UNIVERSITY OF BIRMINGHAM

Pancreas graft survival after pancreas or pancreas and kidney transplant for insulin-treated diabetes

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

October 2007

For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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1 Aims

The aims of this report were to address the following questions submitted by the Driver Medical Group:

1.1 Primary Questions

- What is the natural history of a pancreas or pancreas and kidney transplant for insulin treated diabetics?

1.2 Secondary Questions

- How often do patients have to go back on insulin because of failure of the transplant?
- What is the time scale, how many transplants have failed after 1,3, 5, 10 years?

Further details are given in the request submitted by the Drivers Medical Group (Appendix 1 – Details of Request)

2 Background

Pancreas transplantation is intended to restore normal insulin secretion for patients with diabetes mellitus. The procedure can be performed in uremic diabetic patients simultaneously with kidney transplant (SPK), after kidney transplant (PAK), or solo (PTA) in non-uremic diabetic patients.

Simultaneous pancreas and kidney transplant (SPK)

SPK can be offered to most diabetic candidates for cadaveric kidney transplant. Patients are generally between 18-60 years of age with type 1 diabetes mellitus, end stage renal disease (ESRD), and usually have other diabetic complications. Dialysis is not a necessary criterion as long as ESRD is present.

In most SPK transplants, both organs come from the same cadaver donor. However, it is possible to have a SPK transplant from a living donor using one-half a pancreas (segmental graft). Furthermore, it is possible to do a living donor kidney transplant simultaneously with a cadaver donor pancreas transplant.

Pancreas after kidney transplant (PAK)

Pancreas after kidney transplantation is generally the option chosen for patients who have a living donor for the kidney. The disadvantage of PAK, requiring two operations, is offset by the higher probability of the recipient remaining dialysis-free long term than with a cadaver donor kidney transplant. However, it is also more difficult to detect rejection of a solitary pancreas transplant and thus there may be a slightly lower pancreas graft survival rate (GSR: percent of insulin independent recipients) with a PAK than for SPK. Unlike the SPK transplant, where both grafts come from the same donor, the kidney graft cannot be used as a surrogate marker for rejection that may be occurring in the pancreas.

Pancreas transplant alone (PTA)

PTA has been done mostly in patients with hypoglycemic unawareness or labile diabetes (including patients with frequent episodes of ketoacidosis) due to the limited treatments available for these patients. These

patients have failed insulin-based management and may have incapacitating clinical or emotional problems with exogenous insulin therapy. However, any gains from insulin independence must be weighed against the side effects of immunosuppression.

(Sutherland D, Hamatry M. Pancreas Transplant for Insulin-Dependent Diabetes. ICSI Technology Assessment Report, 2003).

3 Methods

Outline methods were submitted to the Drivers Medical Group by email and acceptance subsequently confirmed by e-mail and telephone (Appendix 2 – Outline methods).

Methods were as follows:

- A search for studies looking at the long-term success rates of pancreas, or pancreas and kidney, transplants for type I diabetes mellitus was undertaken, including sources such as MEDLINE, EMBASE and the Cochrane Library.
- Registry data and recent well-conducted systematic reviews of appropriate cohorts, particularly recent UK data, were sought in preference to primary studies.
- Patterns of graft survival rates (GSRs) over time were extracted and tabulated, with notable agreement or disagreement between different data sets noted.

3.1 Searches

3.1.1 Existing Reviews.

Searches to identify existing systematic reviews on this topic were performed utilising the well-established ARIF search protocol (7.3 Appendix 3 – Search strategies)

3.1.2 Primary Studies

Searches were predominantly undertaken by an information specialist with additional searches by a research reviewer (7.3 Appendix 3 – Search strategies). Both interacted to ensure searches were conducted appropriately.

