

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy

The pancreas is an organ in the body that makes insulin. Some conditions such as chronic pancreatitis (long-term inflammation of the pancreas) and some pancreatic tumours may require an operation to remove all, or part, of the pancreas. Diabetes develops in these patients as their bodies can no longer make enough insulin. A procedure called autologous pancreatic islet cell transplantation involves the removal of the cells responsible for insulin production, called islet cells, from the pancreas after it has been surgically removed. These cells are then inserted into the patient's liver with the aim of restarting insulin production within the body.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2008.

Procedure name

- Autologous pancreatic islet cell transplantation for prevention of diabetes mellitus after pancreatectomy

Specialty societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Diabetic Association
- British Transplant Society.

Description

Indications and current treatment

Pancreatectomy

Chronic pancreatitis is the ongoing inflammation of the pancreas causing abdominal pain as well as impaired endocrine and exocrine function. In some patients, total or partial pancreatectomy is carried out to alleviate the pain, resulting in the development of insulin-dependent diabetes.

Total or near-total pancreatectomy may also be used for some patients such as with benign endocrine tumours.

Exogenous insulin

Treatment of insulin-dependent type 1 diabetes is with the administration of exogenous insulin, usually through multiple daily subcutaneous injections. There are different types of insulin with varying times of onset and durations of action.

What the procedure involves

Autologous pancreatic islet cell transplantation is carried out as an adjunct to total or partial pancreatectomy. It involves the infusion of islet cells from the patient's own pancreas into their liver. The aim of the procedure is to improve glycaemic control which declines after pancreatectomy.

The procedure is carried out at the same time as the pancreatectomy operation, and with the patient remaining under general anaesthesia.

Following removal of the pancreas, the islet cells are isolated and prepared for transplantation. This process can take a few hours. Heparin may be administered intravenously immediately before or after islet cell transplantation with the intention of preventing clot formation around the transplanted cells. Insulin is also administered immediately before or after transplantation with the intention of protecting the islet cells from glucose toxicity. Under continuous portal vein pressure monitoring, the islet cells are infused slowly through a catheter either directly into the portal vein or into one of its tributaries (such as the omental, mesenteric or colic vein).

Efficacy

Insulin requirements

In a case series of 64 patients who underwent total pancreatectomy and islet autotransplantation, 69% (44/64) achieved complete insulin independence and 12% (8/64) achieved partial insulin independence (follow-up period not reported). Patients who had not had previous pancreatic operations and those who had previously had procedures to the head of the pancreas were more

likely to have a greater islet yield and achieve insulin independence than other patients¹.

In a case series of 48 patients, 39 were able to be evaluated for postoperative diabetes. Insulin independence was achieved in 51% (20/39) of patients at least one month after the procedure, five of whom later required insulin (median follow-up: 5 years). The probability of sustained insulin independence after 2 years was 34% (calculated using Kaplan-Meier analysis with mean follow-up of 2.7 years). One patient in this group was insulin independent at 10-year follow-up. Of the patients who had partial pancreatectomy and islet autotransplantation, 80% (4/5) remained insulin independent during 6 years of follow-up².

In a case series of 45 patients, most of whom had total pancreatectomy, 40% (18/45) remained insulin independent at a mean follow-up of 18 months³.

In another case series (of 40 patients), 21 patients were assessed at 6-month follow-up and five (24%) were insulin independent. At 3-year follow-up all 14 patients who were assessed were classed as either having diabetes or impaired glucose tolerance⁴.

One case series compared outcomes for 24 patients who had pancreatectomy and islet autotransplantation and 13 patients who had pancreatectomy alone. Patients who had islet autotransplantation had significantly lower mean daily insulin requirements than those who did not at follow-up assessments over 3 years ($p < 0.005$). In this study, 78% (7/9) of patients who received approximately 2500 IEQ/kg (islet equivalents per kilogram of body weight) achieved insulin independence during follow-up and 36% (5/14) who received less than 2500 IEQ/kg achieved insulin independence (follow-up ranged from 7 days to 3 years)⁵.

In a case series of 24 patients, 96% (23/24) of patients were insulin independent after islet autotransplantation; however, 33% (8/24) developed hyperglycemia requiring insulin between 1 and 8 years later⁶.

Finally, a case series of 13 patients reported that 85% (11/13) of patients achieved insulin independence for at least 6 months and 38% (5/13) achieved insulin independence for at least 2 years following islet autotransplantation⁷.

Safety

Mortality

There were no deaths directly related to islet autotransplantation reported in the literature.

Complications related to islet transplantation

In the case series of 48 patients, one patient had suspected asymptomatic portal vein thrombosis (on ultrasound) which appeared to have resolved 1 week postoperatively. In addition, two patients, who also had splenectomy

at the time of transplantation, had uncontrollable splenic hilar bleeding due to increased portal pressure².

A case series of 40 patients reported that complications for the 16 most recent patients in the series included pancreatic fistula and rupture and subsequent resection of spleen (raw data not reported)⁴. A case series from the same centre, which included the first 24 patients in the series, reported one case each of portal vein thrombosis, splenic infarction and splenic thrombosis requiring splenectomy⁵.

Finally, a case report described a patient who developed an idiosyncratic acute reaction to heparin, mediated through heparin-dependent platelet autoantibodies ('heparin-induced thrombocytopenia') following total pancreatectomy and islet autotransplantation. The patient was fully heparinised after pancreatectomy and before islet transplantation. Exploration and thrombectomies of the right femoral artery, external iliac artery, and the posterior and anterior tibial arteries were carried out. Results from coagulation studies confirmed that the patient was positive for heparin-induced thrombocytopenia and thrombosis 8 days after the procedure⁸.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to autologous pancreatic islet cell transplantation for prevention of diabetes mellitus after pancreatectomy. Searches were conducted of the following databases, covering the period from their commencement to 04/02/08: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were excluded because of the difficulty of appraising methodology unless they reported specific adverse events that were not reported in the published literature.
Patient	Patients undergoing pancreatectomy.
Intervention/test	Autologous pancreatic islet cell transplantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 259 patients from seven case series and one case report.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing assessments of this procedure

There were no published reviews identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

- Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. NICE interventional procedures guidance 13 (2007). Available from www.nice.org.uk/IPG13

Table 2 Summary of key efficacy and safety findings on autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy

