasma glucose was 391 mg/dL (range 130-612 mg/dL).

Autologous stem cell transplantation (AHSCT) involves a three stage process: 1) stem cell mobilisation of peripheral blood $CD34^+$ cells[5]; 2) immune ablation of the recipient's self-reactive lymphocytes and 3) re-infusion of the harvested stem cells from step one (Skyler 2007). All patients underwent a stem cell mobilisation regimen which involved two, one hour infusions of cyclophosphamide (2 g/m^2), 12 hours apart. In addition, granulocyte colony stimulating factor (GCSF) was injected subcutaneously (10 μg/kg per day) starting one day after cyclophosphamide infusion and continuing until leukapheresis[6] was completed. Leukapheresis was initiated when the patient's $CD34^+$ cells reached 10 cells/μl and the removal of white cells continued until the number of progenitor cells harvested reached a minimum of 3.0×10^6 $CD34^+$ cells/kg body weight. These cells were then frozen in liquid nitrogen. Immune ablation of self-reactive lymphocytes was achieved by a one-hour intravenous administration of cyclophosphamide (50 mg/kg per day) given on days five, four, three and two before stem cell infusion. In addition rabbit antithymocyte globulin was administered on these days. The frozen stem cells were infused on day zero and GCSF was administered subcutaneously from day five post-infusion until the neutrophil count exceeded 1000/μl (Voltarelli et al 2007).

[5] Hematopoietic stem cells express the CD34+ surface marker
[6] Leukapheresis is a procedure by which the white blood cells are removed from a donor's blood which is then transfused back into the donor.

Mean time from diagnosis to stem cell mobilisation was 38.4 days (range 25-56 days) and the mean hospital stay (from conditioning to discharge) was 19.2 days (range 15-24 days). The mean number of $CD34^+$ cells infused was 11.0 x 10^6/kg (range 5.8-23.1 x 10^6/kg). Engraftment or the growth of new neutrophils (>500/μl) and platelets (>20,000/μl) took place 8-10 days (mean 9.1 days) and 0-15 days (mean 11.4 days) post-transplantation, respectively. Most patients experienced the common adverse events associated with transplantation due to the drugs used in the mobilisation and conditioning phases of the treatment, including nausea, vomiting, febrile neutropenia and alopecia. The most serious short-term (up to day 14) adverse event recorded was pneumonia in one patient which responded to treatment. At one year follow-up, one patient presented with autoimmune hypothyroidism and transient renal dysfunction which were successfully treated. One patient also reported at one-year follow-up with mild hypergonadotrophic hypogonadism. No mortality was reported (Voltarelli et al 2007).

Mean follow-up was 18.8 months (range 7-36 months). The first enrolled patient was lost to follow-up due to failure of treatment. Pre-treatment insulin doses for this patient were 0.48 IU/kg per day which increased to 1.7 IU/kg per day at 12-months. C-peptide levels are an indirect measure of β-cell function, with higher levels indicating greater function. C-peptide levels were measured pre and post-transplantation for all patients. Patient one did not demonstrate an increase in C-peptide levels from baseline (0.4 ng/mL) to 12-month follow-up (0.3 ng/mL). In addition, this patient's HbA_{1c} levels increased and remained high throughout follow-up (7.6%, 8.2%, 8.9%, 9.7% and 11.1% at 0, 3, 6, 9 and 12-month follow-up). The protocol for the study was changed after this patient was lost to follow-up and therefore these data were not included in further analysis.

Prior to the mobilisation of stem cells, all patients required a mean dose of 0.38 IU/kg per day (range 0.13-0.58) of exogenous insulin. Although the reported length of follow-up varied for patients, one patient remained insulin free for 35 months, four patients for at least 21 months and seven patients for at least six months. Two patients experienced a late response to treatment and were insulin free for one and five months, respectively. All patients complied with self monitoring of glucose levels and there was a statistically significant ($p < 0.5$) decrease in HbA_{1c} levels post-transplantation which was maintained during follow-up. The mean peak-stimulated, pre-treatment C-peptide level was 1.3 ng/mL. In patients with mean peak-stimulated C-peptide levels measured at six months post-transplantation, 11/13 (84.6%) reported an increase (4.0 ng/mL). At 12-months, 8/10 (80%) of patients followed-up recorded an increase in C-peptide levels (3.7 ng/mL), as did the all of the four patients followed-up at 24-months (4.5 ng/mL) and the one patient at 36-months. Mean anti-GAD levels decreased over follow-up time from pre-treatment levels of 31.8 ± 25.5 U/ml to 17.3, 12.5 and 18.7 U/ml at six, 12 and 24 months, however this decrease was not statistically significant (Voltarelli et al 2007) probably reflecting the modest