An information specialist and a research reviewer scanned the search results for relevance based on information in the title and abstract. Articles that adhered to the following broad criteria were obtained in full for further scrutiny, as were any systematic reviews on this topic:

Design: registry data or large cohorts
Population: adults with SPK, PAK or PTA; recent UK and worldwide data
Outcome: pancreas graft survival rate
Exclusion: islet cell transplantation

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Full copy articles were assessed for their match to the questions being addressed (external validity) and the most informative articles (closest match to population [Section 1.1 Primary Questions], longest follow-up) subjected to further scrutiny and reporting.

4 Results

4.1 Data sources identified

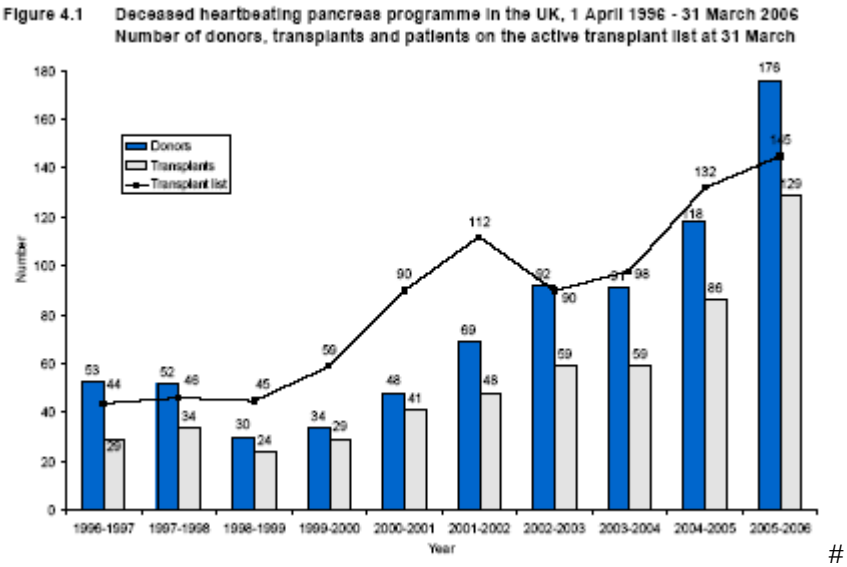
The number of transplants performed worldwide is small, but growing steadily year on year, with numbers exceeding 1,000/annum by early in the 21st century (Boudreau & Hodgson, 2007). The vast majority of transplants are performed in North America and Europe, with >70% performed in the US alone (Gruessner & Sutherland, 2002). We identified national registries reporting GSR% over time for both the UK and the US and a recent analysis based on the International Pancreas Transplant Registry. These were the most relevant, up to date and data rich sources identified. They are discussed in detail below.

4.2 UK, US and international graft survival rates

4.2.1 UK transplant data

Transplant Activity in the UK (Statistics and Audit Directorate, UK Transplant, August 2006) reports UK transplant activity for the financial year 2005-2006 and summarises transplant data from the National Transplant Database and the NHS Organ Donor Register. The number of pancreas tranplants has risen steadily from around 30/annum in the late 1990s to 129 in the most recent financial year reported.

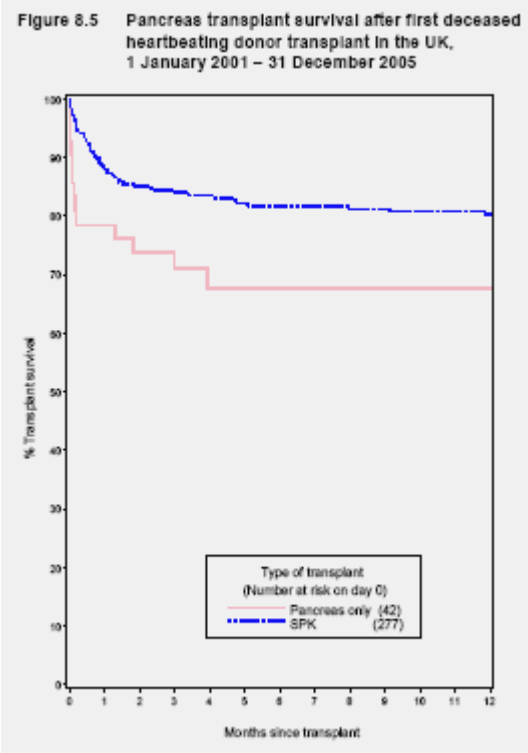
Figure 1 Donors, transplants and transplant list April 1996-March 2006 (reproduced from Transplant Activity in the UK, 2006)