Abbreviations used: IEQ/kg, islet equivalents per kilogram of body weight						
Study details	Key efficacy findings				Key safety findings	Comments
<p>Gruessner RA et al (2004)¹</p> <p>Case series Country: USA Study period: Feb 1997 – June 2003</p> <p>n = 64</p> <p>Population: patients with chronic pancreatitis due to familial or idiopathic disease (45%), pancreas divisum (20%), alcohol abuse (20%), biliary disease (10%). Previous pancreatic operations: Puestow drainage (25%), distal pancreatectomy (10%), Whipple procedure (4%).</p> <p>Age: mean 35 ± 14 years Sex: 33% male</p> <p>Technique: total pancreatectomy and autotransplantation of islet tissue.</p> <p>Follow-up: not reported</p> <p>Disclosure of interest: none stated</p>	<p>Insulin requirements (follow-up period not reported)</p>				No safety outcomes reported.	<p>This is a more recent study from the same centre as Wahoff et al (1995)². It reports outcomes for some of the same patients.</p> <p>Generalisability:</p> <ul style="list-style-type: none"> Familial or idiopathic disease was the most common cause of chronic pancreatitis in this group (45%) 40% had undergone previous pancreatic operations All patients underwent total pancreatectomy
	Sub-group (number in each group not reported)	Median islet yield (IEQ/kg)	Complete insulin independence	Partial insulin independence*		
	No previous pancreatic operation (60% of total group)	3249	71%	-		
	Previous Puestow drainage	1052	18%	-		
	Previous distal pancreatectomy	2112	20%	-		
	Previous Whipple procedure	4719	100%	-		
	Received islet yield > 2500	n/a	72%	17%		
	Received islet yield < 2500	n/a	5%	10%		
	ALL PATIENTS	-	69% (44/64)	12% (8/64)		
	<p>*Measured by detectable C-peptide level, one insulin injection required per day and absence of a sliding scale</p> <p>Factors associated with insulin independence</p> <ul style="list-style-type: none"> Islet yield >2500IEQ/kg (see above table) 					

Abbreviations used: IEQ/kg, islet equivalents per kilogram of body weight			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Wahoff DC et al (1995)²</p> <p>Case series Country: USA Study period: Feb 1977 – April 1995</p> <p>n = 48</p> <p>Population: patients with chronic pancreatitis due to familial or idiopathic disease (56%), alcohol abuse (19%), biliary disease (17%), pancreas divisum (4%), iatrogenic causes (4%). Previous pancreatic operations: sphincterotomy (38%), drainage (23%), resection (23%), excision (2%). Previous diabetes: 4%</p> <p>Age: mean 35 years (12–60) Sex: 12% male</p> <p>Technique: pancreatic resection (n = 48) and intraportal islet autotransplantation (n = 46)</p> <ul style="list-style-type: none"> • Total pancreatectomy: 56% (27/48) • Near-total pancreatectomy (> 95%): 33% (16/48) • Partial pancreatectomy (50–90%): 10% (5/48) <p>Follow-up: median 5 years</p> <p>Disclosure of interest: none stated</p>	<p>Insulin requirements (of 39 patients available for evaluation of postoperative diabetic status)</p> <ul style="list-style-type: none"> • Insulin independence 1 month after transplant: 51% (20/39) • 5 of these 20 patients later required insulin • Probability of sustained insulin independence in all 39 patients after 2 years (Kaplan-Meier analysis; mean follow-up: 2.7 years): 34% • 1 patient remained insulin independent at 10-year follow-up • Insulin independence during 6 years of follow-up in 5 patients who had partial pancreatectomy: 80% (4/5) 	<p>Mortality:</p> <ul style="list-style-type: none"> • 1 early death due to perforation of colon and sepsis (related to pancreatic resection) <p>Complications related to islet infusion: 6% (3/48)</p> <ul style="list-style-type: none"> • Portal vein thrombosis on ultrasound but no symptoms (1) • Uncontrollable splenic hilar bleeding (due to increased portal pressure) in patients who had splenectomy at time of transplant (2) <p>No life-threatening complications were caused by islet infusion.</p>	<p>This study is from same centre as Gruessner et al 2004¹ (above) and reports on earlier cases.</p> <p>Generalisibility:</p> <ul style="list-style-type: none"> • Familial or idiopathic disease was the most common cause of chronic pancreatitis in this group (56%) • 85% had undergone previous pancreatic operations • 89% underwent total or near total pancreatectomy

Abbreviations used: IEQ/kg, islet equivalents per kilogram of body weight			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Ahmad SA et al (2005)³</p> <p>Case series Country: USA Study period: July 2000 – June 2004</p> <p>n = 45</p> <p>Population: Patients with chronic pancreatitis due to familial or idiopathic disease (87%), alcohol abuse (4%), other (9%).</p> <p>Previous pancreatic operations: pancreaticoduodenectomy (22%), distal pancreatectomy (4%), lateral pancreaticojejunostomy (20%) Previous diabetes: 2%</p> <p>Age: mean 38 years (16 – 62) Sex: 33% male</p> <p>Technique: pancreatic resection and autotransplantation of islet tissue</p> <ul style="list-style-type: none"> • Total pancreatectomy: 56% (25/45) • Completion pancreatectomy: 35% (16/45) • Partial pancreatectomy: 9% (4/45) <p>Follow-up: mean 18 months (1–46)</p> <p>Disclosure of interest: none stated</p>	<p>Insulin dependence</p> <ul style="list-style-type: none"> • 18 patients (40%) remained insulin independent at follow-up (mean: 18 months) • 27 patients (60%) required insulin at follow-up <p>Most patients who became insulin independent required some insulin to treat intermittent hyperglycaemia at time of discharge from hospital.</p> <p>Factors associated with insulin independence (univariate analysis):</p> <ul style="list-style-type: none"> • Female gender • Lower body weight • Greater islet yield (IEQ) 	<p>Mortality: 7% (3/45)</p> <ul style="list-style-type: none"> • 1 patient with known steatohepatitis died 6 months after the procedure due to liver failure • 2 deaths (2 days and 6 weeks after discharge) not related to the procedure <p>Postoperative complications:</p> <ul style="list-style-type: none"> • Delayed gastric emptying: 9% (4/45) • Deep vein thrombosis: 9% (4/45) • Pulmonary embolism: 7% (3/45) • Urinary tract or central line infection: 7% (3/45) • Symptomatic intra-abdominal haematoma: 7% (3/45) • Pneumonia: 2% (1/45) • Wound infection: 2% (1/45) • Intra-abdominal abscess: 2% (1/45) • Pneumothorax: 2% (1/45) • Neuropraxia: 2% (1/45) 	<p>The reported complications were for the whole procedure and some/all may relate to pancreatectomy not the islet autotransplantation itself.</p> <p>Study objective: to identify prognostic factors associated with successful islet autotransplantation.</p> <p>Generalisibility:</p> <ul style="list-style-type: none"> • Familial or idiopathic disease was the most common cause of chronic pancreatitis in this group (87%) • 36% had undergone previous pancreatic operations • 91% underwent total or completion pancreatectomy