sample size and the substantially inter-patient variability. Although independence from insulin therapy and increased levels of C-peptide indicate an improvement in β-cell function, longer follow-up is required. In addition, newly diagnosed Type 1 diabetics often experience a short period of remission which may cloud the interpretation of these initial results in the absence of a comparator. It is unclear whether the benefits reported in this study were due to immune reconstitution or to the regeneration of the β-cells (Skyler 2007). Follow-up duration for this study was considered inadequate to draw any conclusions regarding the safety and effectiveness of AHSCT, however follow-up data were reported by Couri et al in 2009.

Although the 2009 study reported further follow-up data on the original 15 patients who underwent AHSCT, the study group recruited an additional eight patients (n=23, mean age 18.4 years, range 13-31 years) (level IV intervention evidence). The treatment protocol remained the same for these additional patients, however length of follow-up varied with a mean of 29.8 months but a range from 7-58 months (median 30 months). Mean time from diagnosis to stem cell mobilisation was 37.7 days (range 24-56 days) and the mean hospital stay (from conditioning to discharge) was 18.6 days (range 15-24 days). The mean number of $CD34^+$ cells infused was 10.52 x 10^6/kg (range 4.98-23.19 x 10^6/kg). Engraftment or the growth of new neutrophils (>500/μl) and platelets (>20,000/μl) took place 8-11 days (mean 9.3 days) and 0-18 days (mean 10.4 days) post-transplantation, respectively. In addition to the adverse events reported in 2007, one patient developed Graves disease and nine patients developed a oligospermia or a sperm deficiency from drug toxicity. It is unclear whether or not this condition was permanent or transient, however the nine patients were all young (aged 16-24 years) and this may be considered a serious consequence of treatment (Couri et al 2009).

Of the 23 patients, 12 (52%) experienced a continuous time free from insulin (mean 31 months, range 14-52 months) and eight (34.8%) experienced transient time free from insulin. The eight transient patients resumed insulin use at a low dose (0.1-0.3 IU/kg). Suspension from insulin therapy occurred 6-34 days post- AHSCT. One patient remained insulin free for more than four years, four patients for at least three years, three patients for at least two years and four patients for at least one year. Three patients did not experience any period of insulin-free therapy and these patients did not reduce their HbA_{1c} levels below seven per cent. For those insulin free patients, HbA_{1c} levels post-transplantation decreased compared to baseline (p<0.001) and remained low throughout follow-up. In the continuous insulin-independent group the mean (SE) area under the curve of C-peptide levels increased significantly from 225.0 ng/mL (75.2) per two hours pre- AHSCT to 785.4 ng/mL (90.3) per two hours at 24 months (p < 0.001) post-AHSCT and to 728.1 ng/mL (144.4) per two hours at 36 months (p = 0.001). In the transient insulin-independent group, mean (SE) area under the curve of C-peptide levels also increased from 148.9 ng/mL (75.2) per two hours

pre- AHSCT to 546.8 ng/mL (96.9) per two hours at 36 months (p = 0.001), which was sustained at 48 months (Couri et al 2009).

COST IMPACT

In Australia, for the year 2004-05, diabetes accounted for 1.9 per cent of the year's total allocated recurrent health expenditure with a direct health-care expenditure of $989 million. It is estimated that expenditure on Type 1 diabetes accounted for 14% of this expenditure, at $139 million and $22 million related to diabetes prevention services. The greatest proportion of diabetes expenditure was on hospital services, $371 million (37.5%) followed by out-of-hospital medical services, $288 million (29.1%), diabetes-related pharmaceuticals, $275 million (27.8%), and research, $55 million (5.6%).

The National Diabetes Services Scheme (NDSS) provides access to products and services including syringes, insulin infusion pump consumables and blood and urine glucose testing reagents that are required for self-management of diabetes at prices subsidised by the Australian Government. The state and territory governments contribute co-payments for needles and syringes. In 2006–07, there were 844,062 people registered with the NDSS and the Australian government expenditure on the NDSS in that financial year was approximately $114 million (Pieris-Caldwell et al 2008).