#

National pancreas follow-up data is only available for transplants performed since January 2001 and follow-up beyond one year is not reported due to the small sample size beyond this time. No PAK transplants are reported in this dataset. The majority (277) of transplants were SPK and the remainder (42) PTA.
A plot from the report showing graft survival rate (GSR) for the first 12 months is reproduced in Figure 2. Separate curves are shown for PTA and SPK. There is some evidence to suggest that SPK transplant survival is better than that for PTA (p=0.007).

Figure 2 Pancreas transplant survival after first deceased heartbeating donor transplant in the UK, cohort 1st Jan 2001 to 31st December 2005 (reproduced from Transplant Activity in the UK, 2006)



4.2.2 US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Annual Report: Transplant Data 1996-2005

This is a large and detailed annual report. We have used the unadjusted GSRs reported for comparability with the methods used for the other data.

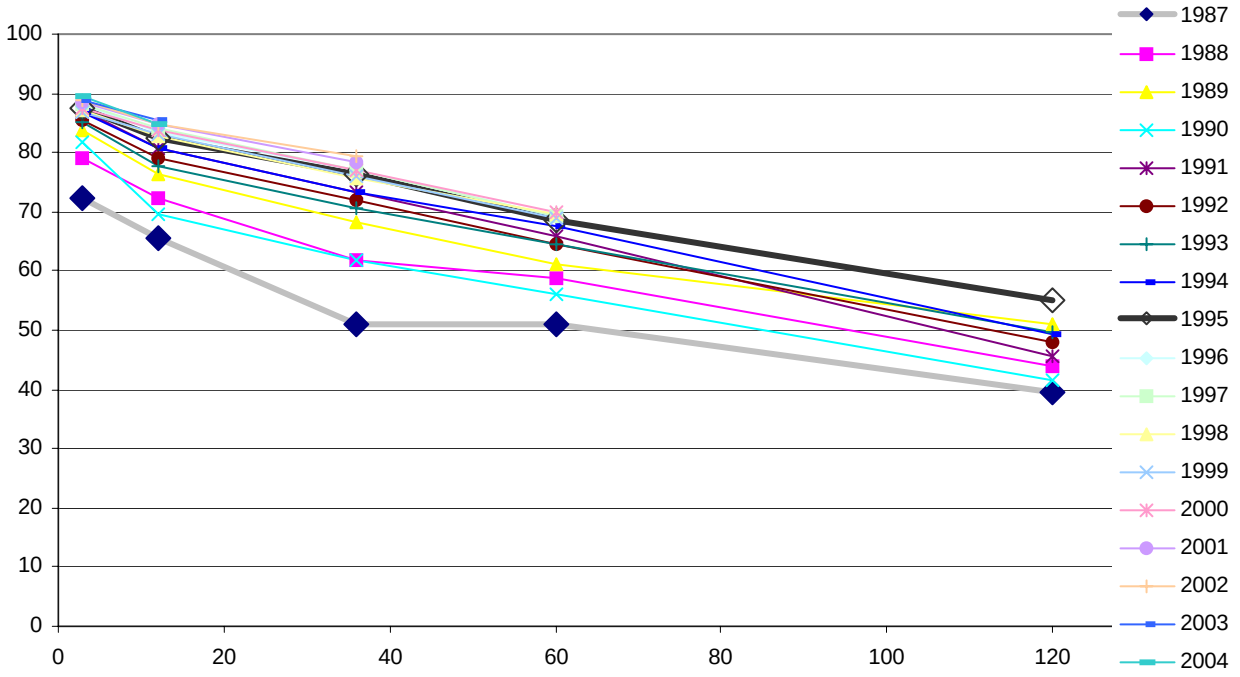
Figure **3** shows the annual data and up to 10 year follow-up for SPK transplants only (~90% of the total pancreas transplants reported). More recently, both PTA and PAK in particular have become more common due largely to the increasing use of live donors, especially for kidney transplants.