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<p>Clayton HA et al (2003)⁴</p> <p>Case series Country: UK Study period: Sept 1994 – July 2001</p> <p>n = 40</p> <p>Population: patients with chronic pancreatitis due to alcohol abuse (45%), familial or idiopathic disease (40%), other (5%). Previous diabetes: 2%</p> <p>Age: mean 44 years (21 – 65) Sex: 48% male</p> <p>Technique: pancreatic resection and autotransplantation of islet tissue</p> <ul style="list-style-type: none"> Total pancreatectomy: 78% (31/40) Partial pancreatectomy: 13% (5/40) Completion pancreatectomy: 10% (4/40) <p>Follow-up: maximum 6 years</p> <p>Disclosure of interest: none stated</p>	<p>Diabetic status (measured by oral glucose tolerance test)</p> <table border="1"> <thead> <tr> <th>Follow-up</th> <th>Normal</th> <th>Impaired</th> <th>Diabetic</th> </tr> </thead> <tbody> <tr> <td>6 months (n = 21)</td> <td>5</td> <td>9</td> <td>7</td> </tr> <tr> <td>1 year (n = 23)</td> <td>1</td> <td>11</td> <td>11</td> </tr> <tr> <td>2 years (n = 18)</td> <td>2</td> <td>7</td> <td>9</td> </tr> <tr> <td>3 years (n = 14)</td> <td>0</td> <td>4</td> <td>10</td> </tr> <tr> <td>4 years (n = 14)</td> <td>1</td> <td>4</td> <td>9</td> </tr> <tr> <td>5 years (n = 8)</td> <td>1</td> <td>1</td> <td>6</td> </tr> <tr> <td>6 years (n = 5)</td> <td>0</td> <td>1</td> <td>4</td> </tr> </tbody> </table> <p>Insulin dependence and graft function</p> <table border="1"> <thead> <tr> <th>Follow-up</th> <th>Median insulin dose (IU/day)</th> <th>Median HbA1c* (%)</th> <th>Median fasting C-peptide (ng/ml)</th> </tr> </thead> <tbody> <tr> <td>6 months (n = 18)</td> <td>6</td> <td>6.6</td> <td>1.03</td> </tr> <tr> <td>1 year (n = 26)</td> <td>7</td> <td>7.3</td> <td>1.39</td> </tr> <tr> <td>2 years (n = 17)</td> <td>12</td> <td>6.6</td> <td>0.66</td> </tr> <tr> <td>3 years (n = 13)</td> <td>15.5</td> <td>8.5</td> <td>0.68</td> </tr> <tr> <td>4 years (n = 13)</td> <td>21</td> <td>7.8</td> <td>1.31</td> </tr> <tr> <td>5 years (n = 7)</td> <td>35</td> <td>8.2</td> <td>0.51</td> </tr> <tr> <td>6 years (n = 5)</td> <td>43</td> <td>8.0</td> <td>1.68</td> </tr> </tbody> </table> <p>* HbA1c = glycosylated haemoglobin</p> <p>Summary: the islet grafts continued to function to 6 years but the level of function appeared to deteriorate as demonstrated by increased daily insulin requirements and increased proportion of patients with impaired or diabetic profiles.</p> <p>Factors associated with insulin independence There was no statistically significant correlation between the amount of islet cells transplanted and the outcome of the procedure.</p>			Follow-up	Normal	Impaired	Diabetic	6 months (n = 21)	5	9	7	1 year (n = 23)	1	11	11	2 years (n = 18)	2	7	9	3 years (n = 14)	0	4	10	4 years (n = 14)	1	4	9	5 years (n = 8)	1	1	6	6 years (n = 5)	0	1	4	Follow-up	Median insulin dose (IU/day)	Median HbA1c* (%)	Median fasting C-peptide (ng/ml)	6 months (n = 18)	6	6.6	1.03	1 year (n = 26)	7	7.3	1.39	2 years (n = 17)	12	6.6	0.66	3 years (n = 13)	15.5	8.5	0.68	4 years (n = 13)	21	7.8	1.31	5 years (n = 7)	35	8.2	0.51	6 years (n = 5)	43	8.0	1.68	<p>Mortality: 10% (4/40)</p> <ul style="list-style-type: none"> 1 patient died due to a postoperative cerebrovascular accident 3 late deaths unrelated to the procedure <p>Complications 'included' (in the 16 most recent patients)</p> <ul style="list-style-type: none"> Pancreatic fistula Rupture and subsequent resection of spleen 	<p>The complications reported in this study are only for the last 16 patients in the series because complications in the first 24 patients are reported in an earlier article (White SA et al (2001)).</p> <p>The follow-up data are incomplete. The authors state that this is because patients were not always able to attend appointments and some patients were referred from non local areas.</p> <p>Generalisibility:</p> <ul style="list-style-type: none"> Alcohol abuse was the most common cause of chronic pancreatitis in this group (87%) No patients had undergone previous pancreatic operations 88% underwent total or completion pancreatectomy <p>This study includes a higher proportion of patients who had total pancreatectomy and who had chronic pancreatitis due to alcohol abuse than other studies in table 2.</p>
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<p>White SA et al (2001)⁵</p> <p>Case series Country: UK Study period: 1994 – 1999</p> <p>n = 24 (plus 13 patients who had total pancreatectomy alone)</p> <p>Population: patients with chronic pancreatitis due to familial or idiopathic disease (54%), alcohol abuse (33%), other (13%). Previous pancreatic operations: drainage procedure (25%), celiac plexus or thoracoscopic nerve ablation (17%), sphincterotomy (17%), distal pancreatectomy (13%), cystgastrostomy (8%)</p> <p>Age: median 44 years Sex: 42% male</p> <p>Technique: pancreatic resection and intraportal autotransplantation of islet tissue</p> <ul style="list-style-type: none"> • Total pancreatectomy: 79% (19/24) • Partial pancreatectomy: 8% (2/24) • Completion pancreatectomy: 13% (3/24) <p>Follow-up: range 15 months to 5 years</p> <p>Disclosure of interest: none stated</p>	<p>Insulin dependence Follow-up ranged from 7 days to 3 years.</p> <ul style="list-style-type: none"> • 13% (3/24) of patients were insulin independent at the time of publication • 78% (7/9) of patients who received approx 2500 IEQ/kg developed insulin independence • 36% (5/14) of patients who received < 2500 IEQ/kg developed insulin independence • All patients had functioning islet grafts (demonstrated by C-peptide levels; raw data not reported) throughout follow-up • During the study period, islet transplant patients had significantly lower HbA1c levels and 24-hour insulin requirements than patients who had pancreatectomy alone <p>Mean insulin dose (IU/day) (95% CI)</p> <table border="1"> <thead> <tr> <th></th> <th>Islet transplant (n = 24)</th> <th>Pancreatectomy alone (n = 13)</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>Discharge</td> <td>18.2 (12.7-23.7)</td> <td>49.3 (37.9-60.7)</td> <td>0.002</td> </tr> <tr> <td>3-6 months</td> <td>12.3 (6.6-18.0)</td> <td>36.3 (13.6-60.0)</td> <td>0.002</td> </tr> <tr> <td>12 months</td> <td>16.1 (9.3-22.9)</td> <td>42.8 (32.0-53.7)</td> <td>0.0019</td> </tr> <tr> <td>24 months</td> <td>15.8 (9.7-21.9)</td> <td>52.5 (17.2-87.0)</td> <td>0.005</td> </tr> <tr> <td>36 months</td> <td>22.6 (10.9-34.2)</td> <td>40 (10.2-69.8)</td> <td></td> </tr> </tbody> </table>			Islet transplant (n = 24)	Pancreatectomy alone (n = 13)	p-value	Discharge	18.2 (12.7-23.7)	49.3 (37.9-60.7)	0.002	3-6 months	12.3 (6.6-18.0)	36.3 (13.6-60.0)	0.002	12 months	16.1 (9.3-22.9)	42.8 (32.0-53.7)	0.0019	24 months	15.8 (9.7-21.9)	52.5 (17.2-87.0)	0.005	36 months	22.6 (10.9-34.2)	40 (10.2-69.8)		<p>30-day mortality</p> <ul style="list-style-type: none"> • Islet transplant group: 4% (1/24). The patient died of a cerebrovascular accident 4 weeks postoperatively). • Pancreatectomy alone: 8% (1/13). The patient had chronic renal allograft nephropathy and was treated with immunosuppressive therapy because of a previous kidney transplant. <p>Complications related to the islet autotransplantation: 13% (3/24)</p> <ul style="list-style-type: none"> • Portal vein thrombosis (1) • Splenic infarction (1) • Splenic thrombosis requiring splenectomy (1) 	<p>This is an earlier study from the same centre as Clayton et al 2003. It reports outcomes for some of the same patients.</p> <p>Generalisibility:</p> <ul style="list-style-type: none"> • Familial or idiopathic disease was the most common cause of chronic pancreatitis in this group (54%) • 50% had undergone previous pancreatic operations • 92% underwent total or completion pancreatectomy
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<p>Oberholzer et al (2000)⁷</p> <p>Switzerland Case series Study period: Mar 1992 – Mar 1999</p> <p>n = 13</p> <p>Population: patients with chronic pancreatitis (n = 7) or benign tumours (n = 6). Median age: 44 years Male: 42%</p> <p>Technique: pancreatic resection and autotransplantation of islet tissue</p> <ul style="list-style-type: none"> • Total pancreatectomy: 23% (3/13) • Subtotal pancreatectomy: 23% (3/13) • Partial pancreatectomy: 54% (7/13) <p>Follow-up: mean 3.3 years</p> <p>Disclosure of interest: none stated</p>	<p>Insulin dependence</p> <ul style="list-style-type: none"> • Insulin independence for ≥ 6 months: 85% (11/13) • Insulin independence for ≥ 1 year: 54% (7/13) • Insulin independence for ≥ 2 years: 38% (5/13) • 2 patients required prolonged insulin treatment 		No safety outcomes reported.	<p>Generalisibility:</p> <ul style="list-style-type: none"> • Benign pancreatic tumour was the indication for surgery in nearly half of this group • No patients had undergone previous pancreatic operations • 92% underwent total or completion pancreatectomy 	
	Subgroup	Insulin independence at any time (%)			Range of duration of insulin independence
	Chronic pancreatitis (n = 7)	86% (6/7)			6–54 months
	Benign tumour (n = 6)	83% (5/6)			6–48 months
	Total or sub-total pancreatectomy (n = 6)	67% (4/6)			8–54 months
	Partial pancreatectomy (n = 7)	100% (7/7)			6–48 months
	Received islet yield >2500 IEQ/kg (n = 6)	100% (6/6)			6–54 months
	Received islet yield <2500 IEQ/kg (n = 7)	71% (5/7)			6–48 months