No literature was identified describing the cost of autologous stem cell transplantation for delaying onset of clinically overt Type 1 diabetes. However it is hoped that the initial costs of immunosuppression, followed by the isolation, purification and transplantation of stem cells would offset future health care costs in terms of insulin use and in the alleviation or mitigation of the more serious long-term side effects of insulin dependent diabetes including retinopathy and neuropathy.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

This small case-series demonstrated that autologous stem cell transplantation is a viable technique for the remission of Type 1 diabetes in the majority of patients, however it remains to be seen whether or not the benefits outweigh the risks, including those of drug toxicity. A randomised controlled trial should be conducted that includes a group of patients who receive no intervention or only immunosuppression or immunomodulation. In addition, long-term follow-up data for

all patients needs to be reported. It would be prudent to await the results of the randomised controlled trials summarised in the comparator section.

HEALTHPACT ACTION:

As many patients who undergo immunosuppression treatment with cyclosporine experience remission to disease, the results from this study may be heavily confounded. Therefore that no further review by HealthPACT is currently required as routine scanning will identify any relevant studies published in the future.

NUMBER OF INCLUDED STUDIES

Total number of studies	2
Level IV intervention evidence	2

REFERENCES:

Catanzariti, L., Faulks, K. & Waters, A. M. (2008). *Incidence of Type I diabetes in Australia 2000-2006: first results*, Australian Institute for Health and Welfare, Canberra. Available from: http://www.aihw.gov.au/publications/cvd/iot1dia00-06-fr/iot1dia00-06-fr.pdf

Couri, C. E., Oliveira, M. C. et al (2009). 'C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus', *JAMA*, 301 (15), 1573-1579.

Health Funding Authority (2000). *Diabetes 2000*, Health Funding Authority, Wellington. Available from: http://www.moh.govt.nz/moh.nsf/7004be0c19a98f8a4c25692e007bf833/4735077ed3fd9b56cc256a41000975ca/$FILE/Diabetes2000.PDF

Nguyen, H. T., Ghevondian, N. & Jones, T. W. (2008). 'Detection of nocturnal hypoglycemic episodes (natural occurence) in children with type 1 diabetes using an optimal Bayesian neural network algorithm', *Conf Proc IEEE Eng Med Biol Soc*, 2008, 1311-1314.

NSW Stem Cell Network (2007). *Novel Clinical Trials with Stem Cells* [Internet]. Available from: http://www.stemcellnetwork.org.au/newsletter/latest_news.htm [Accessed 10th February].

Openshaw, H., Nash, R. A. & McSweeney, P. A. (2002). 'High-dose immunosuppression and hematopoietic stem cell transplantation in autoimmune disease: clinical review', *Biol Blood Marrow Transplant*, 8 (5), 233-248.

PBS (2010). *Online searchable version of the Schedule of Pharmaceutical Benefits* [Internet]. Australian Government Department of Health and Ageing. Available from: http://www.pbs.gov.au/html/healthpro/home [Accessed 10th February].

Pieris-Caldwell, I., Templeton, M. et al (2008). *Diabetes: Australian facts 2008*, Australian Institute for Health and Welfare, Canberra. Available from: http://www.aihw.gov.au/publications/cvd/daf08/daf08.pdf

Richter, B., Bergerhoff, K. et al (2007). *Cochrane Metabolic and Endocrine Disorders Group* [Internet]. The Cochrane Library. Available from: http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/ENDOC/frame.html [Accessed 9th February].

Skyler, J. S. (2007). 'Cellular therapy for type 1 diabetes: has the time come?', *JAMA*, 297 (14), 1599-1600.

Statistics New Zealand (2008). *National population estimates tables* [Internet]. Available from: http://www.stats.govt.nz/tables/nat-pop-est-tables.htm [Accessed 8th September].

Type 1 Diabetes TrialNet (2010). *TrialNet Studies* [Internet]. Available from: http://www.diabetestrialnet.org/patientinfo/studies.htm [Accessed 4th February].

Voltarelli, J. C., Couri, C. E. et al (2008). 'Autologous hematopoietic stem cell transplantation for type 1 diabetes', *Ann N Y Acad Sci*, 1150, 220-229.

Voltarelli, J. C., Couri, C. E. et al (2007). 'Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus', *JAMA*, 297 (14), 1568-1576.

Wikipedia (2010). *Allogeneic and autologous transplantation* [Internet]. Available from: http://en.wikipedia.org/wiki/Main_Page [Accessed 10th February].

SEARCH CRITERIA TO BE USED:

Autoantibodies/blood
Diabetes Mellitus, Type 1/blood/*therapy
Hematopoietic Stem Cell Mobilization
Hematopoietic Stem Cell Transplantation
Transplantation Conditioning
Transplantation, Autologous