There is evidence of a steady improvement over time. The most recent year for which 10 year follow-up is available is 1995. This year and the start of the series, 1987, are highlighted with thicker lines in the plot. There is some evidence that GSRs may have continued to rise since 1995 but follow-up is too short to assess the nature and extent of any further improvements. There have been substantial gains in technical

failure rates (not relevant to DVLA) and more moderate recent gains in immunological failure rates (over time); the latter is indicated by the fairly moderate differences in gradients between the series once the initial period following transplant is successfully negotiated.

These data and those for the much smaller numbers of PAK and PTA will be discussed further in section 4.3 below.

Figure 3 Trends over time SPK from OPTN/SRTR annual data (years 1987 and 1995 in bold lines)



4.2.3 International Pancreas Transplant Registry

Gruessner & Sutherland report on 19,000 pancreas transplants reported to the International Pancreas Transplant Registry as of October 2002. Nearly three quarters of these were performed in the US, with around 5,000 performed elsewhere.

They report a progressive improvement over time from 75% GSR at the beginning of the series (1988-89) to 85% by 2000-01 (SPK), 53% to 77% (PAK) and 48% to 73% (PTA), consistent with the UK Transplant and US OPTN/SRTR data reported above. These improvements were due to both decreases in technical failure rates and immunological failure rates. The later reduced from 5% to 2% (SPK), 27% to 6% (PAK) and 37% to 9% (PTA).

Contemporary pancreas transplant outcomes were calculated separately for 1996-2002 US and non-US cases. For the US, reported GSR% are very consistent with the UK and US registry data with outcomes at one year of 84% SPK (n=5,784), 76% PAK (n=1,033) and 77% PTA (n=470). Immunological failure rates for technically successful transplants in this period were 2% (n=5,231), 7% (n=907) and 8% (n=404)

respectively. Age did not significantly influence outcome for SPK (82% to 85%, 10-19 to 60-69). For PAK one year GSRs improved from 69% for ages 20-29 to 83% for 60-69, and similarly for PTA (41% to 65%). Pancreas GSRs were identical for Type I (n=5,356) and Type II (n-288) diabetes (84%).

Non-US pancreas transplants were overwhelmingly SPK (n=2,163 for 1996-2002). Outcomes were as good or better as the US data, with one year pancreas GSR very similar (85%).

4.3 Comparison over time of UK and other data

Table 1 compares the limited short-term data from the UK registry (2001 onwards) with the US registry data for 1995 (the most recent year with 10 year follow-up available) and 2004 (the most recent year with one year follow-up available).

Table 1 Pancreas transplant survival rate: UK and US registry data over time (figures as reported)

Type	**SPK (%)**		**PAK (%)**		**PTA (%)**	
Data source	**UK 2001- n=277** % (95%CI)	**OPTN/SRTR 1995 n=913 2004 n=881** % (se)	**UK 2001- -** % (95%CI)	**OPTN/SRTR 1995 n=67 2004 n=419** % (se)	**UK 2001- n=42** % (95%CI)	**OPTN/SRTR 1995 n=36 2004 n=121** % (se)
30 days/1 mo	88 (84, 91)	-	-	-	79 (63-88)	-
90 days/3 mo	84 (80-88)	87.4 (1.1) 89.4(1.0)	-	77.8 (5.0) 85.7(1.8)	74 (57-85)	86.1 (5.8) 91.6(2.5)
1 year	80 (75-85)	82.3 (1.3) 84.7(1.2)	-	70.3 (5.5) 77.9(2.1)	68 (51-80)	63.9 (8.0) 77.0(3.9)
3 years	-	76.2 (1.4) -	-	55.3 (6.0) -	-	44.4 (8.3) -
5 years	-	68.6 (1.6) -	-	49.1 (6.1) -	-	23.7 (7.2) -
10 years	-	54.9 (1.8) -	-	21.3 (5.4) -	-	15.8 (6.6) -