Abbreviations used: IEQ/kg, islet equivalents per kilogram of body weight			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Fontana et al (1994)⁶</p> <p>Italy</p> <p>Case series</p> <p>Study period: Feb 1979 – Sept 1983</p> <p>n = 24</p> <p>Population: Patients with chronic pancreatitis</p> <p>Age: range 35–57 years</p> <p>Sex: 75% male</p> <p>Technique: near total (>95%) pancreatectomy and autotransplantation of islet tissue.</p> <p>Method of administration of islet cells:</p> <ul style="list-style-type: none"> • Direct injection into portal vein (n = 6) • Infused into portal vein via percutaneous catheterisation (n = 6) • Injection into the peritoneum (n = 11) • Intramuscular injection (n = 1) <p>Follow-up: 3 years</p> <p>Disclosure of interest: none stated</p>	<p>Insulin requirements</p> <ul style="list-style-type: none"> • Insulin independent after surgery: 96% (23/24) • The patient who had intramuscular islet cell injection failed immediately • Normal glycometabolic control (to date): 50% (12/24) • Development of hyperglycemia requiring insulin 1-8 years after procedure: 33% (8/24) <p>Factors associated with insulin independence (at follow-up)</p> <ul style="list-style-type: none"> • Greater number of transplanted islets (raw data and significance not reported) • Intrahepatic transplant (p < 0.05) 	<p>Mortality</p> <ul style="list-style-type: none"> • 3 deaths: 1 at 2 years and 2 at 3 years after the procedure (causes of death not reported but not related to the procedure according to the authors) <p>Postoperative complications</p> <p>No complications reported</p>	<p>This article was a one-page report and only a few details were provided.</p> <p>Generalisibility:</p> <ul style="list-style-type: none"> • No patients had undergone previous pancreatic operations • All patients underwent near total pancreatectomy • In nearly half of the patients, islet cells were injected into the peritoneum

Abbreviations used: IEQ, islet equivalents per kilogram of body weight			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Rastellini et al (2006)⁸</p> <p>USA</p> <p>Case report</p> <p>Study period: not reported</p> <p>n = 1</p> <p>Population: female patient aged 20 years with chronic pancreatitis due to congenital abnormalities.</p> <p>Technique: total pancreatectomy and autotransplantation of islet tissue.</p> <p>Follow-up: 35 days</p> <p>Disclosure of interest: not stated</p>	Not reported	<p>Postoperative complications</p> <p>Patient developed heparin-induced thrombocytopenia on postoperative day one. The patient required thrombectomies of the right femoral artery, external iliac artery, and the posterior and anterior tibial arteries.</p>	<p>The authors noted that adverse reactions, especially as serious as this, are rare and that they have not heard of any other reports of this complication after autologous islet transplantation.</p>

Validity and generalisability of the studies

- The studies in table 2 reported outcomes after different types of pancreatectomy (completion, partial, near-total and total). The amount of pancreatic tissue removed is likely to affect the outcome of the islet transplantation.
- Many patients had undergone previous pancreatic procedures.
- Patients in the studies had various causes of chronic pancreatitis; however, the most common causes in most studies were familial or idiopathic.
- Some studies included patients who already had diabetes (Wahoff DC et al. 1995, Ahmad SA et al. 2005, Clayton et al. 2003).

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

- Prof Derek Gray, Prof Peter Lodge (Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland); Mr Vasilios Papalois, Steve White (British Diabetic Association); Mr John Casey, Dr Chas Newstead (British Transplant Society); Paul Johnson (Diabetes UK).

Safety

- Theoretical and anecdotal adverse events included portal vein thrombosis, portal hypertension, hepatic infarction, liver steatosis, liver failure, intra-abdominal haemorrhage, bile leakage, spleen rupture, disseminated intravascular coagulation, infection, intrahepatic sepsis and islet cell pulmonary emboli.
- Several Advisers stated that the main risks were due to the pancreatectomy procedure rather than islet autotransplantation.
- Uncertainties about safety included preparation of islets (whether or not the tissue should be purified) and the maximum volume of tissue that should be

infused (a low yield of islets leads to a large volume of tissue being infused and the potential for increased portal pressure particularly compared with allogeneic transplantation).

Efficacy

- Key efficacy outcomes included long-term insulin independence, improved glycaemic control, normal glucose tolerance, lesser degrees of graft function (indicated by C-peptide levels) without insulin independence but with avoidance of severe hypoglycaemia, HbA_{1c} levels, prevention of long-term diabetic complications, and quality of life.
- Uncertainties about efficacy included long-term insulin independence and controversy regarding the timing of total pancreatectomy (a healthier pancreas would allow a better islet yield but pancreatectomy would not be indicated).

Other comments

- Specialist Advisers stated that the comparators to this procedure are total pancreatectomy or pancreatic resection without islet autotransplantation (with insulin injections if required).
- Four Specialist Advisers thought that this procedure was established practice (worldwide) and no longer new.
- Specialised facilities for islet isolation are required, as are experienced radiological and clinical staff.
- There are two international registries which include allogeneic transplantation and autotransplantation, and transplant activity in the UK should be submitted to UK transplant (though there is no funding for this as yet).
- All Specialist Advisers thought this procedure would affect less than 10 specialist centres in the UK.

Issues for consideration by IPAC

- Title: a Specialist Advisor suggested 'autologous pancreatic islet cell transplantation following total pancreatectomy for improved glycaemic control'.

- Title: consider pancreatic resection vs pancreatectomy (to cover all types of operation: total, near total or partial).

References

1. Gruessner RWG. (2004) Transplant options for patients undergoing total pancreatectomy for chronic pancreatitis. *Journal of the American College of Surgeons* 198: 559-567.
2. Wahoff DC, Papalois BE, Najarian JS et al. (1995) Autologous islet transplantation to prevent diabetes after pancreatic resection. *Annals of Surgery* 222: 562-575.
3. Ahmad SA, Lowy AM, Wray CJ et al. (2005) Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. *Journal of the American College of Surgeons* 201: 680-687.
4. Clayton HA, Davies JE, Pollard CA et al. (2003) Pancreatectomy with islet autotransplantation for the treatment of severe chronic pancreatitis: the first 40 patients at the Leicester general hospital. *Transplantation* 76: 92-98.
5. White SA, Davies JE, Pollard C et al. (2001) Pancreas resection and islet autotransplantation for end-stage chronic pancreatitis. *Annals of Surgery* 233: 423-431.
6. Fontana I, Arcuri V, Tommasi GV et al. (1994) Long-term follow-up of human islet autotransplantation. *Transplantation Proceedings* 26: 581-
7. Oberholzer J, Triponez F, Mage R et al. (2000) Human islet transplantation: lessons from 13 autologous and 13 allogeneic transplantations. *Transplantation* 69: 1115-1123.
8. Rastellini C, Brown ML, and Cicalese L. (2006) Heparin-induced thrombocytopenia following pancreatectomy and islet auto-transplantation. *Clinical Transplantation* 20: 156-158.

Appendix A: Additional papers on autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ahmad SA, Lowy AM, Wray CJ, et al. (2005) Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. <i>Journal of the American College of Surgeons</i> 201: 680-687.	n = 45 Follow-up: 18 months	Factors associated with insulin independence (univariate analyses) included: female, lower body weight, more islet equivalents per kg body weight transfused.	More recent study from same centre included in table 2.
Alsaif F, Molinari M, Al Masloom A et al. (2006) Pancreatic islet autotransplantation with completion pancreatectomy in the management of uncontrolled pancreatic fistula after Whipple resection for ampullary adenocarcinoma. <i>Pancreas</i> 32: 430-431.	n = 1 Follow-up: 1 year	84-year-old patient who had completion pancreatectomy with islet autotransplantation after pancreaticojejunosotomy for carcinoma. Patient remained insulin independent at follow-up with no evidence of tumour recurrence.	Larger studies included in table 2.
Arias-Diaz J, Calleja J, Vara E et al. (1994) Delayed islet autotransplantation after total pancreatectomy. <i>Transplantation Proceedings</i> 26: 3521-3522.	n = 1 Follow-up: 6 months	35-year-old patient who had near-total pancreatectomy with delayed islet autotransplantation (2 days later once diabetic status was confirmed) for alcoholic chronic pancreatitis. Patient remained insulin independent at follow-up.	Larger studies included in table 2.
Berney T, Rudisuhli T, Oberholzer J et al. (2000) Long-term metabolic results after pancreatic resection for severe chronic pancreatitis. <i>Archives of Surgery</i> 135: 1106-1111.	n = 4 Follow-up: 6.3 years	Perioperative mortality: 1.5% Perioperative morbidity: 21% Actuarial survival at 10 years: 54% Diabetes-free survival at 10 years: 26% (not related to type or extent of pancreatic resection).	Larger studies included in table 2.
Berney T, Mathe Z, Bucher P et al. (2004) Islet autotransplantation for the prevention of surgical diabetes	n = 7 Follow-up:	Mortality : 0 Insulin independence at follow-up: 86% (6/7)	Larger studies included in table 2.

after extended pancreatectomy for the resection of benign tumors of the pancreas. Transplantation Proceedings 36: 1123-1124.	5 years	All patients, including one on insulin, displayed positive basal and glucagon-stimulated C-peptide levels.	
Cameron JL, Mehigan DG, Harrington DP et al. (1980) Metabolic studies following intrahepatic autotransplantation of pancreatic islet grafts. Surgery 87: 397-400.	n = 1 Follow-up: 1 year	51-year-old patient had near-total pancreatectomy with islet autotransplantation. At 6 months, patient became hyperglycemic and required insulin therapy with no evidence of graft function.	Larger studies included in table 2.
Cameron JL, Mehigan DG, Broe PJ et al. (1981) Distal pancreatectomy and islet autotransplantation for chronic pancreatitis. Annals of Surgery 193: 312-317.	n = 8 Follow-up: 1 year	All patients developed portal hypertension during the procedure. Mortality: 13% (1/8) Patient required treatment for portal hypertension and subsequently died of hepatic necrosis. All patients had hyperglycemia requiring insulin therapy immediately after surgery. 6 patients became normoglycemic at an average of 28 days following the transplant.	Larger studies included in table 2.
Carroll PB, Ricordi C, Riolo, HR et al. (1992) Intrahepatic human islet transplantation at the University of Pittsburgh: results in 25 consecutive cases. Transplantation Proceedings 24: 3038-3039.	n = 2 Follow-up: 7 and 17 months	Insulin independence at follow-up: 2/2	Larger studies included in table 2.
Farney AC, Najarian JS, Nakhleh RE et al. (1991) Autotransplantation of dispersed pancreatic islet tissue combined with total or near-total pancreatectomy for treatment of chronic pancreatitis. Surgery 110: 427-437.	n = 26 Follow-up: 5.7 years	Perioperative mortality: (1/26) a complication of pancreatectomy. Insulin independence \geq several months after surgery: 35% (9/26) Of whom: 5 remained insulin independent at follow-up, 1 died insulin independent at 6 years, 3 required insulin 8 to 18 months after surgery. Insulin independence was related to number of islets recovered and degree of pancreatic fibrosis. Morbidity related to the intraportal-dispersed pancreatic islet tissue transplantation was low.	More recent study from same centre included in table 2.
Farney AC, Hering BJ, Nelson L et	n = 29	Insulin independence any time	More recent