This table is consistent with the findings of Gruessner & Sutherland using the international registry (IPTR) data. The UK and US GSR rates are very comparable given the associated confidence intervals and standard errors (95%CI is +/- 1.96se).

Looking at the US data for 1995 we can see that there is still a substantial failure rate between 5 and 10 years. Just under 80% of SPK surviving at 5 years are still surviving at 10 years. The failure rate in this period is even higher for PAK and PTA, although the sample sizes are smaller and the uncertainty correspondingly greater. There is no indication in the data available that the failure rate slows significantly at

any point between 5 and 10 years. There are no relevant series with longer follow-up available given that the procedure was only introduced in 1987 and older series are not relevant to todays techniques and immunological regimens.

4.4 Limitations of this report

Although not a systematic review the data reported is from high quality national and international registries which attempt to provide comprehensive coverage of all cases. There are no better cohort data available. However, the number of transplants taking place worldwide is small, of the order of 1,000/annum and rapid advances in technology have led to marked improvement in outcomes over time. As outcomes improve there will be increasingly limited room for further gains due to improved technology but it is not clear that this point has yet been reached.

5 Conclusion

The steady and continuing improvement in technology means that it is impossible to answer this question with any degree of certainty. The best available long-term data is from the OPTN/SRTR 1995 cohort. This can be regarded as an estimate of the minimum GSR% at each timepoint reported. The annual improvements for each successive cohort are not particularly large, after the substantial improvements in the first few years after the technology was introduced, from the late 1980s to early 1990s.

Current data for SPK suggests that the failure rate between 5 and 10 years may be of the order of around 4% per year and that this is likely to be a conservative estimate. The failure rate for the newer techniques using live donor(s) may be substantially higher, but the sample sizes are small and the technology in an earlier stage of development at the time these data were collected.

6 References

Boudreau R, Hodgson A. Pancreas transplantation to restore glucose control: review of clinical and economic evidence [Technology Report number 84]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of October 2002. *Clin Transpl* 2002:41-77

Sutherland D, Hamatry M. Pancreas Transplant for Insulin-Dependent Diabetes. ICSI Technology Assessment Report, 2003

Transplant Activity in the UK. Statistics and Audit Directorate, UK Transplant, August 2006

US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Annual Report: Transplant Data 1996-2005

7 Appendices

7.1 Appendix 1 – Details of Request

Date of request	9 August 2007
Lead Medical Adviser issuing request	Name – Dr Simon Rees Secretary to the Diabetes Panel
Contact details	Drivers Medical Group DVLA Sandringham Park Swansea Vale Llansamlet Swansea SA7 0AA [redacted] [redacted]

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

We need to know:

1. What is the natural history of a pancreas or pancreas and kidney transplant for insulin treated diabetics?
2. How often do patients have to go back on insulin because of failure of the transplant?
3. What is the time scale, how many transplants have failed after 1,3, 5, 10 years?

2. Please give a background to the question. Why has DMG raised this problem?

DVLA have seen an increase in the number of notifications from drivers who have had insulin-treated diabetes; had a transplant and have been taken off insulin.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background information on the *options* and *issues,* which might be important for the problems, you describe.

No references but discussion with Professor Frier (details below)

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel member.

Professor Brian M Frier (Chairman)
BSc Ed MD FRCP
Consultant Physician and Diabetologist
Department for Diabetes
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH16 4SA

[redacted]

5. What is the nature of the target population of the issue detailed above? Eg. age profile, vocational drivers, young drivers, other co-morbid features.