al. (1998) No late failures of intraportal human islet autografts beyond 2 years. Transplantation Proceedings 30: 420.	Follow-up: 9 years	during follow-up: 46% (11/24) Of whom: 5 lost function 3 to 24 months after surgery, 5 remain insulin independent at 4 to 12 years, 1 died at 6 years (not related to procedure). Duration of insulin independence was related to the number of islets transplanted.	study from same centre included in table 2.
Forster S, Liu X, Adam U et al. (2004) Islet autotransplantation combined with pancreatectomy for treatment of pancreatic adenocarcinoma: a case report. Transplantation Proceedings 36: 1125-1126.	n = 1 Follow-up: 2 years	63-year-old patient who had extensive pancreatectomy and islet autotransplantation for carcinoma. Patient did not achieve insulin independence.	Larger studies included in table 2.
Froberg MK, Leone JP, Jessurun J et al (1997) Fatal disseminated intravascular coagulation after autologous islet transplantation. Human Pathology 28 (11) 1295-1298.1997.	n = 1 Follow-up: 4 hours	Patient developed disseminated intravascular coagulation and fatal haemorrhagic shock and died 4 hours after the procedure. Portal pressure rose from 20cm H ² O before infusion to 34cm H ² O afterwards	Larger studies included in table 2.
Hesse UJ, Hering BJ, Bretzel RG et al. (1994) Efficiency of highly purified islets autotransplanted into the portal vein after total pancreatectomy. Transplantation Proceedings 26: 3525-3526.	n = 1 Follow-up: 2 years	37-year-old patient who had total pancreatectomy and islet autotransplantation for recurrent acute pancreatitis. Patient remained insulin independent at follow-up.	Larger studies included in table 2.
Hinshaw DB, Jolley WB, Hinshaw DB et al. (1981) Islet autotransplantation after pancreatectomy for chronic pancreatitis with a new method of islet preparation. American Journal of Surgery 142: 118-122.	n = 5 Follow-up: 7-21 months	Insulin independence any time after surgery: 80% (4/5) Of whom: 2 patients remain insulin independent (at 7 and 14 months) and 2 now require insulin.	Larger studies included in table 2.
Illouz S, Webb M, Pollard C. et al (2007) Islet autotransplantation restores normal glucose tolerance in a patient with chronic pancreatitis. Diabetes Care 30 (12) e130	n = 1	43-year old woman with CP and had an abnormal oral glucose tolerance test (OGTT) before pancreatectomy but since surgery has had normal results. Patient remains insulin independent 5 years after transplantation.	Larger studies included in table 2.
Jindal RM, Fineberg SE, Sherman S et al (1998) Clinical experience with autologous and allogeneic pancreatic islet transplantation. Transplantation 66: 1836-1841.	n = 6 Follow-up: 5.5 months	Insulin independence: 6/6 (mean follow-up of 5.5 month)	Larger studies included in table 2.
Johnson PR, White SA, Robertson GS et al. (1999) Pancreatic islet autotransplantation combined with	n = 7 Follow-up:	Mortality: 1 patient died of a stroke 4 weeks postoperatively Insulin independence at any	More recent study from same centre

total pancreatectomy for the treatment of chronic pancreatitis - the Leicester experience. Journal of Molecular Medicine 77: 130-132.	not reported	time: 4/7 Of whom, 2 patients remained insulin independent, 2 patients required insulin after 1 month and 2 patients required reduced insulin doses.	included in table 2.
Lee BW, Jee JH, Heo JS et al. (2005) The favorable outcome of human islet transplantation in Korea: experiences of 10 autologous transplantations. Transplantation 79: 1568-1574.	n = 10 Follow-up: 13 months	Insulin independence at follow-up: 8/10 During follow-up, 2 patients required insulin. Factors affecting insulin independence included pancreatectomy extent and underlying cystic neoplasm disease.	Larger studies included in table 2.
Liu X, Forster S, Adam U et al. (2001) Islet autotransplantation combined with total pancreatectomy for treatment of pancreatic adenocarcinoma. Transplantation Proceedings 33: 662-663.	n = 1 Follow-up: not reported	63-year-old patient who had extensive pancreatectomy and islet autotransplantation for carcinoma. Patient did not achieve insulin independence.	Duplicate of Forster S et al. (2004) (see above)
Mehigan DG, Bell WR, Zuidema G. et al (1980) Disseminated intravascular coagulation and portal hypertension following pancreatic islet autotransplantation. Annals of Surgery 191 (3) 287-293.	n = 5 Follow-up: not stated	1 patient developed severe portal hypertension and acute disseminated intravascular coagulation immediately following transplantation. After this case, the subsequent 4 cases received heparin and aprotinin added to islet tissue and had only minor elevations of portal pressure.	Larger studies included in table 2.
Mittal V, Toledo-Pereyra LH, Sharma M et al (1981) Acute portal hypertension and disseminated intravascular coagulation following pancreatic islet autotransplantation after subtotal pancreatectomy. Transplantation 31: 302-304.	n = 1 Follow-up: 31 days	38-year-old patient who had subtotal pancreatectomy islet autotransplantation for chronic pancreatitis. Patient developed acute portal hypertension and disseminated intravascular coagulation and died 31 days after the procedure.	Larger studies included in table 2.
Morel PH, Buhler L, Deng S et al. (1994) Islets of Langerhans autotransplantation in humans. Transplantation Proceedings 26: 3527-3528.	n = 4 Follow-up: 6 weeks to 14 months	Insulin independence at last follow-up: 75% (3/4).	Larger studies included in table 2.
Morrow CE, Cohen JI, Sutherland DE et al. (1984) Chronic pancreatitis: long-term surgical results of pancreatic duct drainage, pancreatic resection, and near-total pancreatectomy and islet autotransplantation. Surgery 96:	n = 10 Follow-up: 5 years	Insulin independence at follow-up: 1/10 3 patients were insulin independent for 4, 5, and 15 months, respectively, but subsequently required insulin.	Larger studies included in table 2.

608-616.		5 patients had insulin requirements immediately after surgery.	
Najarian JS, Sutherland DE, Baumgartner D et al. (1980) Total or near total pancreatectomy and islet autotransplantation for treatment of chronic pancreatitis. <i>Annals of Surgery</i> 192: 526-542.	n = 10 Follow-up: 1-15 months	Same patients as in above study (Morrow et al 1984).	Larger studies included in table 2.
Oberholzer J, Mathe Z, Bucher P et al. (2003) Islet autotransplantation after left pancreatectomy for non-enucleable insulinoma. <i>American Journal of Transplantation</i> 3: 1302-1307.	n = 2 Follow-up: 3 and 6 years	81- and 73-year-old patients who had pancreatectomy and islet autotransplantation for insulinoma. Both patients were insulin independent at follow-up.	Larger studies included in table 2.
Pyzdrowski KL. (1992) Preserved insulin secretion and insulin independence in recipients of islet autografts. <i>New England Journal of Medicine</i> 327: 220-226.	n = 5 Follow-up: not reported	The same patients are reported in Farney et al (1991) (see above).	Larger studies included in table 2.
Rafael E, Tibell A, Ryden M et al. (2008) Intramuscular autotransplantation of pancreatic islets in a 7-year-old child: a 2-year follow-up. <i>American Journal of Transplantation</i> 8: 458-462.	n = 1 Follow-up: 27 months	7-year-old with hereditary pancreatitis who had total pancreatectomy and intramuscular islet transplantation. Patient had improved quality of life, a normal HbA _{1c} level, low insulin requirement and no recurrent hypoglycaemia.	Larger studies included in table 2.
Rastellini C, Shapiro R, Corry R et al. (1997) Treatment of isolated pancreatic islets to reverse pancreatectomy-induced and insulin-dependent type I diabetes in humans: a 6-year experience. <i>Transplantation Proceedings</i> 29: 746-747.	n = 5 Follow-up: 3-64 months	Insulin independence at follow-up: 80% (4/5) (follow-up: 3-64 months)	Larger studies included in table 2.
Rilo H L, Ahmad SA, D'Alessio D et al (2003) Total pancreatectomy and autologous islet cell transplantation as a means to treat severe chronic pancreatitis. <i>Journal of Gastrointestinal Surgery</i> 7: 978-989.	n = 22 Follow-up: not reported	Insulin independence at discharge: 41% (9/22) 27% (6/22) required minimal insulin at discharge. Major complications included: acute respiratory distress syndrome (n = 2), intra-abdominal abscess (n = 1), and pulmonary embolism (n = 1).	Larger studies included in table 2.
Robertson RP, Lanz KJ, Sutherland DE et al. (2001) Prevention of diabetes for up to 13 years by autoislet transplantation after pancreatectomy for chronic pancreatitis. <i>Diabetes</i> 50: 47-50.	n = 6 Follow-up: 6.2 years	5 patients remained insulin independent at follow-up. 3 patients had decreased insulin responses to glucose over time.	Larger studies included in table 2.

Rossi RL, Braasch JW, Nugent FW et al. (1983) Segmental pancreatic autotransplantation for chronic pancreatitis. American Journal of Surgery 145: 437-442.	n = 3 Follow-up: 18, 6, 2 months	All patients were insulin independent at follow-up.	Larger studies included in table 2.
Rossi RL, Soeldner JS, Braasch JW et al. (1986) Segmental pancreatic autotransplantation with pancreatic ductal occlusion after near total or total pancreatic resection for chronic pancreatitis. Results at 5- to 54-month follow-up evaluation. Annals of Surgery 203: 626-636.	n = 8 Follow-up: 31 months	Insulin independence at follow-up: 88% (7/8) 1 patient required insulin 2 years after grafting.	Larger studies included in table 2.
Sutherland DE, Matas AJ, Goetz FC et al. (1980) Transplantation of dispersed pancreatic islet tissue in humans: autografts and allografts. Diabetes 29 Suppl 1: 31-44.	n = 3 Follow-up: 1 year, 15 months	1 patient died of peritonitis 10 days after procedure (not related to islet transplantation). 2 patients were insulin independent at follow-up.	Larger studies included in table 2.
Toledo-Pereyra LH, Rowlett AL, Cain W. (1984) Hepatic infarction following intraportal islet cell autotransplantation after near-total pancreatectomy. Transplantation 38 (1) 88-89.	n = 1 Follow-up: 10 days	Patient developed hepatic infarction and disseminated intravascular coagulation and after the procedure and died 10 days later.	Larger studies included in table 2.
Toledo-Pereyra LH. (1984) Islet cell autotransplantation: Risks, complications, and long-term follow-up. Transplantation Proceedings 16: 829-830.	n = 7 Follow-up: Up to 6 months	Insulin independence at follow-up: 4/7 Mortality and complications: 1 patient had disseminated intravascular coagulation, portal hypertension and systemic hypotension and died 1 month postoperatively 1 patient had intra-abdominal bleeding and colonic fistula and died 3 months postoperatively 1 patient had systemic hypotension 3 days postoperatively and died on day 5.	Larger studies included in table 2.
Toledo Pereyra LH. (1983) Islet cell autotransplantation after subtotal pancreatectomy. Archives of Surgery 118: 851-858.	n = 6 Follow-up: 1-25 months	Insulin independence at follow-up: 2/6 (at 25 and 20 months) Mortality: 2/6 - 1 patient died at 1 month of disseminated intravascular coagulation, 1 patient died at 3 months of surgical complications and sepsis.	Larger studies included in table 2.
Tosatti E, Valente U, Campisi C et al. (1980) Segmental pancreas autotransplantation in man	n = 3 Follow-up:	Insulin independence at follow-up: 3/3 Complications: 1 patient had a	Larger studies included in table 2.

following total or near total pancreatectomy for serious recurrent chronic pancreatitis. Transplantation Proceedings 12: 15-18.	12, 14, 16 months	pancreatic fistula which healed after 2 months	
Traverso LW, Abou-Zamzam AM, and Longmire WP, Jr. (1981) Human pancreatic cell autotransplantation following total pancreatectomy. Annals of Surgery 193: 191-195.	n = 4 Follow-up: discharge – 2 years	All patients required insulin at follow-up (1 patient died of insulin overdose 1 year after procedure).	Larger studies included in table 2.
Valente U, Ferro M, Campisi C et al. (1980) Report of clinical cases of islet autotransplantation. Transplantation Proceedings 12: 202-204.	n = 10 Follow-up: not reported	Insulin independence at follow-up: 9/10.	Larger studies included in table 2.
Valente U. (1985) Islet and segmental pancreatic autotransplantation after pancreatectomy: Follow-up of 25 patients for up to five years. Transplantation Proceedings 17: 363-365.	n = 25 Follow-up: 5 years	Insulin independence at 5-year follow-up: 2/25 1 patient was insulin independent for 2 years but now requires insulin.	More recent study from same centre included in table 2.
Valente U. (1986) Is islet and segmental pancreas autotransplantation an efficient technique for iatrogenic diabetes prevention? Consideration of 27 cases. Transplantation Proceedings 18: 1141-1142.	n = 27 Follow-up: 6 years	Same patients as described above.	More recent study from same centre included in table 2.
Valente U. (1986) Critical evaluation of clinical and metabolic parameters in 27 cases of islet and segmental pancreas autotransplantation. Transplantation Proceedings 18: 1825-1826.	n = 27 Follow-up: 7 years	Same patients as described above.	More recent study from same centre included in table 2.
Wahoff DC, Papalois BE, Najarian JS et al. (1995) Clinical islet autotransplantation after pancreatectomy: determinants of success and implications for allotransplantation? Transplantation Proceedings 27: 3161.	n = 36 Follow-up: to 10 years	Insulin independence initially: 47% (17/36) Of whom, 4 later required insulin Number of islets transplanted was the main determinant of insulin independence.	More recent study from same centre included in table 2.
Wahoff DC, Paplois BE, Najarian JS et al. (1996) Islet Autotransplantation after total pancreatectomy in a child. Journal of Pediatric Surgery 31: 132-135.	n = 1 Follow-up: 5 years	12-year-old patient who had total pancreatectomy and islet autotransplantation for idiopathic chronic pancreatitis. Patient remained insulin dependent at follow-up.	More recent study from same centre included in table 2.
Walsh TJ, Eggleston JC, and Cameron J. (1982) Portal hypertension, hepatic infarction,	n = 1 Follow-up:	56-year-old patient who had subtotal pancreatectomy and islet autotransplantation for	Larger studies included in table 2.