Drivers of all ages

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

The duration of driving licences, i.e. whether a review or non-review licence is issued.

7. What is the latest date that an ARIF response would be of value? 1 / 10 / 07

7.2 Appendix 2 – Outline methods

- A search for studies looking at the long-term success rates of pancreas, or pancreas and kidney, transplants for type I diabetes mellitus will be undertaken, including sources such as MEDLINE, EMBASE and the Cochrane Library.
- Recent well-conducted systematic reviews will be preferred over primary studies.
- If primary studies are required, we will focus on published studies based on recent UK data and employing a simple cohort design with long-term follow-up; relevant economic evaluations based on good quality empirical data will also be considered.
- Methodological quality of all included papers will be commented upon.
- Where appropriate and possible data on relevant outcomes will be extracted and tabulated, with notable agreement or disagreement between different data sets noted.
- Further analysis will depend on the information available.
- It is anticipated that there may be a period after transplant where failure rates remain significant, then dropping to non-significant over time. We will endeavour to identify key time periods where the levels of risk vary substantially.

7.3 Appendix 3 – Search strategies

7.3.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

(June 2007)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments

- NICE guidance (all programmes)
- Evidence Based Commissioning Collaboration (Trent R & D Support Unit). Links to Trent Purchasing Consortia reports and Wessex DEC reports (both no longer published)
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- STEER Reports (no longer published)
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases

- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

7.3.2 Search strategies

Database: Cochrane Library (Wiley) 2007 Issue 3
Search Strategy:

#1 pancreas near transplant*
#2 pancreatic near transplant*
#3 MeSH descriptor Pancreas Transplantation explode all trees
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Treatment Outcome explode all trees
#6 MeSH descriptor Follow-Up Studies explode all trees
#7 MeSH descriptor Cohort Studies explode all trees
#8 MeSH descriptor Survival explode all trees
#9 MeSH descriptor Prognosis explode all trees
#10 (#5 OR #6 OR #7 OR #8 OR #9)
#11 (#4 AND #10)

Database: Ovid MEDLINE(R) 1950 to August Week 2 2007
Search Strategy:

1 exp Pancreas Transplantation/
2 natural history.mp. or exp Natural History/
3 prognosis.mp. or exp Prognosis/
4 exp Treatment Outcome/ or outcome$.mp.
5 exp Survival/ or survival.mp. or exp Graft Survival/
6 or/2-5
7 exp Cohort Studies/ or cohort.mp.
8 exp Follow-Up Studies/ or follow-up.mp.
9 or/7-8
10 1 and 6 and 9
11 limit 10 to humans

Database: EMBASE 1980 to 2007 Week 33
Search Strategy:

1 exp KIDNEY PANCREAS TRANSPLANTATION/ or exp PANCREAS TRANSPLANTATION/
2 exp SURVIVAL/ or exp GRAFT SURVIVAL/
3 exp PROGNOSIS/
4 exp Treatment Outcome/
5 natural history.mp.
6 or/2-5
7 exp COHORT ANALYSIS/
8 exp Follow Up/

9 or/7-8
10 1 and 6
11 10 and 9
12 limit 11 to human

Other databases/sites searched (22/8/2007):

AHRQ
CADTH
DACEHTA
HAS
NZHTA
SBU
Merck Manual
Clinical Evidence
NICE
NCCHTA
Attract
CRD
TRIP
National Guidelines ClearingHouse
HES Online

General internet searches:

TRIS Online (National Transportation Library)
TRL (Tranportation Research Laboratory)
CARE Europe
DVLA
Monash University Accident Research Centre
NHTSA (National Highway Traffic Safety Association)
LTSA NZ
US Driving Assessment Symposia
Driving Assessment 2001, 2003 and 2005 International Driving Symposia on Human Factors in Driver Assessment, Training and Vehicle Design Various locations

Search terms used: transplant, pancreas, pancreatic, kidney