and liver failure complicating pancreatic islet autotransplantation. Surgery 91: 485-487.	not reported	alcohol-induced chronic pancreatitis. Patient developed portal hypertension, subsequent hepatic infarction and died of liver failure.	
Webb MA, Illouz SC, Pollard CA et al. (2006) Long-term maintenance of graft function after islet autotransplantation of less than 1000 IEQ/kg. Pancreas 33: 433-434.	n = 1 Follow-up: 10 years	39-year-old patient who had total pancreatectomy with intrasplenic islet autotransplantation for idiopathic chronic pancreatitis. Patient had perioperative splenic infarction and subsequent splenectomy. Patient remained insulin dependent at follow-up but with reduced requirements.	More recent study from same centre included in table 2.
White SA, Dennison AR, Swift SM et al. (1998) Intraportal and splenic human islet autotransplantation combined with total pancreatectomy. Transplantation Proceedings 30: 312-313.	n = 16 Follow-up: 26 months	Mortality: 1 patient died at 1 month, after perioperative carotid thrombosis. Insulin independence at any time: 38% (6/16) Insulin independence at last follow-up (26 months): 6% (1/16).	More recent study from same centre included in table 2.
White SA, London NJ, Johnson PR et al. (2000) The risks of total pancreatectomy and splenic islet autotransplantation. Cell Transplantation 9: 19-24.	n = 5 Follow-up: 1 year	Complications: wedge splenic infarct (1), emergency splenectomy (1), portal vein thrombosis (1). Insulin independence at 1 year: 2/5.	More recent study from same centre included in table 2.
White SA, Robertson GS, Davies JE et al. (1999) Splenic infarction after total pancreatectomy and autologous islet transplantation into the spleen. Pancreas 18: 419-421.	n = 1 Follow-up: not reported	22-year-old female patient who had a splenic infarction after splenic islet autotransplantation.	More recent study from same centre included in table 2.
Wray CJ, Ahmad SA, Lowy AM et al. (2005) Clinical significance of bacterial cultures from 28 autologous islet cell transplant solutions. Pancreatology 5: 562-569.	n = 28 Follow-up: not reported	89% (25/28) patients had bacterial culture-positive media solutions. Only 4 patients (14%) had an infectious complication from which bacteria was isolated that corresponded to bacteria in their islet cell preparation.	Larger studies included in table 2.

Appendix B: Related NICE guidance for autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy

Guidance	Recommendation
Interventional procedures	<p data-bbox="488 506 1274 604">Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. NICE interventional procedures guidance 257 (2007)</p> <p data-bbox="488 611 1284 978">1.1. The evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus shows short-term efficacy with some evidence of long-term efficacy. The evidence on safety shows that serious complications may occur as a result of the procedure. The long-term immunosuppression required is also associated with a risk of adverse events. In units with established experience in allogeneic pancreatic islet cell transplantation, the procedure may be used with normal arrangements for clinical governance (see also section 2.5.2).</p> <p data-bbox="488 989 1284 1220">1.2. During consent, clinicians should ensure that patients understand the potential complications of the procedure and the uncertainty about its efficacy in the long term. They should provide patients with clear, written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended.</p> <p data-bbox="488 1230 1268 1461">1.3. Patient selection for this procedure should involve a multidisciplinary team. Selection criteria should take into account that the procedure is particularly indicated for patients with hypoglycaemia unawareness and/or those already on immunosuppressive therapy because of renal transplantation.</p> <p data-bbox="488 1472 1268 1598">1.4. Further audit and research should address the effect of the procedure on quality of life and its long-term efficacy particularly in relation to the complications of diabetes (see section 3.1).</p>

Appendix C: Literature search for autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy

Database	Date searched	Version searched
CDSR (via Cochrane Library)	01/02/2008	Issue 1, 2008
DARE & HTA database (via CRD)	01/02/2008	—
CENTRAL (via Cochrane Library)	01/02/2008	Issue 1, 2008
MEDLINE	01/02/2008	1950 to January Week 4 2008
EMBASE	01/02/2008	1980 to 2008 Week 04
PreMedline	01/02/2008	January 31, 2008
CINAHL	01/02/2008	1982 to December Week 1 2007
British Library Inside Conferences (BLIC)	01/02/2008	—
National Research Register (NRR) Archive/ United Kingdom Clinical Research Network (UKCRN) Portfolio database	01/02/2008	—
Current Controlled Trials	01/02/2008	—

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1. "Islets of Langerhans Transplantation"/ (5739)
2. exp "Islets of Langerhans"/ (29603)
3. islet\$.tw. (29069)
4. (autoislet\$ or auto-islet\$).tw. (7)
5. (beta adj3 cell\$).tw. (36761)
6. or/2-5 (64960)
7. Cell Transplantation/ (4768)
8. Transplantation, Autologous/ (35731)
9. Transplantation, Homologous/ (62457)
10. transplant\$.tw. (229375)
11. (autotransplant\$ or auto-transplant\$).tw. (4861)
12. or/7-11 (284466)
13. 6 and 12 (6472)
14. 1 or 13 (8079)
15. Pancreatitis, Chronic/ (552)

16. Pancreatitis/ (32647)
17. Pancreatitis.tw. (32820)
18. exp Pancreatic Neoplasms/ (37825)
19. (pancreas\$ adj3 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$ or malignan\$)).tw. (27171)
20. Pancreatectomy/ (6870)
21. Pancreatectomy.tw. (4261)
22. (pancreas\$ adj3 resection\$).tw. (2817)
23. or/15-22 (82805)
24. 14 and 23 (742)
25. Animals/ (4159802)
26. Humans/ (10024340)
27. 25 not (25 and 26) (3141649)
28. 24 not 27 (280)